Study title: STAMPOUT: Study of Antibody for Methamphetamine Outpatient Therapy
Protocol number: M200C-1801
NCT number: NCT03336866
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STAMPOUT:
Study of **A**ntibody for **M**etham**p**hetamine **Ou**tpatient **T**herapy

Protocol Identifying Number: M200C-1801
Principal Investigators: Lynn Webster, MD and Peter Winkle, MD
IND Sponsor: InterveXion Therapeutics, LLC
IND Number: 110,179
Version Number: 9
20 Aug 2019

SUMMARY OF CHANGES AND JUSTIFICATIONS

Original protocol effective date: 08 September 2017

Note: As applicable for current changes only, additions are indicated in underlined text and deletions are indicated in strikethrough text in the affected sections of the document.

Item or Section(s)	Justification
Version 2	***Effective Date: 20 December 2017***
2.1 Background Information	To note that nonclinical studies supporting this clinical protocol have been completed.
2.2 Rationale; 6.1.4 Preparation	To limit the maximum dose of IXT-m200 given to 1500 mg as done in the Phase 1 protocol TOA62936.
4.1.3 Exploratory Endpoints; 5.2 Participant Exclusion Criteria; 7.1.1 Study Specific Procedures; 7.3.3 Inpatient Stay, Extension Stay, and Follow-up; 7.3.6 Schedule of Events Table; 8.1 Specification of Safety Parameters	To delete reference to cardiac output measures and analysis. Cardiac output measurement is not feasible along with other measurements using currently accessible equipment and was to be used for an exploratory endpoint only.
5.1 Participant Inclusion Criteria	To clarify medically acceptable forms of birth control.
5.2 Participant Exclusion Criteria; 7.1.1 Study Specific Procedures; 7.3.6 Schedule of Events Table	To update and add normal ranges for vital signs; to annotate the collection of vital signs at -0.25 hr relative to the first METH dose; and to add a window of ±5 min for collection.
6.1.2 Formulation, Appearance, Packaging, and Labeling	To correct the methamphetamine vial size to 1 mL.
7.1.1 Study Specific Procedures	To allow for repeated ECG recordings; to add a window of ±10 min for collection; and to add that subjects will rest supine for 5 minutes prior to taking vital sign measurements.
7.1.1 Study Specific Procedures; 7.3.6 Schedule of Events Table	To add criteria for appropriate subjective responses on Day 1 and remove DEQ assessment at 5 min after the METH doses.
7.2.1 Clinical Laboratory Evaluations	To update Serum Chemistry and Urinalysis tests and time points.
7.2.2 Other Assays or Procedures	To correct the sample size required for IXT-m200 serum PK and Immunogenicity analysis.
7.3.1 Screening	To note that either HIV antibody or nucleic acid tests may be done.
7.3.3 Inpatient Stay, Extension Stay, and Follow-up	To note priority order of tests to be done at the same time point.
7.3.3 Inpatient Stay, Extension Stay, and Follow-up; 7.3.6 Schedule of Events Table	To note that C-SSRS assessments will be done on Day 22 for those discharging, or Day 29 for those participating in the inpatient extension stay.
7.3.3 Inpatient Stay, Extension Stay, and Follow-up; 7.3.4 Final Study Visit; 7.3.6 Schedule of Events Table	To reduce the number of SCID-DSM-V assessments during follow-ups.
7.3.6 Schedule of Events Table	To reduce the number of ECG recorded on METH challenge days.
13.4 Participant and Data Confidentiality	To update the source of the Certificate of Confidentiality to NIH and add award identification.

Item or Section(s)	Justification
Version 3	***Effective Date: 09 March 2018***
Schematic of Study Design; 6.1.8 Dose Adjustments/ Modifications/Delays; 7.3.3 Inpatient Stay, Extension Stay, and Follow-up; 7.3.6 Schedule of Events Table	Replace the term 'normal', 'normalization', or 'defined' with 'acceptable' or 'accepted' in reference to vital signs.
1 Key Roles	To update the phone numbers for Sponsor Medical Expert, address for the Principal Investigator, update the Medical Monitor name and contact information.
5.2 Participant Exclusion Criteria	To change the alcohol dependence criteria for exclusion criteria (#8) to DSM-5.
5.2 Participant Exclusion Criteria; 7.1.1 Study Specific Procedures	To remove incorrectly defined normal ranges for vital signs, oxygen saturation, and respiration rate (#11).
5.2 Participant Exclusion Criteria; 7.6 Prohibited Medications, Treatments, and Procedures	To add donation of platelets to the list of exclusionary criteria (#19) and prohibited procedures.
6.1.2 Formulation, Appearance, Packaging, and Labeling	To update the IXT-m200 label information with manufacturing date and lot numbers. To update the METH vial information as changed over time by the provider NIDA.
6.1.5 Dosing and Administration	To update the fluid allowances relative to dose administration for both Study Agent and Challenge Agent. To provide the timing for meal provision after Study Agent dosing.
6.2 Study Agent Accountability Procedures	To allow for multiple shipments of METH if the first shipment is not adequate to complete the study due to expiration date or higher than expected subject retention and use.
7.1.1 Study Specific Procedures;	To note that subjects should be resting supine for 5 min prior to vital sign collection, and to update the timing of the pre-dose collection point.
7.1.1 Study Specific Procedures; 7.2.3 Specimen Preparation, Handling, and Storage; 7.2.4 Specimen Shipment	To note that samples will be processed, stored, and shipped per laboratory manual.
7.1.1 Study Specific Procedures	Update list of questions to be included in the DEQ and the questions that will be used to determine appropriate subjective responses on Day 1. This was done to shorten the time necessary for completion and to make it more comparable to similar studies.
7.2.1 Clinical Laboratory Evaluations	To clarify the requirements for quantitative urinalysis, reduce the frequency of pregnancy tests to approximately monthly, and to add screening serology details.
7.2.1 Clinical Laboratory Evaluations; 7.3.6 Schedule of Events Table	To add the analysis of cytokines to the clinical laboratory evaluation list and schedule of events table so that it is not overlooked.
7.2.2 Other Assays or Procedures	Change the processing of blood samples for METH and AMP PK from serum to plasma; plasma is more commonly used in human sample testing for METH. To update blood and urine collection volumes necessary.
7.3.1 Screening	To remove 'nucleic acid' word duplication.

Item or Section(s)	Justification
7.3.3 Inpatient Stay, Extension Stay, and Follow-up	To add cytokine sample collection to the events on Inpatient Stay (Day 4).
7.3.5 Early Termination Visit	To clarify that samples will be taken if the subject is willing to stay long enough.
7.3.6 Schedule of Events Table	To update vital sign, ECG, and DEQ baseline measurement time point; to clarify that a 24 hr post-METH time point ECG will be recorded, to change the time points for METH PK collections, to add a spot collection of urine prior to METH challenge dosing regimen for baseline measurement, and to add cytokine sample collection details.
8.6 Safety Oversight	To remove the stated frequency of DSMB meetings so that changes may be made within the DSMB Charter without requiring a protocol revision, and to rearrange the section for clarity of roles.
10.3 Analysis Datasets	To remove the Enrolled Population and replace it with a Qualification Safety Population for analysis, and to clarify the Safety Population description.
10.4.1 General Approach; 10.4.2 Analysis of the Primary Efficacy Endpoint(s)	To delete the references to serum concentrations of METH and to remove measures that are no longer assessed by the DEQ.
13.3.1 Consent/Assent and Other Informational Documents Provided to Participants	To add that the ICF will state that it is possible that binge use of METH after receiving IXT-m200 could be extremely dangerous and possibly life-threatening.
Appendix	Deleted list of significant changes as it only repeated information from this table.
Version 4	***Effective Date: 16 March 2018***
5.2 Participant Exclusion Criteria	Updated (#7) to clarify past year suicide attempt and/or suicidal ideation are exclusionary. Emphasized PI discretion to exclude any who are considered at risk for suicide.
7.1.1 Study Specific Procedures	Updated Table 6 to add blood volumes necessary to analyze cytokines. Corrected number of samples and resulting volumes for IXT-m200 and METH PK collections.
7.2.1 Clinical Laboratory Evaluations	Removed requirement for quantitative urine glucose testing since blood glucose will be determined on the same days as urinalysis testing.
Version 5	***Effective Date: 30 May 2018***
Schematic of Study Design	Throughout the protocol hemodynamic results are noted to be evaluated at the discretion of the Investigator. The text of 'pre-defined hemodynamic limits' was inadvertently left in the schematic.
5.2 Participant Exclusion Criteria' 7.3.6 Schedule of Events Table	By administrative error, SCID-DSM-5 was referenced in this protocol while the intention was to only use the DSM-5 criteria for evaluating drug or alcohol use. Psychiatric evaluation is taken during medical history and also includes the C-SSRS. To correct Exclusion criteria #6 and 7.3.6 footnote 'b' as intended, reference to DSM-5 is removed.
7.2.1 Clinical Laboratory Evaluations	To update the Urinalysis testing requirements. The same tests are to be conducted but listed as microscopic rather than macroscopic.
7.3.1 Screening; 7.3.6 Schedule of Events Table	By administrative error, SCID-DSM-5 was referenced in this protocol while the intention was to only use the DSM-5 criteria for evaluating drug or alcohol use. Reference to SCID is removed.

Item or Section(s)	Justification
7.3.2 Enrollment/Baseline; 7.3.3 Inpatient Stay, Extension Stay, and Follow-Up; 7.3.5 Early Termination Visit	Assessments of METH use should be made 'since last visit' rather than 'past 30 days' to allow for coverage between missed or delayed visits.
7.3.3 Inpatient Stay, Extension Stay, and Follow-Up	Inserted the parenthetical (Day 105 only) under 'Outpatient Follow-up (Days 84, 105 [±3 days])' to match the previously updated footnote 'a' in 7.3.6.
7.3.6 Schedule of Events Table	The Day 5 pre-dose ECG will collect the same data as the Day 4 24 hour ECG, thus both are not required. Correction was made to footnote g to indicate which one will be done.
Version 6	***Effective Date: 26 Apr 2019***
Statement of Compliance; Protocol Summary; 1 Key Roles; 5.4.1 Reasons for Withdrawal or Termination; 6.2 Study Agent Accountability Procedures; 7.2.1 Clinical Laboratory Evaluations; 7.3.1 Screening; 7.7 Rescue Medications, Treatments, and Procedures; 8.5 Study Halting Rules; 8.6 Safety Oversight; 9 Clinical Monitoring; 11 Source Documents and Access to Source Data/Documents; 12 Quality Assurance and Quality Control; 14.3 Protocol Deviations; 13.4 Participant and Data Confidentiality; 14.1 Data collection and Management Responsibility	Minor edits to text to accommodate the addition of Anaheim Clinical Trials site.
1 Key Roles	Updated Sponsor's Medical Expert phone number.
5.3 Strategies for Recruitment and Retention	Added additional options for transportation of subjects to site.
6.1.1 Acquisition	Removed specified shipper of IXT-m200 vials.
7.3.1 Screening; 7.3.3 Inpatient Stay, Extension Stay, and Follow-up	Clarified that DSM-5 criteria would be used to diagnose SUDs at Screening and to assess severity during certain follow-ups, and that assessments of METH and other drug use would be performed separately.
7.3.3 Inpatient Stay, Extension Stay, and Follow-up	Added text for specific questions to be asked of subjects who affirm their use of METH since the last visit. Incorporates changes from Administrative Letter dated 28 Jun 2018.
7.3.6 Schedule of Events Table	Updated footnotes 'l' and 'k' to add time windows around the PK sample collection points per Administrative Letter 2 dated 15 Aug 2018.

Item or Section(s)	Justification
8.2.2 Relationship to Study Agent	Removed statement "Causality of the AEs are not part of the discontinuation criteria or of determining drug related toxicity unless it is clearly unrelated to study drug administration." due to ambiguity.
15.1 Study Leadership	Removed the annual meeting requirement and allowed for ad hoc meetings instead.
Version 7	***Effective Date: 10 Jul 2019***
Schematic of Study Design	Change the number of subjects per dose group in Cohort 3.
1 Key Roles	Corrected the zip codes for Anaheim site and Medical Monitor.
4.1 Description of the Study Design	The purpose for updating the STAMPOUT protocol to version 7 is to adjust the dose level ratio for cohort 3 to reflect study performance to date. Enrollment has been completed in cohorts 1 and 2. The unblinded statistician has reported that more than 10 subjects in the 6 mg/kg group have completed Day 22 which means the target number for the low dose group has been exceeded. The amendment adjusts the cohort 3 configuration from 12 - placebo, 12 - 6 mg/kg, 12 – 20 mg/kg to 12 – placebo, 24 – 20 mg/kg. There are no additional anticipated safety risks based on interim safety data; there have been no SAEs, nor any AEs above Grade 2. The reason for the large initial number of enrollees was to compensate for the high expected early (prior to Day 22) dropout rate, which has not been realized. By dropping the collection of additional, and unnecessary, subjects in the low dose group, we will have a better chance of reaching our target enrollment in the high dose group and completing the study successfully.
Version 8	***Effective Date: 06 Aug 2019***
4.1.1 Primary Endpoint	Corrected 'serum' to 'plasma' as METH concentrations are determined in plasma samples.
5.2 Participant Exclusion Criteria	Added '(nicotine only)' to criterion #9 to clarify that marijuana is not allowed during the inpatient stay.
7.1.1 Study Specific Procedures	Under Psychiatric Evaluation, text was added to specify the definition of a significant finding on the C-SSRS. A sentence was also added to allow for ad hoc administration of the C-SSRS if indicated.
7.2.1 Clinical Laboratory Evaluations	Replaced 'Quest Diagnostic' with 'Local lab' as both sites will be using their own local lab. Also deleted the term 'E subunit' from the pregnancy test description as it was incorrect.
7.7 Rescue Medications, Treatments, and Procedures	Descriptions of treatment for METH withdrawal and psychosis were added.
14.1 Data Collection and Management Responsibilities	Text added to clarify that each Investigator will keep their own study files in appropriate facilities.
Version 9	***Effective Date: 20 Aug 2019***
2.2 Rationale; 6.1.4 Preparation	Reference to a 'maximum dose of 1500 mg' has been deleted throughout the protocol. The previous version of the protocol may have been confusing at a site level because it allowed up to 20 mg/kg IXT-m200 and up to 100 kg body weight (2000 mg IXT-m200), but limited the maximum dose to 1500 mg.

