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

Protocol Number: M200C-2102

IND Sponsor: InterveXion Therapeutics, LLC

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SPONSOR APPROVAL AND SIGNATURE PAGE

W. Brooks Gentry, M.D.
Chief Medical Officer

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Chief Operating Officer

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the National Institute on Drug Abuse (NIDA) Terms and Conditions of Award. The Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from InterveXion Therapeutics and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(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 a new consent needs to be obtained from participants who provided consent using a previously approved consent form.

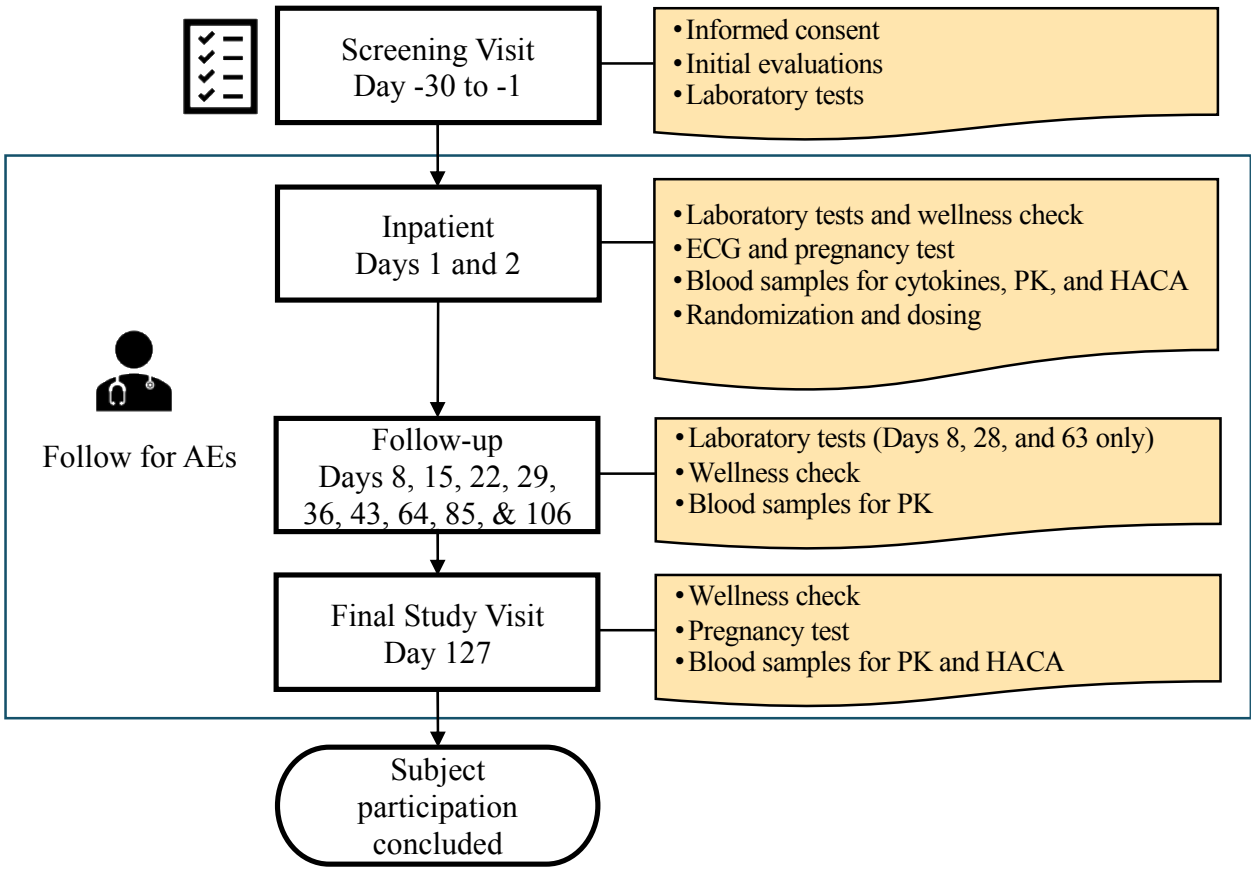
Investigator Signature/Date: _____

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	A Phase 1, Double-Blind, Randomized, Placebo-Controlled, Single-Dose Intravenous Study to Evaluate the Safety and Pharmacokinetics of IXT-m200 in Healthy Participants
Study Description:	This Phase 1 study will evaluate the safety and pharmacokinetics of a single 3-g dose of IXT-m200 given by intravenous infusion to healthy participants.
Objectives:	Primary Objective: To evaluate the safety and tolerability of a single 3-g intravenous dose of IXT-m200 in healthy participants via physical examinations and adverse event