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LIST OF ABBREVIATIONS

Abbreviation	Meaning
AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AMP	amphetamine
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BMI	body mass index
bpm	beats per minute
CFR	Code of Federal Regulations
ch-mAb7F9	See IXT-m200
CNS	central nervous system
CP1 2010	Club Phase 1 working group grading scale recommendations published in 2010
CPK	creatine phosphokinase
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV%	coefficient of variation
DEQ	drug effects questionnaire
DLT	dose limiting toxicity
DSMB	Data and Safety Monitoring Board
DSM-V or –IV	Diagnostic and Statistical Manual of Mental Disorders
ECG	electrocardiogram
eCRF	electronic Case Report Form
ELISA	enzyme linked immunosorbent assay
FDA	Food and Drug Administration
GCP	good clinical practices
GI	gastrointestinal
HACA	human anti-chimeric antibody
HBsAG	hepatitis B surface antigen
HepC	hepatitis C
HIV	human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonisation
IgG	immunoglobulin G
IgM	immunoglobulin M
IRB	Institutional Review Board
IV	intravenous
IXT-m200	chimeric anti-methamphetamine antibody, also called ch-mAb7F9
mAb	monoclonal antibody
mAb7F9	murine form of IXT-m200, or ch-mAb7F9
MDMA	3,4-methylenedioxymethamphetamine, also called ecstasy
METH	methamphetamine
mol-eq	molar equivalent, also mol-equiv
N	number
NAT	nucleic acid testing
NIDA	National Institute on Drug Abuse

Abbreviation	Meaning
NIH	National Institutes of Health
PBO	placebo
PD	pharmacodynamic
PI	Principal Investigator
PK	pharmacokinetic
QC	quality control
RBC	red blood cell
SA	self-administration
SAE	serious adverse event
SAP	statistical analysis plan
sc	subcutaneous
SCID	structured clinical interview for diagnosis
SD	standard deviation
SEM	standard error of the mean
SMC	safety monitoring committee
SOP	standard operating procedure
$t_{1/2}$	elimination half-life
THC	tetrahydrocannabinol
TOA62936	Phase 1a study of IXT-m200
Vd	volume of distribution
WBC	white blood cell

STATEMENT OF COMPLIANCE – PRA HEALTH SCIENCES

The trial will be conducted in accordance with the International Council for Harmonisation (ICH) E6, the Guideline for Good Clinical Practice (GCP) Code of Federal Regulations (CFR) on the Protection of Human Subjects (45 CFR Part 46), and the National Institute on Drug Abuse Terms of Award. The Principal Investigator (PI) will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. Key personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator: Lynn Webster, MD

Signed and dated: L Webster 20 Aug 19

STATEMENT OF COMPLIANCE – ANAHEIM CLINICAL TRIALS

The trial will be conducted in accordance with the International Council for Harmonisation (ICH) E6, the Guideline for Good Clinical Practice (GCP) Code of Federal Regulations (CFR) on the Protection of Human Subjects (45 CFR Part 46), and the National Institute on Drug Abuse Terms of Award. The Principal Investigator (PI) will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. Key personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator: Peter Winkle, MD

Signed and dated: _____ 8/21/19

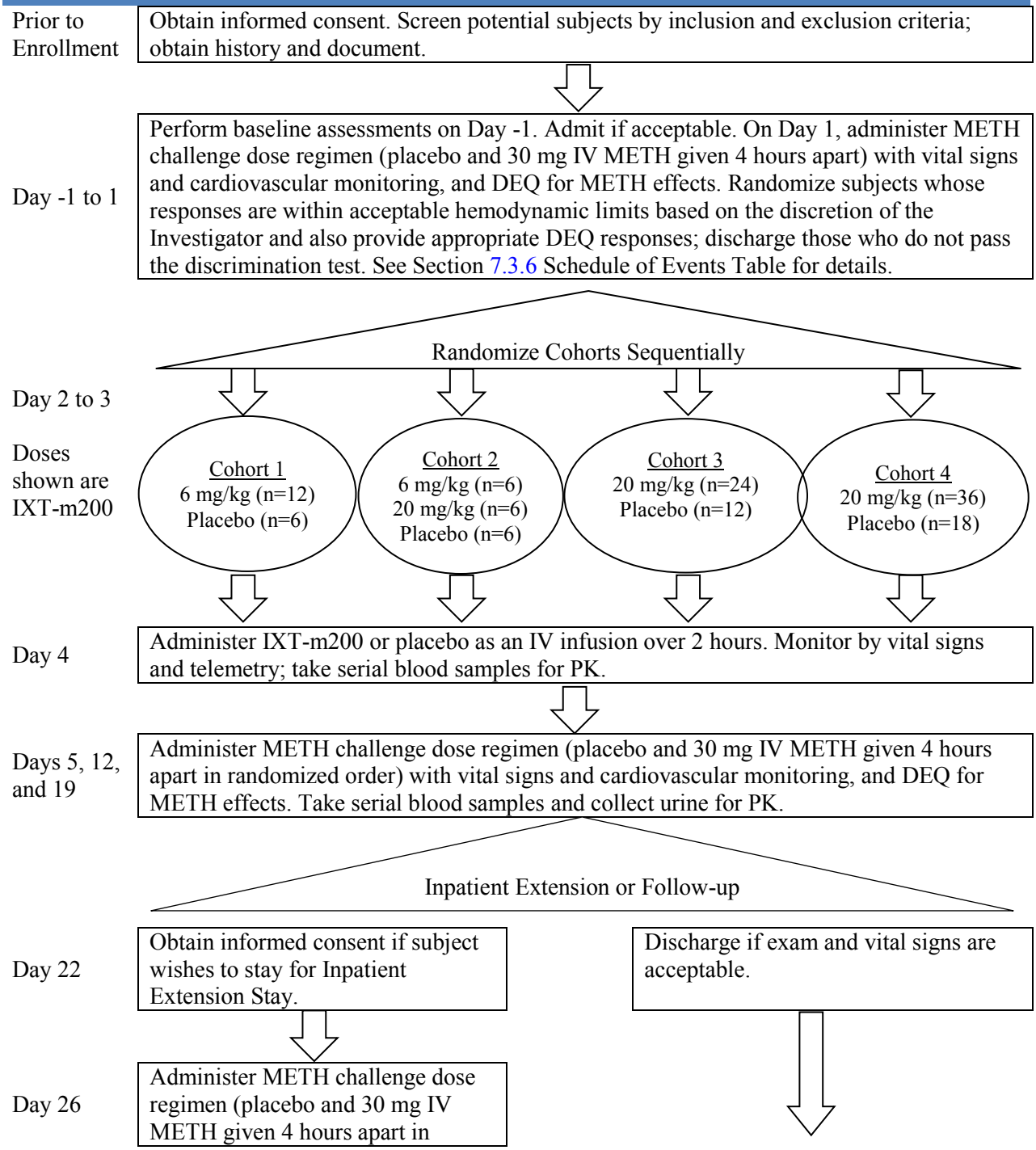
PROTOCOL SUMMARY

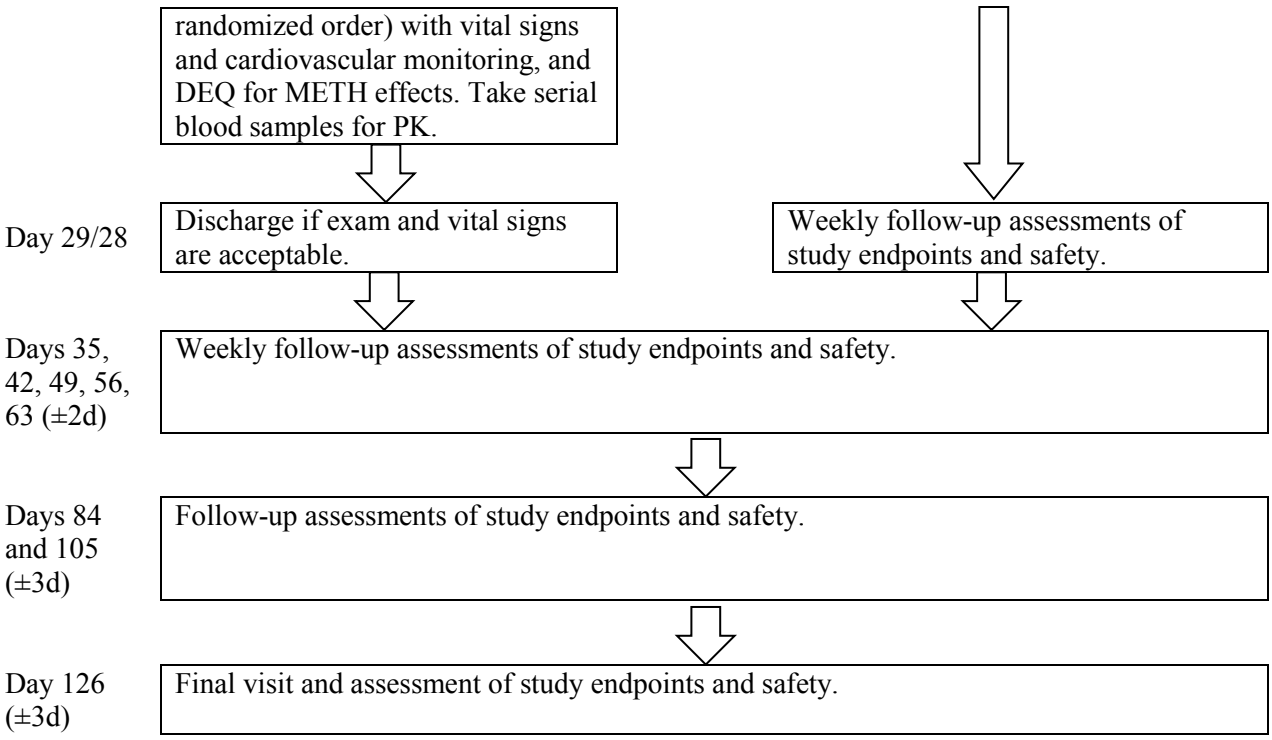
Title:	STAMPOUT: Study of Antibody for Methamphetamine Outpatient Therapy
Summary:	This is a parallel-group, placebo-controlled, double-blind safety study of IXT-m200 in otherwise healthy subjects with methamphetamine (METH) use disorders. An adequate number of subjects will be enrolled to ensure approximately 42 completers. Four cohorts will receive single doses of IXT-m200 (6 or 20 mg/kg) or placebo followed by a series of weekly METH challenges during a 23-day inpatient stay. Subjects who successfully complete study procedures through Day 22 may continue into an optional Inpatient Extension for an additional 7-day duration (through Day 29). Outpatient follow-up visits will continue through Day 126. Changes in METH effects, as well as safety, pharmacokinetics (PK) of IXT-m200 and METH, and immunogenicity will be analyzed.
Objectives:	Primary Objective: To determine the effect of IXT-m200 on METH PK parameters relative to placebo. Secondary Objectives: To determine the effect of IXT-m200 on METH subjective effects, and to evaluate the safety and tolerability and PK of single, intravenous (IV) doses of IXT-m200 relative to placebo followed by weekly IV METH challenges in subjects with METH use disorders.
Endpoint	Primary Endpoint: • Change in serum METH area under the concentration-time curve (AUC) or C_{max} resulting from METH challenge doses following single IV doses of IXT-m200. Secondary Endpoints: • Change in subjective effects of METH challenge doses as measured by drug effects questionnaires (DEQ; ie, reduction of 'High'). • Safety and tolerability of IXT-m200 followed by METH challenges as measured by physical examinations and vital sign, adverse event (AE), electrocardiogram (ECG), clinical laboratory testing, and immune response by measurement of anti-IXT-m200 antibody levels. • Pharmacokinetics of IXT-m200 following single administration.
Population:	Approximately 126, generally healthy males and females aged 21-50, non-treatment seeking, METH-using subjects who have METH use disorders will be recruited to retain 42 completed subjects.
Phase:	2a
Number of Sites:	2 - PRA Health Sciences, Salt Lake City, UT; Anaheim Clinical Trials, Anaheim, CA
Description of Study Agent:	IXT-m200 is a chimeric anti-methamphetamine monoclonal antibody. Doses will be 6 or 20 mg/kg given by 2 hour IV infusion. Challenge Agent: (+)-Methamphetamine hydrochloride (METH; 30 mg) will be administered by IV bolus administration over 2 minutes. Placebo: commercially available normal saline for use as placebo for IXT-m200 and METH.

Study Duration: 18 months

Participant Duration: 4.5 months

SCHEMATIC OF STUDY DESIGN





1 KEY ROLES

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2 INTRODUCTION

2.1 BACKGROUND INFORMATION

Study Agent
IXT-m200, also called ch-mAb7F9, is a chimeric monoclonal antibody (mAb) that binds METH with high affinity. The product contains a murine METH-binding variable region and the constant domains of a human immunoglobulin G (IgG) 2κ. This antibody isotype was chosen because of the lower risk of immune response compared to an IgG_1 or IgG_3. IXT-m200 targets METH, does not rely on binding to any endogenous target for its action, and was demonstrated to be safe and well tolerated in a previous clinical investigation (see below).

Through the binding of METH in the bloodstream, it is anticipated that IXT-m200 will alter the PK of METH and decrease concentrations of METH at its active sites in the brain. In an acute setting, the presence of IXT-m200 should therefore decrease the perceived pleasurable effects of METH. Over the longer term, when combined with conventional behavior modification therapy, IXT-m200 should reduce the frequency of METH use over time.

Nonclinical Summary
A significant body of nonclinical work in rats indicates that IXT-m200 may be effective as a treatment for METH use disorders. The potential human efficacy of IXT-m200 is demonstrated by 5 important in vivo preclinical studies using the murine version of the antibody, called mAb7F9. The studies and results are summarized in Table 1.

Table 1. Summary of nonclinical studies in rats with mAb7F9

Study ID	Description	Brief Summary of Results
SMO/EML-2194 Owens et al., 2011[1]	Long-term in vivo function of mAb7F9 – mAb7F9 administered once after first 24 hours of a 2 week continuous sc METH infusion	MAb7F9 was administered at a dose (180 mg/kg) that provided an equal number of binding sites to METH molecules in the body. MAb7F9 redistributed and retained METH in the serum (shown by increased METH serum concentrations) throughout the 2 weeks even though the mAb was outnumbered by METH after the first hour.
WBG-2787 Laurenzana et al., 2014[2]	Effects on METH stimulated locomotor activity and rearing in an overdose model – mAb7F9 administered 30 minutes after a 1 mg/kg IV METH dose	MAb7F9 reduces distance traveled at less than molar equivalent (mol-eq) doses to METH molecules (Figure 1). Duration of METH effects and number of rearing events were reduced at equimolar dosing. Peak activity was reduced immediately after administration, significantly at the 1 mol-eq dose. METH Vd and clearance were reduced, with a proportional METH $t_{1/2\lambda z}$ increase following 1 and 0.32 mol-eq doses.
SMO/VCU-0001 Beardsley et al., manuscript in prep	Relapse/reinstatement testing in a SA model - mAb7F9 was used to block/reduce continuation of METH-primed relapse to METH SA	Following SA training and extinction, mAb7F9 produced dose-dependent changes in number of presses on a disconnected lever following a METH priming dose. 30 mg/kg mAb7F9 did not change the baseline response, 56 mg/kg resulted in non-significant increased responding, and 100 mg/kg produced significant decreased responding following the third mAb dose (Figure 2).
SMO/MH-3015 Hambuchen et al., 2014[3]	Repeated mAb7F9 dosing with effects on METH stimulated locomotor activity and rearing	MAb7F9 loading dose followed by 2 weekly (141 mg/kg) administrations reduced 0.56 mg/kg METH-induced horizontal locomotion and rearing throughout dosing during the 60-120 minute post METH interval. MAb7F9 treatment also decreased duration of 1.68 mg/kg METH-induced behaviors 10 and 14 days after discontinuation of mAb treatment (Figure 3).

Study ID	Description	Brief Summary of Results
WBG-3013 Stevens et al., 2014[4]	Bioequivalence testing of mAb7F9 vs. IXT-m200 effects on METH PK	MAb7F9 and IXT-m200 produce similar METH PK changes as expected. Ligand cross reactivity studies suggest IXT-m200 will not bind to endogenous molecules or other medications.

hrs = hours; IV = intravenous; mAb7F9 = murine form of IXT-m200, or ch-mAb7F9; METH = methamphetamine; mol-eq = molar equivalent; PK = pharmacokinetic; SA = self-administration; sc = subcutaneous; SD = standard deviation; SEM = standard error of the mean.

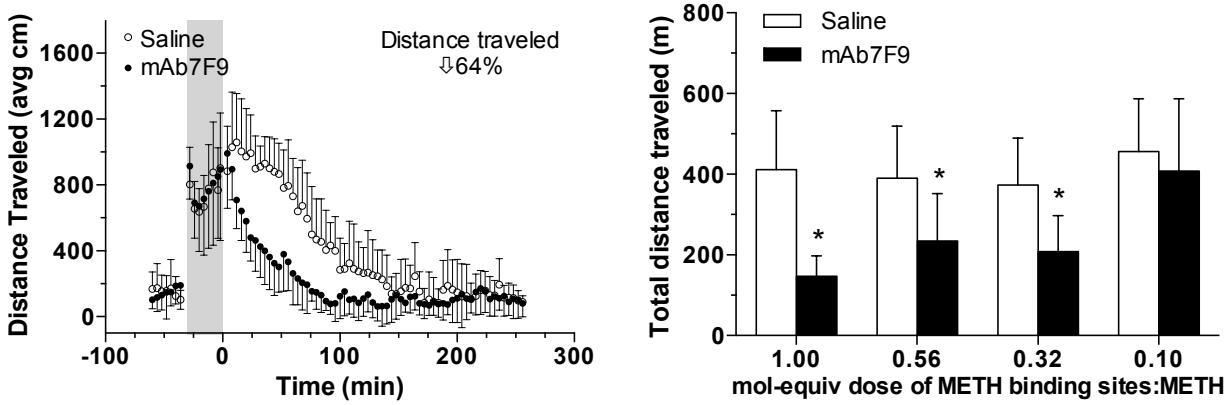

Figure 1. METH effects were reduced by mAb7F9. The left panel shows the distance traveled (±SD) by rats (n=6) dosed with METH only (open circles) or METH plus 1 mol-eq mAb7F9 (closed circles). Baseline behavior was recorded between -60 to -30 min. METH was given at -30 minutes followed by mAb administration at time 0. The right panel shows the results quantified from all 4 mAb7F9 doses. * = P <0.05 vs. saline for that mAb dose.

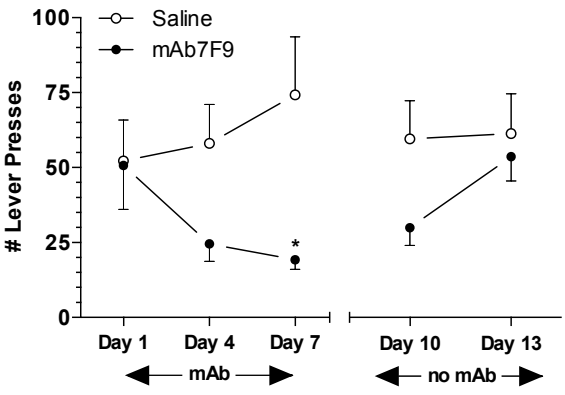

Figure 2. Active lever presses by rats (n=12) during self-administration sessions when mAb was administered 6 hrs prior to the session (Days 1, 4, & 7) and when mAb was not administered (Days 10 & 13), in groups treated with 100 mg/kg mAb7F9 (filled circles) or saline (open circles). Bars show ±SEM. The asterisk represents a significantly different value from the saline control group during the same session ($p<0.05$).

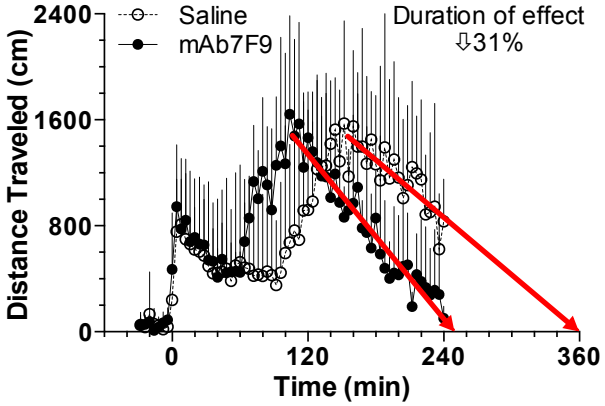

Figure 3. Distance traveled over time (+SD) after a 1.68 mg/kg METH dose given at time 0 in mAb7F9 (closed circles, n=5) and vehicle-treated (open circles, n=6) rats 14 days after the last of 3 mAb doses. The best-fit linear regression line (in red) was fit to the terminal portion of the horizontal locomotion-time curve. This line estimated the termination of activity and therefore the relative difference in the duration of METH effects between treatment groups.

Nonclinical Studies Supporting the Current Clinical Protocol

A series of 4 nonclinical studies were completed in rats to address the potential for IXT-m200 to exacerbate METH effects. These studies were designed to identify potential toxicities resulting from higher blood concentrations of METH in the presence of IXT-m200, or from increased METH self-administration (SA) by a user in an effort to overcome the reduction of METH effects by the antibody.

In each of the 4 studies, rats were acclimated to high doses of METH over a 14-day period to make them tolerant to high doses of METH, similar to what occurs in human chronic METH users. By the last day, rats survived three 4 mg/kg doses of METH spaced 4 hours apart. Three days later (Day 17), rats were dosed with 0, 5, or 20 mg/kg IXT-m200. The following day, a series of METH binges used to simulate a patient's attempts to surmount the antibody's effects was initiated. On Day 18, rats were given 4 doses of METH 6 mg/kg spaced 2 hours apart. This binge dosing regimen was repeated on Days 21 and 24 for certain studies and groups.

The 4 studies (GLP toxicology, cardiovascular effects, METH PK, and METH distribution) collected different outcome measurements while using the same METH administration protocol. Results are summarized below (Table 2).

Table 2. Summary of nonclinical studies supporting testing in METH users

Study reference	Summary of end points and results
20099217 - GLP toxicology	• This study evaluated clinical signs, body weights, body weight gain, food consumption, ophthalmology, clinical pathology parameters (hematology, coagulation, clinical chemistry, and urinalysis), toxicokinetic parameters, gross necropsy findings, organ weights, and histopathologic examinations. • No IXT-m200-related mortality or target organs were identified. There were early deaths attributed to high doses of METH in all groups. • There were no IXT-m200-related clinical signs or changes in food consumption, ophthalmology, clinical chemistry parameters, urinalysis parameters, or corticosterone levels in this study. There were no IXT-m200-related organ weight changes, macroscopic pathology observations, or microscopic observations. Findings present among animals that died prior to scheduled termination were consistent with METH toxicity. • Systemic exposure to METH during the METH binge regimen increased with increasing dose of IXT-m200, but was less than dose proportional. • 2 of 13 animals given 20 mg/kg IXT-m200 screened positive for immunogenicity on Day 54.
20098702 - Safety Pharmacology (Cardiovascular effects)	• This study evaluated cardiovascular parameters and body temperature/activity by telemetry, clinical signs, body weights and gains, food consumption, toxicokinetic parameters, gross necropsy findings, and organ weights. • Following administration of IXT-m200, four telemetered animals died after METH binge dosing. All were considered related to the high doses of METH administered. • METH challenges on Days 18, 21, and 24 were associated with increased activity, body temperature, heart rate, and blood pressure; there was a trend toward attenuated blood pressure response at 20 mg/kg IXT-m200 only on Days 18 and 21 (but not on Day 24). • Minor changes in organ weights were present that had a dose-dependent trend, including increased liver, prostate, thymus, and thyroid weights and organ to body/brain weight ratios, but the toxicological relevance of these changes was

	undetermined as no histological evaluation was performed.
20106937 - GLP METH PK	• This study evaluated clinical signs, body weights, body weight gain, limited functional observational battery, PK parameters, and gross necropsy findings. • No IXT-m200-related mortality or clinical signs were observed. • There were no major differences in METH exposure between male and female rats, though female area under the concentration-time curve (AUC) was higher on all binge Days and at all antibody dose levels. • The AUC of METH trended higher with increasing IXT-m200 dose level as expected.
2429-002 - METH Distribution	• This study evaluated radiolabeled METH serum PK parameters, rates and routes of excretion, and tissue distribution on Day 18. • IXT-m200 altered serum PK of ^{14}C-METH as expected by increasing the maximum concentration (C_{max}). IXT-m200 did not notably change the excretion of ^{14}C-METH. • Quantitative Whole Body Autoradiography (QWBA) images were analyzed to determine the effects of IXT-m200 on the tissue distribution of ^{14}C-METH. At 30 min post-METH dose, data in males indicates the highest relative METH concentrations were kidney > ex- and intra-orbital lacrimal glands > spleen > submaxillary gland > liver. Females were similar. • Based on QWBA data collected over 72 hours, IXT-m200 does not appear to markedly change the relative distribution of METH administered at extremely high levels (6 mg/kg), though clearance from tissues may be increased by the presence of antibody.

Clinical Research Summary

A Phase 1a study of the safety of single doses of IXT-m200 in healthy humans was completed in 2013.[5] In this first clinical study, 42 subjects (17 females) were dosed in 5 groups (0.2, 0.6, 2, 6, and 20 mg/kg IXT-m200), with 10 subjects receiving placebo (saline). Pharmacokinetic results indicate that IXT-m200 is similar to other IgGs, with an elimination half-life of ~18 days, volume of distribution (V_d) of ~5 L and elimination clearance of ~200 mL/d. The disposition of IXT-m200 does not appear to be affected by dose.

There were no serious adverse events (SAEs) or serious adverse reactions during the conduct of the study. Only 1 AE was definitely attributed to IXT-m200. A single subject experienced a Common Terminology Criteria for Adverse Events (CTCAE v.4.0) Grade 3 infusion reaction half-way through the IXT-m200 infusion. The subject experienced a brief period of bronchospasm, in which the subject and PI heard a single expiratory wheeze. The infusion was stopped and the subject was treated with solu-medrol and diphenhydramine. No further symptoms were noted. The subject required outpatient therapy later for bronchitis. Because the infusion reaction and bronchitis were mild and short-lived, the study continued with no protocol changes.

Samples from all subjects were tested for immunogenicity, ie, anti-IXT-m200 antibodies. Samples from only 4 (12.5%) IXT-m200 treated subjects were confirmed to have low titers. One of these 4 subjects also provided a predose sample that screened positive for anti-IXT-m200 antibodies. The development of anti-IXT-m200 antibodies did not appear to be dose-related.

Overall there were no apparent safety or tolerability concerns identified when IXT-m200 was dosed over the range from 0.2 to 20 mg/kg. Therefore, a maximum tolerated dose was not reached.

Relevant Literature
Results from the Phase 1a study of IXT-m200 were published in Stevens et al., 2014.[5] In addition, many of the nonclinical studies using mAb7F9 (Table 1), and the studies with IXT-m200 (Table 2), have been described above with references where available. We are not aware of other clinical studies of an anti-METH mAb or vaccine.

Clinical studies of vaccines against other drugs of abuse such as nicotine and cocaine have been published.[6-11] However, these have typically been unsuccessful due to the inability to generate sufficient antibody titers against the target drug. A mAb can be dosed to high/sufficient levels as it does not rely on the immune system of the patient for antibody production as does a vaccine.

Context of the Study
As there are no approved medications for the treatment of METH use disorders, any progress in the field is important. The National Institute on Drug Abuse (NIDA) reports that the most effective current treatments for METH addiction are behavioral therapies, such as cognitive-behavioral and contingency-management interventions. IXT-m200 is ultimately intended to be administered in conjunction with behavioral therapy to provide protection against reinforcing effects of METH during relapse to drug use. However, we first need to determine whether IXT-m200 exhibits the ability to alter human METH disposition before initiating studies in combination with behavioral therapy. This will be the first clinical study of a medication developed specifically for METH use disorders to be tested in human METH users.

2.2 RATIONALE

Rationale for the Study
Following the first in human safety study, which has been completed, the clinical development plan for IXT-m200 continues with this study to demonstrate the ability to alter METH PK and reduce or prevent subjective effects. This is a proof of concept study to show that intended effects of IXT-m200 are indeed realized prior to initiating large studies with METH users where IXT-m200 is administered in conjunction with behavioral therapy. IXT-m200 is intended to be used for the prevention of relapse to METH use and it is believed that modifications in the lifestyle of users will be required.

Further, METH users, even those who are highly motivated to stop their use, are at high risk for recidivism to METH use. Any METH-using volunteer who receives a pharmacologic treatment is also therefore at risk for recidivist behavior, and some METH users are at risk for engaging in binge use of METH, resulting in high doses of METH taken in a short period of time. The possibility exists that if users attempt to surmount the effects of IXT-m200 by taking large METH doses that the binding potential for METH will be exceeded. Theoretical risks associated with large doses of METH in the presence of the antibody include increased free METH concentrations, peripheral (eg, cardiovascular) toxicity, and accumulation of METH.

Because of the high recidivism rate and the theoretical risks associated with IXT-m200's effects on METH toxicity, this assessment of the interaction of IXT-m200 with METH will be done prior to further studies of the efficacy of IXT-m200. METH is a US Drug Enforcement Administration Schedule II controlled substance, and can therefore be given in a human laboratory setting. Studying the impact of IXT-m200 on METH effects in a controlled human laboratory setting will give a greater understanding of the risks of the interaction of IXT-m200 with METH compared to METH alone and will improve risk mitigation strategies for later studies.

The hypothesis is that administration of IXT-m200 will alter the METH PK parameters (ie, reduce Vd and increase serum concentrations thereby increasing C_{max} and AUC) and reduce or prevent the subjective effects of subsequent METH challenges. Further, we hypothesize that IXT-m200 will be safe and will not cause increased METH toxicity compared to METH alone in human METH users.

Justification for Route of Administration
IXT-m200 will be administered via IV infusion. This is necessary because it is a protein medication and would be metabolized to inactive components in the gastrointestinal (GI) tract if administered orally. The volume that must be given is too large to allow for intramuscular or subcutaneous (sc) administration. Each dose of IXT-m200 will be diluted in 225 ml of saline and given over 2 hours at progressively increasing infusion rates (Table 5). This infusion plan has been used successfully in the Phase 1a study of IXT-m200.[5] This approach to dosing will allow for rapid response to possible dose-dependent toxicity because of the incremental increases in total dose over time.

Justification for IXT-m200 Doses
The active IXT-m200 doses (6 or 20 mg/kg) were selected for this study because they are both potentially effective in reducing METH effects. Nonclinical studies in rats suggest that when the antibody is administered several days prior to METH challenge administration, the antibody is still effective at reducing METH-induced locomotor activity at a ratio of 30 METH molecules per mAb binding site.[3] (This calculation assumes that the METH dose is confined entirely to the blood volume upon administration.)

During this Phase 2a study, subjects will receive a single dose of IXT-m200 followed by 4 weekly IV challenge doses of 30 mg METH. Using the data from the Phase 1a study of single doses of IXT-m200 in humans, we can predict the serum concentrations over time from doses of 6 or 20 mg/kg. We can also estimate the concentration of METH in blood immediately after a 30 mg IV dose as ~36 μM (assuming a 75 kg person). The minimum concentration of IXT-m200 in serum required to maintain the initial ratio of METH to binding sites at 30 is 90 μg/mL (1.2 μM binding sites). Pharmacokinetic simulations of 6 and 20 mg/kg mAb doses in humans predict that these doses will result in concentrations much greater than 90 μg/ml. With the 6 mg/kg dose, however, concentrations will drop to 90 μg/ml by 3-4 days after dosing.

Based on these modeled data, the ratio of METH to mAb binding sites will be <30 during the entire set of METH challenges after a 20 mg/kg dose. After a 6 mg/kg dose, the ratio should be <30 during the first METH challenge only. Thus, during the second through fourth METH challenges, the effects of IXT-m200 will have waned sufficiently that METH challenges will be administered at what is expected to be subtherapeutic IXT-m200 levels. A goal of this study is to test the effects of METH challenges on IXT-m200 effects as mAb levels decrease to identify the minimum effective serum concentration.

Justification for METH Route of Administration and Doses
METH will be given via the intravenous (IV) route to increase the reliability and reproducibility of subjective (drug effect) responses to METH, and of objective (pharmacokinetic) data describing the interaction of IXT-m200 and METH. The METH doses to be used were selected based on METH doses that are given commonly to humans in a laboratory setting.[12-16] In these previous reports, the doses administered were safe and resulted in reliable, measurable responses. Furthermore, there are no data with METH that suggest non-treatment seeking METH users increase their METH use after participation in a human laboratory study in which IV METH is given. In fact, intravenous-naïve cocaine users given IV cocaine injections did not alter their cocaine use frequency or route of administration after the study[17] Nevertheless, subjects who currently use METH via the snorting or oral routes will have to have a history of smoking or IV METH use because of the concern that exposure to rapid routes of METH will increase risk for escalation of METH use.

METH doses of 30 mg IV have frequently been given in human laboratory studies.[12-16] Single 30 mg IV METH doses are associated with significant increases in positive subjective central nervous system (CNS) effects and in blood pressure and heart rate. These effects reach maximum values at 30 to 60 minutes after the dose[12] and typically dissipate over 3 to 4 hr.[14,18] METH 30 mg IV results in ~20 to 35 mmHg increases in diastolic blood pressure, 40 mmHg increases in systolic blood pressure, and ~25 beats per minute (bpm) increases in heart rate.[12,13] The observed CNS and cardiovascular effects are not associated with greater risks for AEs than with placebo administration.[12] Finally, this dose of METH results in measurable changes in subjective effects that can be further shifted by medications to study efficacy.[13,16]

The METH challenge in this study will consist of 2 IV METH doses (0 and 30 mg) separated by 4 hr. The subjects will receive a total of 4 METH challenges – at baseline (Day 1), then 3 weekly challenges after the single IXT-m200 (or placebo) dose. An additional METH challenge will be given to subjects that elect to stay in the unit a week longer. This approach to METH dosing in human subjects has been used in other studies,[13,15,19] and the dosing regimen allows for pharmacodynamics (PD) and safety assessment of METH dose-effects. METH doses will be given intravenously over 2 minutes to standardize the administration and to reduce the risk of side effects.

Description of Subjects

Non-treatment seeking, METH-using subjects who have mild to moderate (2-6 DSM-5 diagnostic criteria) DSM-5 METH use disorders will be recruited. If, at any point in their participation in the study, a subject indicates a desire for treatment, no more METH challenges will be given to the subject and he/she will be referred for treatment. Subjects who begin treatment for their METH use during the study will complete all follow-up safety evaluations.

The subjects to be recruited for this study will be non-daily METH users (<30 days per month). While there are many patterns of METH use, and it is difficult to quantify, many users take METH from 12 to 20 times per month.[20-22] Furthermore, the subjects in this study should have a stable or regular pattern of METH use. In a study of 350 METH users who had undergone treatment, the number of years from initiation of METH use until the use pattern was regular was 2.14 years.[21]

Attempts will be made to recruit METH users who are less likely to engage in binge METH use. In a cross-sectional survey study of 451 human immunodeficiency virus (HIV)-negative male and female METH users, correlates of binge METH use were determined. The subjects reported using METH on average of 14.6 days per month for an average of 13.6 years, with an average age of initiation of 23 years, and a monthly average consumption of 9.4 g.[20] Approximately 40% of these subjects (183) reported binge use, defined as using large quantities for a period of time, until they ran out of METH, or physically could not take METH anymore. A multivariate model identified the following factors that were associated with METH binge use:

- Number of days of METH use in the last 30 days (16 vs 13)
- History of treatment for METH use
- History of engaging in sex marathons while high on METH
- History of injection METH use
- Higher Beckmans Depression Inventory score (17.2 vs 14.0)
- Initiating METH use due a desire to experiment (vs coping or escape, to lose weight or feel more attractive, to stay awake or get more energy, or to enhance sex or meet sex partners)

Factors that were not associated with binge use included polydrug use, the average number of years of METH use, and the subject's sex. The full model utilizing the factors above accounted for 10% of the

total variance; nevertheless, the factors that were identified were used in developing exclusion criteria, including current IV use, to minimize the risk of binge METH use after participation in this study. Furthermore, data on the METH use patterns of all subjects will be collected and analyzed, and incorporated into an ongoing assessment of risks and recruiting success.

Regular, non-daily METH users who are not interested in or seeking treatment for METH use, and who have used METH for more than 2 years will be recruited. The current primary route of SA will be smoking, snorting, or oral. Users whose current primary route of SA is snorting or oral will have a history of or experience with IV or smoking METH.

Rationale for Selection of This Volunteer Population

1. While the METH doses to be administered are small, and associated with minimal but measureable CNS and cardiovascular effects,[12] scientific ethics and the possible risk of promoting METH addiction dictate that non-METH users cannot be recruited for this study. Furthermore, the target treatment population for IXT-m200 is METH users.
2. Non-treatment seeking METH users will be recruited for this study because the same ethical considerations exist for treatment seeking subjects as for non-METH users. Administration of IV METH to non-treatment seeking subjects may increase their risk of progression to IV METH use, but it is not certain that this will happen. In a report of residential studies involving administration of METH, subsequent psychosocial function and reported drug use were not changed by participation in the studies.[23]
3. Non-daily METH users are more likely to be able to abstain from METH use for the duration of the study. This will minimize the risk for withdrawal from METH which may result from no METH use during the study, or from IXT-m200 administration.
4. Selection of METH users whose primary current route of SA is not IV is important for the following reasons.
    a. Non-injection users are less likely to binge on METH, which decreases the likelihood of overdose complicating the safety profile of IXT-m200.[20]
    b. Non-injection users are likely to be healthier than injection METH users.[24] At this stage in the clinical development of IXT-m200, a greater understanding of the safety profile of IXT-m200 in relatively healthy subjects is needed prior to administration to subjects with comorbid physical illness.

Justification of use of Placebo

Use of placebo is justified in this study to create a comparator control group who also receives the METH challenge doses. Subjects recruited for this study will be non-treatment seeking for their METH use disorder. A single dose of IXT-m200 is not likely to benefit subjects who do not wish to change their METH intake. The use of placebo, therefore, does not place subjects at further risk nor does it prevent them from receiving a likely benefit.

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 KNOWN POTENTIAL RISKS

Monoclonal Antibody Specific Risks

This study will be the second in which IXT-m200 will be given to humans; therefore, all specific risks of IXT-m200 are not known. Animal toxicology and human tissue cross reactivity data suggest that the risk of clinically significant side effects or toxicity in humans should be low.[4] Given that there are more than 50 Food and Drug Administration (FDA)-approved mAb medications, and several with non-endogenous targets that have been approved (Anthim, Abthrax, Synagis, and Zinplava) or are in late stage clinical

trials, risks may be predicted and strategies developed to mitigate these risks based on an understanding of the pharmacology of these approved medications.

Reactions to mAb medications are categorized based on the timing of their occurrence in relation to administration of the medicine. Acute or infusion-related reactions may be defined as adverse pharmacologic events occurring in the first 24 hours following drug administration. Delayed reactions may occur from 24 hours to 14 days after administration, though they usually occur between 5 to 7 days after administration.

Acute or infusion-related reactions may be either allergic, which are immunoglobulin E-mediated Type 1 reactions, or non-allergic, which are mediated by release of proinflammatory cytokines. Both of these types of reactions can involve numerous organ systems, including the skin/cutaneous, cardiovascular, pulmonary, or GI (Table 3). Delayed reactions may present with rash and hives with pruritis, myalgias, and flu-like symptoms including arthralgias and stiffness, headaches, and fatigue.[25-27]

Table 3. Infusion reaction signs and symptoms

Organ system	Signs/symptoms
Skin/cutaneous	Flushing, erythema, swelling of mucus membranes, pruritus, hives, angioedema, maculopapular rash, oropharyngeal or laryngeal edema
Cardiovascular	Tachycardia, hypotension, arrhythmia, chest pain, ischemia or infarction, cardiac arrest
Pulmonary	Nasal congestion, rhinitis, sneezing, bronchospasm, tachypnea, cyanosis, respiratory arrest
Gastrointestinal	Nausea, vomiting, diarrhea, gastroesophageal reflux
Neurological	Headache, syncopy, dizziness, feeling of impending doom
Systemic	Chills, fever, rigors, asthenia

Other mAbs which are similar to IXT-m200 (eg, chimeric; rituximab - an anti-lymphoma mAb) or that target non-endogenous receptors or cell types (raxibacumab - an anti-*Bacillus anthracis* mAb; tefibazumab - an anti-*Staphylococcus aureus* mAb) may be used for predicting the prevalence of these possible risks.

Infusion-related symptoms with other mAbs occur in between 10 and 40% of subjects. With tefibazumab for example, symptoms of headache, gastroesophageal reflux, and erythema were reported in 20% of the subjects and all but 1 were mild in severity. The moderately severe symptom, a headache, resolved with acetaminophen administration.[28] Other infusion-related symptoms of mAbs include chills and/or fever (mild to moderate in severity) which are typically treated effectively with acetaminophen and diphenhydramine.[28-30] Note that severe hypotension, bronchospasm, anaphylaxis, and death are reported with other mAbs that target endogenous cellular or tumor-related sites. Because IXT-m200 should neither bind complement nor endogenous cellular sites, the risks of these catastrophic events should be very low.

Later developing signs and symptoms of mAb administration include nausea, vomiting, pain at the administration site, rigors, headache, dizziness, dyspnea, hypotension, elevated blood pressure, rash, and asthenia. These symptoms are reported to occur infrequently.[28,30]

IXT-m200 Specific Risks

During the Phase 1a study of IXT-m200, there were no SAEs or discontinuations due to treatment-emergent AEs. Overall, 90% of subjects experienced at least 1 AE, but there were no apparent trends in the frequence, relatedness, or severity of AEs with increased dose or between active- and placebo-treated subjects.[5]

Only 1 AE was definitely attributed to IXT-m200. A single subject experienced a CTCAE v.4.0 Grade 3 infusion reaction half-way through the IXT-m200 infusion. The subject experienced a brief period of bronchospasm, in which the subject and PI heard a single expiratory wheeze. The infusion was stopped and the subject was treated with solu-medrol and diphenhydramine. No further symptoms were noted. The subject required outpatient therapy later for bronchitis.

The most frequently reported AEs were increased blood creatine phosphokinase (CPK), upper respiratory tract infection, decreased hemoglobin, headache, increased aspartate aminotransferase (AST) and alanine aminotransferase, proteinuria, decreased white blood cell (WBC) count, and nasal congestion.

Because the IXT-m200 is a mouse-human chimeric antibody, the potential for a human anti-chimeric antibody (HACA) response exists. Following single doses of IXT-m200, only 4 of 32 subjects were confirmed positive for HACA in the Phase 1a study.[5] The development of HACA did not appear to be dose-related.

METH Specific Risks
METH can produce numerous side effects, some of which may be dangerous, including restlessness, dizziness, tremor, increased talkativeness, tenseness, irritability, weakness, insomnia, confusion, and hallucinations. Short-term adverse effects can include increased heart rate, paranoia resembling schizophrenia, hallucinations, aggressive behavior, insomnia, dysesthesias, panic, anxiety, and depression. Some individuals, particularly those who have used high doses of METH, have experienced severe paranoia and hallucinations. METH can produce the sensation of bugs crawling under or on the skin. Headache, a sensation of chilliness, or a sensation of flushing can also occur. Nausea, vomiting, diarrhea, severely decreased appetite, and abdominal cramps can occur as well. Unpleasant mental effects, such as depressed mood and anxiety, may develop at the end of the experiment as the effects of METH wear off. Fatigue and depression often follow METH use.

These effects are rare at the doses and frequencies used in this protocol. However, occasionally extremely sensitive individuals may have some of these effects at lower, less frequent doses. We do not plan to use doses of METH that will produce these symptoms, and our patient recruitment approach should be able to exclude patients who are susceptible to these effects, but since not all the effects of METH are well understood and people's sensitivity to the drug may vary, some of these symptoms may appear. Additionally, subjects that do not tolerate METH administration on Day 1 of this study will not be randomized to treatment and thus not administered additional METH challenges. Physiological signs will be monitored during drug infusion as described above. A physician will be present during drug administration and readily available for the remainder of the inpatient stay.

2.3.2 KNOWN POTENTIAL BENEFITS

IXT-m200 is an investigational product and may convey no benefit to patients. Based on nonclinical studies in rodents, it is believed that the product has the potential to prevent or reduce the reinforcing properties of METH, or the 'high'. Further, high doses of IXT-m200 may lessen the effects of METH doses on blood pressure. Single doses of IXT-m200, as planned for this study, are not likely to have any long-term benefit.

3 OBJECTIVES AND PURPOSE

Primary Objective: To determine the effect of IXT-m200 on METH PK parameters relative to placebo.

Secondary Objectives: To determine the effect of IXT-m200 on METH subjective effects, and to evaluate the safety and tolerability and PK of single, IV doses of IXT-m200 relative to placebo followed by weekly IV METH challenges in subjects with METH use disorders.

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

A dose run-up approach to random-block dose assignment will be used (Table 4). 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.

Table 4. Staged cohort, dose run-up study design

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

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 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.

4.1.1 PRIMARY ENDPOINT

- Change in plasma METH AUC or C_{max} resulting from METH challenge doses following single IV doses of IXT-m200.

4.1.2 SECONDARY ENDPOINTS

- Change in subjective effects of METH challenge doses as measured by DEQ (ie, reduction of 'High' or 'Liking').
- Safety and tolerability of IXT-m200 followed by METH challenges as measured by physical examinations and vital sign, AE, ECG, and clinical laboratory testing, and immune response by measurement of anti-IXT-m200 antibody levels.
- Pharmacokinetics of IXT-m200 following single administration.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 PARTICIPANT INCLUSION CRITERIA

Subjects meeting the following criteria will be considered for inclusion in the study:

1. Subject voluntarily agrees to participate in this study and signs an IRB-approved informed consent form prior to performing any of the screening procedures.
2. Subjects must be able to verbalize understanding of the consent forms, provide written informed consent, and verbalize willingness to complete study procedures.
3. Males or females between 21 to 50 years of age, inclusive.
   a. Female subjects should be of nonchildbearing potential or, they should be nonpregnant, nonlactating, and agree to use medically acceptable forms of birth control (oral contraceptive pills; contraceptive patches; vaginal ring; diaphragm, sponge, or condom with spermicide; hormone injection; or intrauterine device) from screening to end-of-study follow-up, or have a partner who has had a vasectomy.
   b. Male subjects need to have had a vasectomy or agree to use a condom and spermicide in addition to their female partners using a form of birth control. They should agree not to donate sperm for 90 days post IXT-m200 dose.
4. Body mass index (BMI) between 18.0 and 35.0 kg/m^2, inclusive, at screening or check-in. Body weight $\geq$ 50 kg and $\leq$ 100 kg at screening or check-in.
5. Subjects have hematology and chemistry laboratory tests that are within normal (+/- 10%) limits with the following exceptions: a) liver function tests (total bilirubin, ALT, AST, and alkaline phosphatase)

< 3 times the upper limit of normal, and b) kidney function tests (creatinine and BUN) < 2 times the upper limit of normal.

In addition, potential subjects must meet the following METH use criteria:

6. Subjects meet DSM-5 criteria for METH use disorder and are not seeking treatment at the time of the study.
7. Subjects will be experienced METH users with a history of non-therapeutic METH use for 2 or more years. Subjects must have experience with smoking or IV injection of METH.
8. Current METH use (past 30 days) less than daily, self-reported and documented by calendar-based timeline follow-back.
9. Primary current (past 30 days) route of METH SA other than IV (ie, smoking, snorting, or oral).
10. Subjects agree not to take METH from any source outside of the study during their participation in the study. Subjects agree not to take substances that are structurally similar to METH (eg, amphetamine or 3,4-Methylenedioxymethamphetamine [MDMA]).
11. Subjects must provide a negative urine toxicology sample prior to admission to the unit on Day -1 for the study.

5.2 PARTICIPANT EXCLUSION CRITERIA

Subjects presenting with any of the following will not be included in the study:

1. A history of treatment with a monoclonal antibody (mAb) in the past year.
2. Known or suspected allergy sensitivity to IXT-m200 based on known allergies to other mAbs, or which suggests an increased potential for an adverse hypersensitivity to IXT-m200.
3. History of severe allergy (rash, hives, breathing difficulty, etc) to any medications, either prescription or non-prescription, including dietary supplements or herbal medications.
4. History of allergic or environmental bronchial asthma.
5. Clinically significant history of or current abnormality or disease of any organ system, including renal, hepatic, GI, cardiovascular, pulmonary (including chronic asthma), endocrine (eg, diabetes), central nervous, or hematologic systems, or recent clinically significant surgery.
6. Current diagnosis or history of major psychiatric illness in the past two years (eg, affective disorders, schizophrenia, bipolar disorder, major depression, or other psychiatric condition that requires medication) or other current psychiatric condition requiring medication that in the opinion of the Investigator precludes study participation, other than methamphetamine dependence.
7. Considered by the PI to be at imminent risk of suicide or injury to self, others, or property, or the subject has attempted suicide within the past year prior to Screening. Past year (12 months) history of, or current evidence for, suicidal ideation or those who were actively suicidal based on the Columbia-Suicide Severity Rating Scale (C-SSRS).
8. Current dependence on alcohol according to DSM-5 criteria, or heavy use defined as >28 alcoholic drinks per week if male and >21 drinks per week if female in last 30 days (1 alcoholic drink is defined as 12 oz. beer, 4 oz. wine, or 1 oz. distilled spirits).
9. Current dependence on other drugs according to DSM-5 criteria, except amphetamines, or marijuana and nicotine used in moderate amounts (ie, ≤4 cigars or pipes of tobacco per day or ≤30 cigarettes or equivalents per day in last 30 days). Subjects will be allowed to smoke (nicotine only) during the inpatient stay, except from 1 hr before dosing of either METH or IXT-m200 until 2 hr after dosing is complete.
10. History of seizure, epilepsy, severe head injury with residual neurologic effects, multiple sclerosis, or stroke.

11. Abnormal pre-admission vital signs, physical examination, clinical laboratory, ECG, or any safety variable which is considered clinically significant for this population by the PI or Sponsor (or designee).
    a. Abnormal ECG parameters include, but are not limited to ventricular hypertrophy, left axis deviation, atrial or ventricular arrhythmias other than sinus, and prolonged QTc (greater than 500 ms).
    b. Volunteers who have or are suspected to have Gilbert's syndrome will be discussed on a case by case basis by the PI, Medical Monitor, and Sponsor.
12. History of stable or unstable cardiovascular disease.
13. Treatment with any prescription medications or over the counter nutritional supplements within 14 days prior to the first dose of study medication.
14. Ingestion of any approved prescription anti-obesity drug or taken any over-the-counter medication for weight loss within a period of 90 days prior to the first dose of study medication.
15. Ingestion or use of any investigational medication or device within 30 days prior to the first dose of study medication.
16. Acute illness within 5 days prior to the first dose of study medication, eg, flu syndrome, GI virus, or clinically significant indigestion (eg, reflux).
17. Positive result for hepatitis B surface antigen (HBsAG), hepatitis C (HepC) antibody, hepatitis A immunoglobulin M (IgM), or HIV Viral Serology, or nucleic acid testing (NAT) tests at screening.
18. Positive breath alcohol test or positive urine drug test for illicit substances (barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, propoxyphene, MDMA, METH, or amphetamine) on Day -1 (a positive test for tetrahydrocannabinol [THC] may be acceptable if the subject is not intoxicated at the discretion of the Investigator).
19. Subjects with history of donated blood, plasma or platelets in last 30 days, and who do not agree to refrain from blood, plasma, platelets, egg or sperm donation during the study period.
20. Predominant or only route of METH SA is IV.
21. Any subject judged by the PI or Sponsor (or designee) to be inappropriate for the study.

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

A broad spectrum of recruitment methods will be employed, and best practices integrated, to ensure all possible subjects are considered. Database mining, along with Community Outreach, Radio Advertisements, Print and Social Media as needed to increase awareness, will be employed. The clinical site's call center is comprised of trained scheduling and subject/patient recruitment specialists who pre-screen all incoming calls prior to scheduling their pre-screening visits and can handle large volumes of incoming calls. Dedicated recruiters confirm all study visits within 24 hours of the appointment as well as contacting all no-shows or cancelled appointments. Taxi, ride-share, or other transportation service may be utilized to drive participants to and from their appointments in order to enhance subject participation and reduce attrition.

The advertising process, if necessary, would begin with an evaluation of the target population, demographics, media costs, and previous recruitment plan results. The clinical site recruitment team has extensive knowledge regarding all advertising mediums in the local market and surrounding areas.

5.4 PARTICIPANT WITHDRAWAL OR TERMINATION

5.4.1 REASONS FOR WITHDRAWAL OR TERMINATION

Subjects may be withdrawn from the study at any time for reasons including the following:

- at their own request or at the request of their legally authorized representative,
- if a subject indicates a desire for treatment of their METH use,
- the subject meets an exclusion criteria (either newly developed or not previously recognized) that precludes further study participation,
- any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject,
- if, in the PI's opinion, continuation in the study would be detrimental to the subject's well-being, or
- at the specific request of InterveXion (Sponsor) or clinical site.

5.4.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

In all cases, the reason for withdrawal must be recorded in the electronic Case Report Form (eCRF) and in the subject's medical records. If the reason is not known, an attempt must be made to follow up with the subject to establish whether the reason was an AE, and, if so, this must be reported in accordance with the procedures in Section 8.4.1.

If, at any point in their participation in the study, a subject indicates a desire for treatment of their METH use, no more METH challenges will be given to the subject and he/she will be referred for treatment. Subjects who begin treatment for their METH use during the study will complete all follow-up safety evaluations.

As far as possible, all examinations scheduled for the end-of-study evaluations must be performed on all subjects who participate but do not complete the study according to protocol. Subjects will be followed for 126 days. Dropouts may be replaced at the discretion of the PI in conjunction with the Sponsor. The PI will make every effort to contact subjects lost to follow-up and document results.

Subjects who have an ongoing AE at the time of study completion will be followed up until the event resolves, the Sponsor and the PI agree that further follow-up is not medically necessary, or until the subject is lost to follow-up.

5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the PI, IRB, NIDA, Sponsor, and FDA.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

The study may resume once any concerns about safety, protocol compliance, and data quality are addressed and satisfy the Sponsor, IRB, and/or FDA.

6 STUDY AGENT

6.1 STUDY AGENT(S) AND CONTROL DESCRIPTION

6.1.1 ACQUISITION

Study Agent: Sponsor will provide the required number of vials of IXT-m200. The Investigator will be responsible for acquiring commercially available normal saline for dilution of IXT-m200 into its final dose formulation.

Challenge Agent: METH will be requested from the NIDA Drug Supply Program and supplied to the study site(s) upon receipt of the appropriate DEA request forms.

Placebo: The Investigator will be responsible for acquiring commercially available normal saline for use as placebo for IXT-m200 and METH.

6.1.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Study Agent: IXT-m200 is formulated as an injection solution containing approximately 20 mg/mL IXT-m200 in 10 mM sodium phosphate, pH 6.5, 150 mM sodium chloride, and 0.05% w/v polysorbate 80. The product is a clear solution packaged in 10 mL glass vials with flurotec stoppers and flip-off seals. Labels will be similar to the following:

InterveXion Therapeutics®
Anti-methamphetamine IXT-m200
18.5-21.5 mg/mL
Manufactured: 24 Oct 2017
UIP Lot: 073I1017
Catalent Lot: 17032
10 mM sodium phosphate, 150 mM sodium chloride, pH 6.5, with 0.05% Tween 80
Store refrigerated at 2 to 8°C
CAUTION: New Drug – Limited by Federal (or United States) law to investigational use only.
InterveXion Therapeutics, LLC
4301 W. Markham, Slot 831, Little Rock, AR 72205

Challenge Agent: METH is formulated for human use as an injection solution containing approximately 10 mg/mL METH in 120 mM sodium acetate, pH 4.5, and 1% (10 mg/mL) benzyl alcohol. The product is a clear solution packaged in glass vials. The labeling should include the words ‘Methamphetamine HCl Injection’.

Placebo: Normal saline (0.9% sodium chloride) should be a clear solution for injection. Packaging and labeling will be appropriate for use.

6.1.3 PRODUCT STORAGE AND STABILITY

Study Agent: IXT-m200 vials are single-use and should be stored refrigerated at 2 to 8°C. The stability of the product is still under investigation and stability protocols will run concurrent to the study. A previous lot of IXT-m200 remained stable after 48 months of refrigerated storage when the stability protocol was terminated.

Challenge Agent: METH must be stored in a safe, secure area with limited, controlled access in accordance with all local, state, and federal regulations for Schedule II controlled substances. METH vials should be stored at controlled room temperature with protection from light. Stability is typically 2 years from date of manufacture and will be indicated on the Certificate of Analysis (or equivalent) when received.

Placebo: Normal saline should be stored per the manufacturer's recommendations.

6.1.4 PREPARATION

Study Agent: The appropriate amount of IXT-m200 should be diluted into a bag of normal saline so that the total volume is 225 mL prior to dosing; mix by gentle inversion. Rounding to 2 decimal places will be used for drug volume calculations. Doses are stable for 8 hours at room temperature.

Challenge Agent: METH should be dosed undiluted.

Placebo: Normal saline requires no preparation prior to administration.

6.1.5 DOSING AND ADMINISTRATION

Study Agent and Placebo: Subjects in each cohort will be randomized to treatment or placebo on Day 2 or 3. On Day 4, a light meal or snack containing minimal unrefined sugar and caffeine will be provided 1 to 2 hours prior to dosing. Subjects should lie supine or semi-reclined during dose administration and remain in such position for 2 hours following dosing, except during ECG measurements. Subjects should refrain from strenous activity from 72 hours prior to dosing through 48 hours afterward. Fluids will be restricted from 1 hour predose to 2 hours post start of infusion and then allowed ad libitum. A standardized lunch will be provided approximately 4 hours after the beginning of the infusion.

The IXT-m200 infusion start/stop time, infusion rate, infusion volume, cumulative volume at each rate change, whether the infusion was completed, if it was stopped, or stopped and restarted will be recorded in the eCRF.

Challenge Agent and Placebo: Subjects will receive METH (30 mg) and placebo on each challenge day in randomized order, 4 hours apart. The first dose should be administered in the morning, approximately 1 hour after a light meal or snack containing minimal unrefined sugar and caffeine, with the subject semi-reclined. The second dose should be administered similarly, 4 hours after the first dose. A light meal or snack containing minimal unrefined sugar and caffeine will be offered 3 hours after the morning dose, 1 hour before the afternoon dose. Fluids are not restricted but should be kept to moderate levels during METH challenge days.

6.1.6 ROUTE OF ADMINISTRATION

Study Agent and Placebo: IXT-m200 and normal saline will be administered by IV infusion using an infusion pump over 2 hours using the progressively increasing rates of infusion described in Table 5. A 50 mL saline flush should be dispensed after each dose to ensure the entire dose is flushed through the infusion set.

Table 5. Infusion rate progression

Time increment (min)	Administration rate (mL/hr)	Incremental volume (mL)	Total volume (mL)
0-15	10	2.5	2.5
15-30	20	5	7.5
30-45	40	10	17.5
45-60	80	20	37.5
60-90	150	75	112.5
90-120	225	112.5	225

Challenge Agent and Placebo: METH and normal saline will be administered IV. Each dose will be administered by hand over 2 minutes with an observer providing time reminders during the dose.

6.1.7 STARTING DOSE AND DOSE ESCALATION SCHEDULE

In order to monitor the safety and tolerability of IXT-m200 in the METH users, a dose run-up approach to random-block dose assignment will be used so that the lower IXT-m200 dose (6 mg/kg) will be evaluated in a staged cohort of subjects before the higher dose (20 mg/kg) is evaluated (Section 4.1). In conjunction with safety monitoring, this design assures the opportunity to observe early safety findings in at least 12 subjects in the low IXT-m200 dose condition before any subjects are exposed to the high dose condition. Subsequent cohorts will be enrolled 1 week after all members of the previous cohort complete Day 49 of the study, pending safety analysis.

6.1.8 DOSE ADJUSTMENTS/MODIFICATIONS/DELAYS

Study Agent: Subjects will only be randomized and dosed with IXT-m200 if they received and tolerated the METH challenge regimen on Day 1. Additionally, subjects must have responded to the drug effects questionnaire as appropriate to the METH dose administered.

Each subject will receive only a single dose of IXT-m200, therefore no dose adjustment or modification will be done after the infusion is completed. If however, there is an infusion reaction, the dose should be stopped and the subject treated following Section 7.7.

Dose Limiting Toxicity (DLT): An AE (Section 8) will be considered clinically significant if it results in significant impairment of the subject's ability to carry out usual activities or if the AE presents a significant hazard to the subject. Any such AE or SAE will be considered a DLT if it is Grade 3 (see section 8.2.1 for grading scale) unless the event was clearly unrelated to IXT-m200 administration (Section 8.2.2 for definitions and examples). Additionally, all Grade 2 or higher toxicities will be reviewed by the Sponsor, PI, and Medical Monitor for possible classification as a DLT, as defined above.

Challenge Agent: METH dosing will be stopped or not repeated if subjects exhibit vital sign responses out of accepted ranges, or if they exhibit CNS symptoms of paranoia or hallucinations.

6.1.9 DURATION OF THERAPY

Subjects will receive only a single dose of IXT-m200.

6.1.10 TRACKING OF DOSE

All study treatments will be administered in a blinded manner by the PI or designee.

6.2 STUDY AGENT ACCOUNTABILITY PROCEDURES

Study Agent: All required IXT-m200 vials will be shipped to the study sites prior to study initiation. All unused supplies will be checked against the drug accountability records during the study and/or at the end of the study. All unused study drug must be disposed of in accordance with applicable requirements.

Challenge Agent: METH vials will be shipped to the study sites prior to study initiation with additional vials requested as necessary. Any unused drug will be disposed of according to standard practices.

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

7.1.1 STUDY SPECIFIC PROCEDURES

Medical and Medication Histories

- Medical history: A complete medical history will be obtained at screening by interview and any available medical records. Interim medical histories will be obtained at all subsequent time points.
- Medication history: A complete medication history will be obtained by interview and any available medical records, with particular attention to any medications taken in the previous 12 months. Assessment of eligibility should include a review of permitted and prohibited medications.

Physical Examination, Vital Sign Measurement, Height and Weight

- A complete physical examination (excluding rectal/genital and breast examination) will be performed at screening. The physical examination will consist of vital signs and an examination of the following: general appearance, neurological, skin, head, eyes, ears, nose, throat, neck, lymph nodes, chest, heart, abdomen, and extremities.
    - Subsequent exams will be brief (heart, lungs, abdomen, skin, weight, and vital signs), or targeted if AEs or other complaints will require appropriate and more detailed exams.
- Vital sign measurements (heart rate, blood pressures [systolic and diastolic], respiratory rate, temperature [oral], and pulse oximetry readings) will be obtained, after the subject has been resting supine for at least 5 minutes, 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 normalization. On Days 1, 5, 12, 19, and 26 (if applicable), 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. Each test may be repeated once at each time point if the initial result is out of range.
- Height and weight will be obtained during screening, and weight will be obtained on Study Day -1 and all follow-up visits.

Psychiatric Evaluation

Columbia-Suicide Severity Rating Scale: Suicide-related thoughts and behaviors will be assessed using the C-SSRS. Regulatory agencies have been interested in examining suicide-related thoughts and behaviors in patients receiving antidepressant and other drugs used in psychiatric illnesses. In August 2012, the FDA's Division of Psychiatry Products communicated that information regarding suicide-related thoughts and behaviors should be prospectively collected in a standardized format (Columbia Classification Algorithm or Suicide Assessment) from all clinical studies, including Phase 1 studies for all drugs in development to enable the analysis of suicide-related thoughts and behaviors in an aggregated fashion. The tool was developed by a National Institute of Mental Health trial group for the purpose of being a counterpart to the FDA's categorization of suicidal events.

The C-SSRS captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period. The scale includes suggested questions to solicit the type of information needed to determine if a suicide-related thought or behavior occurred. The C-SSRS will be administered by appropriately trained site personnel. A referral to a psychiatrist will be made to in the event of a significant finding on the C-SSRS, i.e., active suicidal ideation with some intent to act, without specific plan, or active suicidal ideation with specific plan or intent in the past 12 months.

All AEs obtained through the questionnaire will be recorded. The Sponsor or its designee will be alerted within 24 hours of the PI's awareness of any SAEs from these questionnaires.

The C-SSRS may be administered at any time to a subject who indicates, or is suspected to have, new suicidal intentions during the study.

Electrocardiogram and Telemetry

- Electrocardiogram (12-lead) will be recorded as outlined in the Schedule of Events (Section 7.3.6; with a window of ± 10 min relative to the nominal time point) after the subjects have been supine for 5 min. Standard ECG parameters including heart rate (HR), QRS, PR, QT, and QTc intervals will be measured. The ECGs will be read by a study physician to assess for any abnormalities. Abnormal ECG parameters include, but are not limited to ventricular hypertrophy, left axis deviation, atrial or ventricular arrhythmias other than sinus, and prolonged QTc (greater than 500 ms). ECGs may be repeated if data quality is compromised due to poor lead placement or machine error.
- Telemetry monitoring will be continuous from 0.5 hours before dosing to 8 hours post dose and until normal: defined as heart rate within 20% of baseline at the final time point. Telemetry will be monitored as it is recorded, and a physician will review the data after completion of the recording.

Biological Specimen and Laboratory Evaluations

- Blood will be taken for clinical laboratory evaluations (Section 7.2.1).
- Blood will be taken for analysis of IXT-m200, detection of anti-IXT-m200 antibodies, or analysis of METH and its metabolite amphetamine (AMP) (Section 7.2.2). Samples will be processed according to guidelines in the study laboratory manual.
- Urine samples will be taken for drug tests and urinalysis.
- Urine will be collected for analysis of METH and AMP elimination time course (Section 7.2.2). Samples will be processed according to guidelines in the study laboratory manual.
- Estimated amounts of blood volumes necessary are summarized in Table 6.

Table 6. Estimated blood volume to be collected from each subject

Reason	Volume per sample (mL)	Number of samples	Total volume (mL)
Screening serology	8.5	1	8.5
Clinical labs (7.2.1; not including cytokines)	15.2	15	228
Cytokines (samples 2 and 3 collected only if an infusion reaction occurs)	27	1 (3)	27 (81)
IXT-m200 PK	5	18	90
METH PK through Day 22 (Day 29)	3	68 (85)	204 (255)
HACA	5	4	20

Subjective Measures

- A DEQ will be administered using a mobile tablet and measured using 100-point visual analog scales anchored from "Not at all" to "Extremely". Questions will include the following, or similar:
  - "Do you FEEL a drug effect right now?"
  - "Are you HIGH right now?"
  - "How GOOD are the drug effects you are feeling right now?"
  - "How STIMULATED do you feel right now?"
  - "Do you DISLIKE any of the effects you are feeling right now?"
  - "Do you LIKE any of the effects you are feeling right now?"
  - "Would you like MORE of the drug you took right now?"
  - "How much do you CRAVE the drug right now?"
- The questionnaire 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 or placebo (PBO; for METH) dose.
- The DEQ administered at 180 minutes relative to each METH or PBO dose will also include the following two questions measured with a bipolar scale.
  - "Would you TAKE this DRUG AGAIN?"
  - "What is your OVERALL DRUG LIKING?"
- Appropriate subjective responses on Day 1 are higher responses on the visual analog scales after the METH dose relative to the placebo dose for the drug liking questions (ie, FEEL, HIGH, STIMULATED). These responses should be an average of ≥11 points higher than the placebo responses in each subject.

7.2 LABORATORY PROCEDURES/EVALUATIONS

7.2.1 CLINICAL LABORATORY EVALUATIONS

Blood and urine samples for clinical laboratory safety assessments will be collected according to standard operating procedures (SOPs). All blood and urine specimens will be sent to a local reference laboratory for analysis and testing. Local lab reference ranges (current published version) will be used for evaluation of results, where values are not otherwised defined in this protocol, at the discretion of the investigator. The procedures for the collection, handling, and shipping of laboratory samples will be specified in the laboratory manual(s) provided to the study site.

Baseline laboratory assessments will be performed on Day -1. Results of these assessments must be available and reviewed before dosing on Day 1. Abnormal screening or Day -1 for protocol-defined laboratory values are exclusionary. The subject may be retested to see if the value/parameter returns to a defined range only if there is a plausible alternative explanation for the out-of-range value. One repeat test is permitted to confirm a plausible explanation for an abnormal value.

Drug and Alcohol
- Qualitative urine drug (amphetamines, MDMA, barbiturates, benzodiazepines, cocaine, opiates, THC, phencyclidine, and propoxyphene) and alcohol breath tests will be performed at screening, upon check-in on Day -1, and at each outpatient follow-up visit.

Hematology
- Erythrocytes: red blood cell (RBC) count, hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, red cell distribution width, and reticulocyte count as an absolute value.
- Leukocytes: WBC and differential (basophils, eosinophils, lymphocytes, monocytes, and neutrophils) reported as absolute values.
- Coagulation: platelet count, prothrombin time measured as international normalized ratio, activated partial thromboplastin time.

Serum Chemistry
- Liver: alkaline phosphatase, ALT, AST (serum glutamic-oxaloacetic transaminase), bilirubin (total, direct, and indirect), gamma-glutamyl transferase, and lactic dehydrogenase.
- Renal: blood urea nitrogen, creatinine, and uric acid.
- Electrolytes, sodium, potassium, chloride, and carbon dioxide.
- General: CPK, albumin, calcium, magnesium, glucose (fasting), phosphate, protein (total), amylase, and lipase.
- Specific: Troponin 1 (only on Days 2, 6, 13, and 20) and prostate specific antigen (PSA; tested only on Days -1, 20, and 126).

Urinalysis
- Microscopic: pH, specific gravity, glucose, ketones, leukocyte esterase, nitrites, occult blood, and protein, RBCs/hpf, WBCs/hpf, bacteria, casts, epithelial cells, mucous threads, and crystals.
- Quantitative: protein and creatinine if microscopic is positive for protein.

Serum Pregnancy Test
- Serum human chorionic gonadotropin test will be performed on all females who have not had a hysterectomy at screening, on Day -1, and approximately monthly at follow-up Days 28, 56, 84, and 126; follicle-stimulating hormone tests will be performed in female subjects of nonchildbearing potential at screening.

Serology (Screening only)
- Hepatitis B surface antigen (HBsAG), hepatitis C (HepC) antibody, hepatitis A immunoglobulin M (IgM), or HIV Viral Serology, or nucleic acid testing (NAT) tests will be performed at screening.

Cytokine analysis (Day 4 only)
- Cytokine IL-1B, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, and TNFα levels will be determined only if any IXT-m200 infusion reaction occurs. Samples should be taken on Day 4 at pre-dose for all subjects, then at 1 and 4 hr after the start of any infusion reaction, if necessary.

7.2.2 OTHER ASSAYS OR PROCEDURES

- Serum PK of IXT-m200: A validated enzyme linked immunosorbent assay (ELISA) procedure will be used to quantitate IXT-m200 in serum samples taken at specified time points (Section 7.3.6) after dosing. Approximately 1 mL per sample is required.

- Plasma PK of METH and AMP: A validated liquid chromatography-mass spectrometry procedure will be used to quantitate METH and AMP in plasma samples taken at specified time points (Section 7.3.6) after dosing. Approximately 1 mL per sample is required.
- Urine PK of METH and AMP: A validated liquid chromatography-mass spectrometry procedure will be used to quantitate METH and AMP in urine samples taken at specified time points (Section 7.3.6) after dosing. Approximately 1 mL per sample is required.
- Immunogenicity of IXT-m200: A validated electrochemiluminescent procedure will be used to quantitate HACA in serum samples taken at specified time points (Section 7.3.6) after dosing. Approximately 1 mL per sample is required.

7.2.3 SPECIMEN PREPARATION, HANDLING, AND STORAGE

Serum, plasma, and urine samples for PK and immunogenicity analysis will be processed, handled and stored according to guidelines in the study laboratory manual.

7.2.4 SPECIMEN SHIPMENT

Specimen shipments will be handled according to guidelines in the study laboratory manual.

7.3 STUDY SCHEDULE

7.3.1 SCREENING

Screening Visit (Within 30 Days Prior to Enrollment)

- Subjects will sign the study-specific informed consent form (ICF) prior to any study-specific screening procedures being performed. The signed ICFs will be retained and archived and another copy will be provided to the subject
- Procedures and assessments at screening will consist of the following to determine eligibility based on inclusion/exclusion criteria:
  - Obtain demographic data
  - Review medical history
  - Review medications history
  - Perform medical examinations (physical examination, vital signs, clinical laboratory, urine drug and alcohol breath tests, and ECG assessments)
  - Assess use of METH and other illicit drugs for the past 30 days
  - Diagnose Substance Use Disorder(s) using DSM-5 criteria
  - Administer C-SSRS (lifetime history version)
  - Collect blood for HBsAg, HepC antibody, hepatitis A IgM, and HIV antibody (or nucleic acid) tests
- Schedule study visits for participants who are eligible and available for the duration of the study

7.3.2 ENROLLMENT/BASELINE

Enrollment (Day -1)

- Review and verify informed consent of potential participant
- Verify inclusion/exclusion criteria
- Review and update medical history
- Record vital signs, results of physical examinations, and ECG assessment
- Administer standardized drug assessment of METH and other drug use since last visit
- Alcohol breath test

- Collect blood/urine for urine drug screen and clinical laboratory assessments. Subjects with positive urine drug or alcohol tests (except for nicotine and marijuana) will not be enrolled, but may return at a later date if they still qualify
- Monitor telemetry for a minimum of 4 hr
- Admit to inpatient unit

7.3.3 INPATIENT STAY, EXTENSION STAY, AND FOLLOW-UP

Adverse events and vital signs will be recorded continuously throughout the inpatient stay and each follow-up visit. At each time point where multiple assessments are to be done, the priority order of collection should be: PK > DEQ > Vital signs > ECG.

Inpatient Stay (Day 1)
- Record vital signs and results of ECG assessment. If not within acceptable limits, do not administer METH challenge
- Start telemetry monitoring and record from 30 minutes prior to 8 hours after METH challenge dosing
- Administer METH challenge doses 4 hours apart
- Complete DEQ following METH challenge doses
- Collect blood and urine for METH PK
  - Continue collecting blood samples through the 72 hour time point
  - Continue collecting urine through 36 hours

Inpatient Stay (Day 2)
- Record results of physical examination, clinical laboratory, and ECG assessments

Inpatient Stay (Day 3)
- Randomize to IXT-m200 dose levels those subjects who 1) tolerated the METH challenge dose regimen as measured by AE and cardiovascular parameters, and 2) who also provided appropriate DEQ responses on Day 1. Discharge subjects who do not meet these criteria
- Collect blood for HACA

Inpatient Stay (Day 4)
- Start telemetry monitoring and record from 30 minutes prior to 8 hours after IXT-m200 dosing
- Collect pre-dose cytokine sample. Collect samples at 1 and 4 hr after the start of any infusion reaction, if necessary.
- Administer IXT-m200 dose
- Collect blood for IXT-m200 PK
  - Continue collecting blood samples through 72 hours post start of the infusion

Inpatient Stay (Days 5, 12, and 19)
- Collect blood for IXT-m200 PK prior to the first METH challenge dose
- Record vital signs and results of ECG assessment. If not within acceptable limits, do not administer METH challenge
- Start telemetry monitoring and record from 30 minutes prior to 8 hours after METH challenge dosing
- Administer METH challenge doses 4 hours apart
- Complete DEQ following METH challenge doses
- Collect blood and urine for METH PK
  - Continue collecting blood samples through the 72 hour time point
  - Continue collecting urine through 36 hours

Inpatient Stay (Days 6, 13, and 20)
- Record results of physical examination, clinical laboratory, and ECG assessments

Inpatient Stay (Day 22)
- Schedule at least the next follow-up visit, more if subject agrees
- Record vital signs and results of physical examination
- Administer C-SSRS (since last assessment) if subject is to be discharged
- Discharge subjects if vital signs and physical exam are acceptable if subject is not participating in the Inpatient Extension Stay

Inpatient Extension Stay (Day 26; Subjects who successfully complete through Day 22 may remain in the unit if they elect to continue the inpatient stay)
- Collect blood for IXT-m200 PK prior to the first METH challenge dose
- Record vital signs and results of ECG assessment. If not within acceptable limits, do not administer METH challenge
- Start telemetry monitoring and record from 30 minutes prior to 8 hours after METH challenge dosing
- Administer METH challenge doses 4 hours apart
- Complete DEQ following METH challenge doses
- Collect blood and urine for METH PK
    - Continue collecting blood samples through the 72 hour time point
    - Continue collecting urine through 36 hours

Inpatient Extension Stay (Day 27)
- Record results of physical examination, clinical laboratory and ECG assessments

Inpatient Extension Stay (Day 28)
- Collect blood for HACA

Inpatient Extension Stay (Day 29)
- Schedule at least the next follow-up visit; more if subject agrees
- Record vital signs and results of physical examination
- Administer C-SSRS (since last assessment)
- Discharge subjects if vital signs and physical exam are acceptable

Outpatient Follow-up (Days 28, 35, 42, 49, 56, 63 [±2 days])
- Record vital signs and results of physical examinations
- Assess severity of Substance Use Disorders using DSM-5 criteria since last administration of the questionnaire (Days 28 (or Day 35 if subject participated in inpatient extension stay) and 63 only)
- Administer standardized drug assessment of METH and other drug use since last visit (Days 28 (or Day 35 if subject participated in inpatient extension stay) and 63 only)
    - Note to administrator, if subject has reported multiple instances of METH use since last visit, instruct them to recall their first time of use since last visit. Ask the following questions:
    - "*Did you take your typical dose of METH as you normally would before you started the study?"* Answer: Yes or No
        - If No, "*Did you try more or less than normal?*" A: More or Less
    - "*How was the high compared to what you typically get from that dose?*" Answer: Scale of 1-5; 1 = Less than expected, 3 = Just as expected, 5 = Better than expected
        - If 1 or 2, "*Did you take more METH to get the high you wanted?*" Answer: Yes or No
            - If Yes, "*Did that get the result you wanted?*" Answer: Yes or No

- Alcohol breath test
- Collect blood/urine for urine drug screen, and clinical laboratory assessments
  - A positive drug screen at a follow-up visit will not exclude the subject from completing the remainder of the study
- Collect blood for IXT-m200 PK
- Collect blood for HACA (Days 28 and 63 only; if those visits are missed, collect at next visit)
- Educate subjects on risk of taking METH or other abused drugs
- Schedule next follow-up(s)

Outpatient Follow-up (Days 84, 105 [±3 days])
- Record vital signs and results of physical examinations
- Assess severity of Substance Use Disorders using DSM-5 criteria since last administration of the questionnaire (Day 105 only)
- Administer standardized drug assessment of METH and other drug use since last visit (Day 105 only)
  - Note to administrator, if subject has reported multiple instances of METH use since last visit, instruct them to recall their first time of use since last visit. Ask the following questions:
  - "*Did you take your typical dose of METH as you normally would before you started the study?"* Answer: Yes or No
    - If No, "*Did you try more or less than normal?*" A: More or Less
  - "*How was the high compared to what you typically get from that dose?*" Answer: Scale of 1-5; 1 = Less than expected, 3 = Just as expected, 5 = Better than expected
    - If 1 or 2, "*Did you take more METH to get the high you wanted?*" Answer: Yes or No
      - If Yes, "*Did that get the result you wanted?*" Answer: Yes or No
- Alcohol breath test
- Collect blood/urine for urine drug screen, and clinical laboratory assessments
  - A positive drug screen at a follow-up visit will not exclude the subject from completing the remainder of the study
- Collect blood for IXT-m200 PK
- Educate subjects on risk of taking METH or other abused drugs
- Schedule next follow-up(s)

7.3.4 FINAL STUDY VISIT

Outpatient Follow-up (Day 126 [±3 days] or as soon as possible)
- Record vital signs and results of physical examinations
- Alcohol breath test
- Collect blood/urine for urine drug screen, and clinical laboratory assessments
- Collect blood for IXT-m200 PK
- Collect blood for HACA
- If ongoing AEs or SAEs are present, schedule follow-ups to continue monitoring until resolved

7.3.5 EARLY TERMINATION VISIT

Early Termination During Inpatient Stay
- Record vital signs, and results of physical examination, and clinical laboratory assessments
- Collect all scheduled blood and urine samples if subject is willing to remain in the unit
- Collect blood for HACA

- Encourage the subject to remain in the unit for the planned duration of inpatient stay if IXT-m200 dose has been administered
- Educate subjects on risk of taking METH or other abused drugs
- Provide references for METH use treatment and facilitate entry if subject is willing
- Schedule follow-up visits if IXT-m200 has been administered and subject is willing

Early Termination During Outpatient Phase
- Record vital signs, and results of physical examination
- Administer standardized drug assessment of METH and other drug use since last visit
- Alcohol breath test
- Collect blood/urine for urine drug screen, and clinical laboratory assessments
- Collect all scheduled blood samples
- Collect blood for HACA
- Educate subjects on risk of taking METH or other abuse drugs
- Provide references for METH use treatment and facilitate entry if subject is willing

7.3.6 SCHEDULE OF EVENTS TABLE

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 7.1.1). 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). (Section 7.1.1).
c. Physical exams will be done once per day as described (Section 7.1.1).
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 (Section 7.1.1).
e. Clinical laboratory assessments will be done once per day as described in Section 7.2.1.
f. Qualitative urine drug and breath alcohol tests will be performed as described in Section 7.2.1.
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 (Section 7.1.1).
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 time point. Telemetry will be monitored as it is recorded, and a physician will review the data after completion of the recording (Section 7.1.1).
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 (Section 6.1.5).
k. IXT-m200 will be administered as a 2-hour IV infusion (Section 6.1.5).
l. Serial blood samples will be taken for assessment of IXT-m200 and METH PK (Section 7.1.1).
    - Pharmacokinetic samples for IXT-m200 will be taken predose (up to 10 min prior), then 2.25, 4, and 6 (± 0.0833), then 12 and 24 (± 0.167), and 72 (± 0.25) 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 (± 0.08333), then 0.0833, 0.25, 0.5 and 1 (± 0.0333), then 2 and 4 (± 0.0833), then 4.0833, 4.25 and 5 (± 0.0333), then 6 and 8 (± 0.0833), then 12, 16 and 24 (± 0.167), then 36 and 72 (± 0.25) 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 time point).
m. Blood samples for measurement of HACA will be taken on Days 3 (baseline), 28, 63, and 126 (Section 7.1.1); 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 (Section 7.1.1).
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 (Section 7.1.1).
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 (Section 7.3.5).
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 (Section 7.1.1).

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 (Section 7.1.1).
c. Physical exams will be done once per day as described (Section 7.1.1).
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 (Section 7.1.1).
e. Clinical laboratory assessments will be done once per day as described in Section 7.2.1.
f. Qualitative urine drug and breath alcohol tests will be performed as described in Section 7.2.1.
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 (Section 7.1.1).
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 time point. Telemetry will be monitored as it is recorded, and a physician will review the data after completion of the recording (Section 7.1.1).
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 (Section 6.1.5).
k. Serial blood samples will be taken for assessment of IXT-m200 and METH PK (Section 7.1.1).
   - 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 (± 0.08333), then 0.0833, 0.25, 0.5 and 1 (± 0.0333), then 2 and 4 (± 0.0833), then 4.0833, 4.25 and 5 (± 0.0333), 6 and 8 (± 0.0833), then 12, 16 and 24 (± 0.167), then 36 and 72 (± 0.25) 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 time point).
l. Blood samples for measurement of HACA will be taken on Days 28, 63, and 126 (Section 7.1.1); 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 (Section 7.1.1).

n. 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 (Section 7.1.1).

7.4 JUSTIFICATION FOR SENSITIVE PROCEDURES

Use of placebo for IXT-m200 is justified in this study to create a comparator control group who also receives the METH challenge doses. Subjects recruited for this study will be non-treatment seeking for their METH use disorder. A single dose of IXT-m200 is not likely to benefit subjects who do not wish to change their METH intake. Therefore, the use of placebo for IXT-m200 does not place subjects at further risk nor does it prevent them from receiving a likely benefit.

Placebo is also used for METH challenge dosing to control for anticipatory cardiovascular and subjective responses. The use of placebo for METH does not place subjects at further risk nor does it prevent them from receiving a likely benefit.

7.5 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

All concomitant medications (ie, prescription medications, over-the-counter medications, and non-prescription medications) 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.

7.5.1 PRECAUTIONARY MEDICATIONS, TREATMENTS, AND PROCEDURES

IXT-m200 may alter the PK of molecules that are structurally similar to METH, therefore subjects should not take drugs such as amphetamine or MDMA.

7.6 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

Subjects are prohibited from the following during the study period:
- Ingesting or using any other investigational drug or device.
- Donating blood, plasma, platelets, eggs or sperm.

Subjects will be encouraged to limit their ethanol consumption to approximately 1 drink per day for women and 2 drinks per day for men while in the study.

7.7 RESCUE MEDICATIONS, TREATMENTS, AND PROCEDURES

- If a Grade 2 infusion reaction occurs (see section 8.2.1 for grading scale), the IXT-m200 or control infusion will be temporarily discontinued. Depending on the progression of the symptoms after the infusion has been stopped, diphenhydramine (25 to 50 mg po or IV); acetaminophen (500 mg po); and/or methylprednisolone (125 mg IV) may be given if deemed necessary by the PI. If the symptoms resolve with discontinuation of the infusion, diphenhydramine and acetaminophen will be administered and the infusion restarted at the next lower rate than the one at which the symptoms occurred.
- If a Grade 3 infusion reaction occurs (see section 8.2.1 for grading scale), the infusion will be stopped and the subject treated as needed to reduce or stop the reaction. The infusion will not be restarted.

Methylprednisolone (125 mg IV), and/or diphenhydramine (25 mg IV) may be given along with bronchodilators and pressors as needed.

- With infusion reactions of any Grade, blood samples will be drawn at 1 and 4 hours after the beginning of the reaction to quantify levels of inflammatory cytokines. Cytokine IL-1B, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, and TNFα levels will be determined. (TNFα typically rises within 1 hour and IL-2, -6 and -10 within 4 hr).
- Hypotension (blood pressure less than 80/50 mmHg or less than 90/60 mmHg with symptoms of dizziness, near syncopy, or nausea, for example) will be treated initially with a fluid bolus (500 to 1000 cc). If hypotension persists, it will be treated with incremental doses of phenylephrine (100 µg IV) if the heart rate is greater than 100 beats per minute (bpm) or ephedrine (5 mg IV) if the heart rate is less than 80 bpm. Continuous heart rate and frequent blood pressure monitoring will accompany the treatment, and subsequent pharmacologic management will be dictated by the responses to the initial treatment. This could include doses of epinephrine (10 µg IV or sc) if the patient is unresponsive to the previous measures.
- Bronchospasm with hypoxemia (pulse oximeter readings less than 93% with dyspnea or tachypnea) will be treated with administration of oxygen via facemask or nasal cannula, along with albuterol inhalers or nebulized breathing treatments if necessary. Epinephrine (10 µg) doses may be given if the event is life-threatening or if the patient is unresponsive to the previous measures.
- Flushing, pruritis, urticaria will be treated with antihistamines (eg, diphenhydramine 25 to 50 mg, po, and/or famotidine 20 mg, po) or steroids (eg, prednisone 0.5 mg/kg, po) if not associated with other life-threatening sequelae.
- In any case in which hypotension do not resolve with the initial treatments outlined above, and they persist for longer than 30 minutes after sufficient treatment (as determined by the PI), 911 will be called and the subjects will sent to the nearest emergency room via ambulance for definitive treatment.
- If subjects exhibit signs or symptoms of METH withdrawal (eg, depression or anhedonia) during the IXT-m200 infusion, the infusion will be stopped and the subject treated appropriately. Immediate care will involve acknowledgment of symptoms, emotional support, and observation. Because symptoms of withdrawal are typically not medically dangerous, this treatment may suffice. There are no approved medications for symptoms of METH withdrawal, but mirtazapine (15 mg po qd), modafinil (100 mg po qd) or buproprion (100 mg po bid) may be started if medically indicated in the opinion of the PI.[31]
- If subjects exhibit signs or symptoms of METH-induced psychosis during their inpatient stay, no further METH challenges will be administered and if the symptoms occur prior to IXT-m200 dosing, the IXT-m200 dose will not be administered. Observation and emotional support will be given to the patient. There are no approved medications for the treatment of METH-induced psychosis. Acute agitation may be treated with small doses of haloperidol until the symptoms lessen (1-5 mg IV over 2-5 min with continuous ECG monitoring). Subjects will then be referred to psychiatric care for definitive diagnosis and treatment.[32]

The research clinics have been designed with the special requirements of pharmacological studies in mind. Emergency medications that might be needed to treat mAb toxicity are kept in the clinic. A hospital maintained crash cart is available near the laboratories. Oxygen and emergency ventilation equipment (Ambubags) are immediately available. ACLS-certified providers and a team is available on site to treat life-threatening events during the in-patient component of the study. Subjects are treated in a reclining position and syncope is unlikely. Normal saline is used as the IV fluid and fluid boluses can be administered if any hypotension is seen. Subjects are not allowed to stand until deemed stable by the investigator. In the event that serious medical complications result from this study, 911 will be called.

7.8 PARTICIPANT ACCESS TO STUDY AGENT AT STUDY CLOSURE

IXT-m200 will not be available to participants following their completion of the study.

8 ASSESSMENT OF SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

Safety parameters that are study endpoints:
- Heart rate, blood pressure, and temperature (Section 7.1.1)
- QT and QTc intervals (Section 7.1.1)

Safety parameters that will be recorded in the safety reporting system:
- Physical exam and vital sign measurements (Section 7.1.1)
- AEs
- ECG and telemetry data (Section 7.1.1)
- Clinical laboratory data (Section 7.2.1)
- Immunogenicity (Section 7.1.1)

8.1.1 DEFINITION OF ADVERSE EVENTS

An **AE** is any untoward medical occurrence in a subject administered IXT-m200 and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of IXT-m200, whether or not related to the IXT-m200.

The AE may be:
- a new illness;
- worsening of a sign or symptom of the condition under treatment or of a concomitant illness;
- an effect of the study medication, including comparator; or
- a combination of 2 or more of these factors.

No causal relationship with IXT-m200 or with the clinical study itself is implied by the use of the term "AE". Pre-existing conditions will not be reported as an AE unless there has been a substantial increase in the severity or frequency of the problem which has not been attributed to natural history.

Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an AE. Planned surgical measures permitted by the clinical study protocol and the condition(s) leading to these measures are not AEs.

Adverse events fall into the categories "nonserious" or "serious".

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS

An SAE is an AE that at any dose:

- results in death;
- is life-threatening;

- requires subject hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity; or
- is a congenital anomaly/birth defect.

The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at immediate risk of death at the time of the SAE; it does not refer to an SAE which hypothetically might have caused death if it were more severe.

Medical and scientific judgment will be exercised in deciding whether other AEs, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above. These will also usually be considered serious.

8.1.3 DEFINITION OF UNANTICIPATED PROBLEMS

Unanticipated problems involving risks to participants or others will include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 SEVERITY OF EVENT

The general approach outlined by the Club Phase 1 (CP1) working group in the British Journal of Clinical Pharmacology in 2010[33] will be used to categorize the severity of all AEs. The stopping rules outlined in Section 8.5 will apply.

The following criteria will be used:

- Grade 1: Transient or mild discomfort; does not interfere with daily activity; no medical intervention/treatment required,
- Grade 2: Mild to moderate limitation in activity, some assistance may be needed; no or minimal intervention/treatment required, including but not limited to mild analgesics, antacids or antibiotics,
- Grade 3: Marked limitation in activity, some assistance usually required; medical intervention/treatment required,
- Grade 4: Extreme limitation in activity, significant assistance required; significant medical intervention/treatment, likely requiring hospitalization.

Regarding vital sign AEs, Section 7.7 defines blood pressure criteria for treatment with fluids and medications. If hypotension is not immediately responsive to medications, this will constitute a Grade 3 reaction and it will be documented as such. Similarly, if bronchospasm (SaO_2 < 93% on oxygen) occurs

and requires medications, this will constitute a Grade 3 reaction, and will be documented as such. The stopping rules outlined in Section 8.5 will apply.

8.2.2 RELATIONSHIP TO STUDY AGENT

Association or relatedness to the study drug will be graded as follows:

DEFINITELY – The AE:
- is clearly related to the investigational agent or research intervention;
- has a temporal relationship to the administration of the study drug;
- follows a known pattern of response;
- occurs in the absence of an alternative cause.

PROBABLY – The AE:
- follows a reasonable temporal sequence from study drug administration;
- abates upon discontinuation of the drug;
- cannot be reasonably explained by the known characteristics of the subject's clinical state.

POSSIBLY – The AE:
- follows a reasonable temporal sequence from study drug administration;
- could have been produced by the subject's clinical state or by other modes of therapy administered to the subject.

UNLIKELY – The AE:
- does not follow a reasonable temporal sequence from study drug administration;
- is readily explained by the subject's clinical state or by other modes of therapy administered to the subject.

UNRELATED – The AE:
- is definitely produced by the subject's clinical state or by other modes of therapy administered to the subject.

8.2.3 EXPECTEDNESS

The Safety Monitoring Committee (SMC; Section 8.6) will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

8.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a Study Monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate eCRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. Unanticipated problems will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity. All AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for nonserious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the Investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.4 REPORTING PROCEDURES

8.4.1 ADVERSE EVENT REPORTING

All AEs (whether serious or nonserious) that occur after the subject has been randomized into a treatment group must be documented on the appropriate pages of the eCRF. For all AEs, the PI will provide an assessment of the AE, its treatment and resolution, and its relationship to IXT-m200. Every attempt should be made to describe the AE in terms of a diagnosis. If appropriate, component symptoms should also be listed below the diagnosis. If only nonspecific signs or symptoms are present, then these should be recorded as a diagnosis.

All subjects who have AEs, whether considered associated with the use of IXT-m200 or not, will be monitored to determine the outcome. The clinical course of the AE will be followed up according to accepted standards of medical practice, even after the end of the period of observation, until a satisfactory explanation is found or the PI considers it medically justifiable to terminate follow-up. Should the AE result in death, a full pathologist's report should be supplied, if possible.

Adverse events will be reviewed by the SMC and Sponsor between cohorts during the interim review. If the PI decides it necessary, AEs may be reviewed at any time by consultation with the SMC and Sponsor.

8.4.2 SERIOUS ADVERSE EVENT REPORTING

The study clinician will complete an SAE form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the designated SAE form and submitted to the SMC and Sponsor within 24 hours of site awareness. See Section 1 for contact information.
- Other SAEs regardless of relationship, will be submitted to the SMC and Sponsor within 72 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until the site Investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the SMC or Sponsor and should be provided as soon as possible.

The study Sponsor will be responsible for notifying FDA of any unexpected fatal or life-threatening suspected AEs as soon as possible but in no case later than 7 calendar days after the Sponsor's initial receipt of the information. The Sponsor is responsible for notifying the FDA of serious, unexpected, AEs that are not fatal or life-threatening as soon as possible, but no later than 15 calendar days, after first knowledge by the Sponsor that the SAE case meets the minimum criteria for expedited reporting.

NIDA Project Officer (PO) Tanya (Tatiana) Ramey MD, PhD will be notified by the Sponsor within 72 hours of the SAE occurrence, and also via NIDA's online Serious Adverse Event Tracking and Reporting System (SAETRS).

Information not available at the time of the initial report will be documented on a follow-up SAE form. SAE information previously sent to the Sponsor will not be duplicated. When a nonserious event becomes serious, details will be forwarded immediately to the Sponsor on the designated SAE report form.

8.4.3 REPORTING OF PREGNANCY

If a subject is found to be pregnant after they have received IXT-m200, they should complete the study, with no further METH challenge doses administered, and be followed to determine the outcome of the pregnancy if the subject is willing. Generally, follow-up will be no longer than 6 to 8 weeks after the estimated delivery date. While pregnancy itself is not considered an AE or SAE, any pregnancy complications will be recorded as an AE or SAE.

Pregnancies should be reported by the Investigator to the Sponsor within 2 days of identification.

8.5 STUDY HALTING RULES

The criteria outlined in section 8.2.1 will be used to categorize the severity of all AEs. No new enrollment and no further study drug will be administered if any 1 of the following events occurs, unless the event was clearly unrelated to study drug administration.

- Two (2) subjects experience a Grade 3 AE.
- One (1) subject experiences a Grade 4 AE.
- A death occurs.

Events unrelated to study drug administration include those that are temporally unrelated to IXT-m200 administration, such as events occurring prior to dosing; or events in which the subject is a passive victim, such as a passenger in a motor vehicle crash.

If any of these conditions are met, the Sponsor, in consultation with both PIs and Medical Monitor, will suspend enrollment until a full safety review is performed. The study Sponsor will inform the Data and Safety Monitoring Board (DSMB) members within 24 hours of this occurrence and will provide the DSMB with AE listing reports. The DSMB will convene an ad hoc meeting by teleconference or in writing as soon as possible. The DSMB will provide recommendations for proceeding with the study. A decision to reinitiate enrollment will be made in consultation with the FDA.

8.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of the SMC which will provide a review of safety data between cohorts. The SMC will be comprised of the PIs from both sites, Project Manager, Study Coordinators, and Medical Monitor. After each cohort, interim safety reports will be prepared by the Study Coordinators and PIs. These safety reports typically consist of the following:

- Summary of vital sign data for each subject within the cohort;
- Summary of physical exam findings within each cohort;

- Safety laboratory data for each subject within the cohort either in hard copy printouts or electronically;
- Summary of AEs for each subject within the cohort;
- Summary of any clinically significant ECG changes for each subject within the cohort; and
- Any other miscellaneous pertinent information for the dose group.

The SMC will hold teleconferences with Dr. Gentry (Chief Medical Officer of InterveXion Therapeutics, Sponsor) after each cohort to discuss the interim safety reports and findings. The safety reports and any recommendations of the DSMB will be reviewed and discussed by the SMC. The PIs and Medical Monitor will sign and date the report prior to moving forward with the next cohort.

A Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise, likely including monoclonal antibody and methamphetamine clinical pharmacology, acute care medicine (cardiovascular and/or emergency), psychiatry or behavioral medicine, statistics, and a patient advocate or representative. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. The DSMB will provide its input to the study Sponsor.

The DSMB will review unblinded data while the SMC will review blinded study data. The DSMB membership is further removed from the study, while the SMC members are on the ground at the study sites with interaction with the actual subjects. Each review group will provide a recommendation to the Sponsor based on their perspectives. The Sponsor, by the actions of it's Chief Medical Officer, W. Brooks Gentry, will determine whether cohort enrollment should continue or if changes should be made.

9 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

The study will be monitored by a Study Monitor. Throughout the course of the study, the Study Monitor will make frequent contact with the PIs. This will include telephone calls and on-site visits. During the on-site visits, the Study Monitor will perform source data verification (a comparison of the data in the electronic data capture systems with the volunteer's medical records including verification of informed consent of participating volunteers). This will require direct access to all original records for each volunteer (eg, clinic charts).

The Study Monitor will also perform drug accountability checks and will request to perform a review of the PI study file to assure completeness of documentation in all respects of clinical study conduct.

Upon completion of the study, the Study Monitor will arrange for a final review of the study files, after which the files should be secured for the appropriate time period. The PI, or appointed delegate, will meet with the Study Monitor during the on-site visits and will cooperate in providing the documents for inspection and responding to inquiries. In addition, the PI will permit inspection of the study files by authorized representatives of the Sponsor or the regulatory agencies.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL AND ANALYTICAL PLANS

Complete details of the statistical analyses to be performed will be documented in a statistical analysis plan (SAP), which will be completed prior to unblinding of the study data. This document will include more detail of analysis populations, summary strategies, and any amendments to the proposed analyses listed here, if necessary. Any changes to the SAP will be outlined in the final study report.

10.2 STATISTICAL HYPOTHESES

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

Primary:
1) Treatment with IXT-m200 will increase systemic METH exposure (C_{max}, AUC) following METH administration compared to PBO. (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 PBO and for overall treatment effect of IXT-m200 compared to PBO.)

Secondary:
1) Treatment with IXT-m200 will decrease subjective effects of METH compared to PBO. (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 PBO and for overall treatment effect of IXT-m200 compared to PBO.)

10.3 ANALYSIS DATASETS

The study analysis populations will consist of:

- Qualification Safety Population: Subjects who receive at least one dose of METH on Day 1.
- Safety Population: All subjects who receive a dose of IXT-m200 on Day 4.
- Pharmacokinetic Population: the PK analysis set will include all subjects in the safety analysis set for whom at least 1 PK parameter can be calculated for METH or IXT-m200.
- Pharmacodynamic Population: 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 allocation, including 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.

10.4 DESCRIPTION OF STATISTICAL METHODS

10.4.1 GENERAL APPROACH

Pharmacokinetic blood samples will be assayed for measurement of concentrations of METH or IXT-m200. Pharmacokinetic parameters will be calculated for these analytes including the following, if possible:

- C_{max} by inspection (without interpolation)
- t_{max} by inspection
- AUC from time 0 to the time of the last quantifiable drug concentration (AUC_{0-t})
- AUC from time 0 to infinity ($AUC_{0-\infty}$)
- percentage of AUC extrapolated
- terminal elimination rate constant (λ_z) and associated $t_{½}$
- clearance (CL)
- Vd

Urine samples will be collected and assayed for measurement of urine concentration of METH. The following PK parameters will be calculated for METH (only), if possible:

- amount excreted in urine (Ae)
- renal clearance (CL_R)

The secondary PD measures and endpoints for assessment of subjective response include measures of balance of drug effects, positive drug effects, negative drug effects, and craving effects as follows:

- Measures of balance of effects:
  - Minimum (E_{min}), Area Under the Effect Curve (AUEC) and Time to E_{max} or E_{min} ($T_{Emax/Emin}$) for 'at the moment' Drug Liking VAS
  - E_{max} and E_{min} for Overall Drug Liking VAS
  - E_{max} for Take Drug Again VAS
- Measures of positive effects:
  - E_{max}, AUEC, and T_{Emax} for High VAS
  - E_{max}, AUEC, and T_{Emax} for Stimulated VAS
- Measures of negative effects:
  - E_{max}, AUEC, and T_{Emax} for Dislike VAS
- Measures of craving effects:
  - E_{max}, AUEC, and T_{Emax} for Crave VAS

10.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The PK population will be used for METH PK analysis. Serum concentration data for METH will be listed for each subject by challenge day, IXT-m200 dose level, and nominal time point, and summarized by IXT-m200 dose level using descriptive statistics, including count (n), mean, standard deviation (SD), SE, median, minimum, maximum, geometric mean and coefficient of variation (CV%). Mean and individual serum concentration versus time profiles for each METH challenge day will be presented graphically on linear and semi-logarithmic scales. PK parameters for METH will be listed for each subject by challenge day and IXT-m200 dose level and summarized by METH challenge day and IXT-m200 dose level using descriptive statistics including the geometric mean and CV%, as appropriate.

A general linear model will be used to compare METH exposure (C_{max} and AUC) following treatment with IXT-m200 compared to PBO. The analysis will compare Day 5 (primary) and Day 12, Day 19, and Day 26 (all secondary) METH exposure for each dose level of IXT-m200 compared to PBO with Day 1 METH exposure included as a covariate. The overall treatment effect of IXT-m200 compared to PBO will be assessed similarly.

10.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

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 values. The changes between Day 1 METH subjective effects (Drug Liking, etc) and Day 5, Day 12, Day 19, and Day 26 will be obtained first for each subject. The analysis will compare the change from baseline values between each dose level of IXT-m200 and PBO. The overall treatment effect of IXT-m200 compared of PBO will be assessed similarly.

The PK population will be used for IXT-m200 PK analysis. Serum concentration data for IXT-m200 will be listed for each subject by treatment group, and nominal time point, and summarized by treatment group, dose level, and nominal time point using descriptive statistics, including count (n), mean, SD, SE, median, minimum, maximum, geometric mean, and CV%. Mean and individual serum concentration versus time profiles for each dose level will be presented graphically on linear and semi-logarithmic scales. Serum PK parameters for IXT-m200 will be listed for each subject by dose level and summarized by dose level using descriptive statistics including the geometric mean and CV%, as appropriate. Statistical comparisons of IXT-m200 treatment groups will not be conducted.

10.4.4 SAFETY ANALYSES

Safety assessments and time points are provided in Section 7.3.6.

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Each AE will be counted only once, and the most severe will be counted in each subject and in each preferred term or system organ class category for the analyses of safety. Summaries will be presented for all AEs (overall and by severity), AEs determined by the Investigator to be related to IXT-m200 (ie, reasonable possibility) (defined as related or with missing relationship) (overall and by severity), serious AEs, and AEs causing withdrawal from the study. Summaries will be presented by treatment group and for all subjects. Subject listings of SAEs and AEs leading to withdrawal will be presented.

In addition, due to a difference in the number of overall METH challenges administered, summaries will also be presented separately for subjects that opt to stay for the Inpatient Extension and subjects that elect to discharge from the clinic on Day 22.

Changes in vital signs, and liver function test data will be summarized descriptively by treatment and time point. Changes in other clinical laboratory and ECG measurement data will be summarized descriptively by time point. All values will be compared with prespecified boundaries to identify potentially clinically significant values, and such values will be listed.

Physical examination findings will be listed by subject and visit.

Medical History will be coded to MedDRA terms. Coded medical history terms will be listed. Scores from the C-SSRS assessment will be listed by subject and visit.

The use of concomitant medications will be summarized by therapeutic class and preferred term using descriptive statistics. Concomitant medications will include all medications taken from the time of IXT-m200 administration through follow-up.

For continuous variables, descriptive statistics (n, mean, SD, SE, median, minimum, and maximum) will be provided for actual values and changes from baseline to each time point. For categorical variables, subject counts and percentages will be provided.

If any subject dies during the study, a listing of deaths will be provided and all relevant information will be discussed in the subject narrative included in the clinical study report (CSR).

10.4.5 ADHERENCE AND RETENTION ANALYSES

Disposition of each analysis population will be summarized using descriptive statistics. Data from subjects who discontinue from the study will also be summarized by last treatment received and reason for discontinuation.

10.4.6 BASELINE DESCRIPTIVE STATISTICS

Demography and baseline characteristics (age, sex, race, ethnicity, body weight, height, and BMI) will be summarized using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum for continuous variables, and the proportion of subjects for categorical variables) for the Safety population.

10.4.7 MULTIPLE COMPARISON/MULTIPLICITY

No adjustments will be made for multiple comparisons.

10.5 SAMPLE SIZE

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 PBO 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.

In a previous study wherein METH challenges were administered following treatment with varenicline in 17 subjects[34], statistically significant reductions were observed in subjective measures of 'Any Drug Effect', 'High', 'Stimulated', and 'Drug Liking'. Utilizing data from this study, the sample size proposed herein of 28 subjects across all IXT-m200 treatments should provide at least 80% power to detect treatment differences of ≥11 points in E_{max} of drug liking, at the 1-sided significance level of 0.025, using a paired means test and correlation of 0.5, and assuming a SD of Drug Liking E_{max} of 20 points.

10.6 MEASURES TO MINIMIZE BIAS

10.6.1 ENROLLMENT/ RANDOMIZATION/ MASKING PROCEDURES

Each potential subject will be assigned a unique number in the screening process (screening number). This number will be used to identify the subject throughout the study. Subjects who qualify will be assigned a unique randomization number to identify the sequence of their treatments.

10.6.2 BREAKING THE STUDY BLIND/PARTICIPANT CODE

Unblinding of treatment assignment during the study is discouraged and should occur only if it is absolutely necessary for the PI, Medical Monitor, Sponsor, or subject to know what he or she received. If

the Sponsor, the PI, or Medical Monitor deems identification of the study drug to the subject as necessary for the purpose of providing urgent subject care, the pharmacy will inform the PI of the assignment, who will notify the Medical Monitor, Sponsor, and subject. The process of unblinding will be appropriately documented in the PI file. The date and reason for the unblinding must be recorded on the subject's eCRF. When possible, the Medical Monitor and Sponsor should be notified prior to unblinding; otherwise, they must be notified within 24 hours after unblinding.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor. The Study Monitor or other authorized representatives of the Sponsor may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study sites will permit access to such records. Investigators will maintain all records pertaining to this study for a period of 2 years following the date a marketing application is approved for the study agent for the indication for which it is being investigated; or if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

The complete data management (data capture, data entry, data validation, checks on plausibility, query handling, data editing after entry, coding, database closure, etc) will be defined in advance within the Data Management Plan. Data analysis will be performed in accordance with the SAP.

12 QUALITY ASSURANCE AND QUALITY CONTROL

The study may be audited by a Quality Assurance Department to assess adherence to the clinical study protocol and Quality System. During the conduct of the study, process-related audits may be performed. An audit certificate will be provided in the appendices of the final CSR outlining any audits and other related activities performed.

The Sponsor (or contractors) may conduct site or contract research organization audits.

Quality control (QC) principles will be applied throughout the performance of this study. Review procedures will be followed for all documents that are generated in relation with the study.

The study sites will generate and implement a study-specific Quality Management Plan describing routine QC and quality assurance activities for assessing the quality of the study data, protections of human subjects, compliance with applicable federal regulations, and ICH E6 GCP guidelines. The PI will ensure all study personnel are appropriately trained and applicable documentations are maintained on-site. Clinical site monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements. Data Management and control processes specific to this study, along with all steps and actions taken regarding data management and data QC, will be described in a Data Management Plan. An explanation will be given for all missing, unused, and spurious data in the relevant sections of the CSR.

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 ETHICAL STANDARD

The Investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6 Guideline for GCP.

13.2 INSTITUTIONAL REVIEW BOARD

The protocol, ICF(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB-approved; a determination will be made regarding whether previously consented participants need to be re-consented.

The Sponsor will be responsible for reporting IRB actions to the NIDA Program Officer. In addition, all significant protocol changes will be approved by NIDA prior to implementation, unless there is an immediate safety concern for participants.

13.3 INFORMED CONSENT PROCESS

13.3.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

The written consent document will embody the elements of informed consent as described in the Declaration of Helsinki and will adhere to the ICH Harmonized Tripartite Guideline for GCP. Informed consent must be obtained before any protocol-specified procedures or interventions are carried out. Informed consent will be obtained in accordance with 21 CFR 50.25 and 45 CFR 46.

The consent form will be written in a language the subject can understand and will contain:

- A statement that the trial involves research.
- An explanation of the purposes of the research.
- The trial procedures to be followed, including all invasive procedures.
- The subject's responsibilities.
- Those aspects of the trial that are experimental.
- The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.
- The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
- The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.
- The compensation and/or treatment available to the subject in the event of trial-related injury.
- The anticipated prorated payment, if any, to the subject for participating in the trial.
- The anticipated expenses, if any, for the subjects participating in the trial.

- That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
- That the monitor(s), the auditor(s), the Institutional Ethics Committee/IRB, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written ICF, the subject or the subject's legally acceptable representative allows such access.
- That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.
- That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participating in the trial.
- The foreseeable circumstances and/or reasons for which the subject's participation in the trial will be terminated.
- The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.
- The expected duration of the subject's participation in the trial.
- The approximate number of subjects involved in the trial.
- The consequences of a subject's decision to withdraw from the research and the procedures for orderly termination of participation by the subject.
- A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus if the subject should become pregnant) which are currently unforeseeable.
- A statement that informs the subject that while the study drug, IXT-m200, is present in their system they may react very differently to their typical doses of methamphetamine and that this response may change over time. Further, the ICF will state that it is possible that binge use of METH after receiving IXT-m200 could be extremely dangerous and possibly life-threatening.

Neither the Investigator, nor the trial staff, should coerce or unduly influence a subject to participate or continue to participate in the trial. The subjects will sign and date the IRB-approved consent form after having their questions answered. Subjects will be provided copies of the signed and dated consent form and any amendments. Original consent forms will be kept on file by the Investigator for possible inspection by Regulatory Authorities and/or the Sponsor and Regulatory Compliance persons.

13.3.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The Investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the ICF prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the ICF will be given to the participants for their records. The rights and welfare of the

participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

13.4 PARTICIPANT AND DATA CONFIDENTIALITY

Subject confidentiality is held strictly in trust by the participating investigators, their staff, and the Sponsor and their agents. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participating subjects. All personal details of subjects will be treated as confidential by the Investigator and staff, and handling of personal data will be in compliance with the Health Insurance Portability and Accountability Act of 1996 and applicable State of Utah Health Information laws.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval from the Sponsor. The Study Monitor or other authorized representatives of the Sponsor may inspect any documents maintained by the Investigator, such as available medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

Certificate of Confidentiality: To further protect the privacy of study participants, a Certificate of Confidentiality is granted by the NIH to all awardees conducting research that collects or uses identifiable, sensitive information. This study is funded by an NIH cooperative agreement with the federal award identifier number U01DA045366. This certificate protects identifiable research information from forced disclosure. It allows the Investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

13.4.1 RESEARCH USE OF STORED HUMAN SAMPLES, SPECIMENS OR DATA

Blood and urine specimens remaining after clinical safety assessments are performed will be stored only until the CSR is approved and submitted.

Blood and urine specimens remaining after PK assessments are performed will be stored by Charles River Laboratories for at least 12 months for future drug metabolism and PK analysis.

No genetic analysis will be performed.

13.5 FUTURE USE OF STORED SPECIMENS

Biological samples will be retained for no longer than 12 months following approval of the CSR and will only be used, if necessary, for repeat testing.

14 DATA HANDLING AND RECORD KEEPING

14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data Management Responsibilities: Data Management is responsible for the accuracy, quality, completeness, and internal consistency of the data from this study. Data handling, including data QC, will comply with international regulatory guidelines, including ICH GCP guidelines. Data Management and control processes specific to this study, along with all steps and actions taken regarding data management and data QC, will be described in a Data Management Plan. The Data Management Plan will be written by the Data Management Department and finalized prior to performing any data validation. MedDRA will be used for coding of AEs and concomitant diseases.

Data Capture Methods: All data will be collected on source documents and then entered in the eCRFs.

Types of Data: An appendix to the Data Management Plan (Source Identification List) will identify any data to be recorded directly in the eCRF (ie, no prior written or electronic record of data), and which data should be considered source data.

Study Records Retention: All documents concerning the study will be kept by each Investigator in appropriate archive facilities for at least 15 years after conduct of the study. The Sponsor will receive the completed eCRFs (upon request, as a PDF file).

Protocol Deviations: A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol. All deviations will be compiled in a centralized location.

Deviations will be classified by whether or not they meet the definition of important protocol deviations. Important protocol deviations are a subset of deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being. Deviations will be categorized by type and will be reviewed on an ongoing basis.

The Investigator will document and explain any deviation from the approved protocol and notify the Sponsor. Protocol deviation notification and reports are submitted to Health Authorities and/or relevant IRB according to applicable requirements/guidelines/law.

14.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

The following records must be retained by the PI:

- Signed ICFs for all subjects
- Screening log (if applicable), and enrollment log
- Record of official communications between the PI and the IRB

- Composition of the IRB or other applicable statement
- Record of all significant communications between the PI and Sponsor
- List of Subinvestigators and other appropriately qualified persons to whom the PI has delegated significant trial-related duties, together with their roles in the study and their signatures
- Copies of CRFs and of documentation of corrections for all subjects
- Drug accountability records
- Record of any body fluids or tissue samples retained
- All other source documents (patient records, hospital record copies, laboratory records, etc)
- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial)

If the PI is unable to continue to store the study records, he must contact the Sponsor to make alternative arrangements. Details of these arrangements should be documented.

14.3 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or manual of procedures requirements. The noncompliance may be either on the part of the participant, an Investigator, or study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:
- 4.5 Compliance with Protocol, Sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, Section 5.1.1
- 5.20 Noncompliance, Sections 5.20.1, and 5.20.2.

It is the responsibility of the sites to use continuous vigilance to identify and report deviations within 2 working days of identification of the protocol deviation, or within 2 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to the NIDA Program Official and Sponsor. Protocol deviations must be sent to the local IRB per their guidelines. The PIs and study staff are responsible for knowing and adhering to their IRB requirements.

14.4 PUBLICATION AND DATA SHARING POLICY

This study will comply with the National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The Sponsor will be responsible for registering and reporting the study in a public registry such as ClinicalTrials.gov.

15 STUDY ADMINISTRATION

15.1 STUDY LEADERSHIP

The Study Team will govern the conduct of the study. The Study Team will be composed of the PI, PRA Director of Global Scientific Affairs (or similar), Sponsor's Chief Medical Officer, and Sponsor's

Operations Director (or similar). The Study Team will meet as necessary to discuss significant safety issues, contemplated major protocol changes, or other items.

16 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the NIDA has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

17 LITERATURE REFERENCES

1. Owens SM, Atchley WT, Hambuchen MD, Peterson EC, Gentry WB. Monoclonal antibodies as pharmacokinetic antagonists for the treatment of (+)-methamphetamine addiction. *CNS Neurol Disord Drug Targets*. 2011;10(8):892-898.

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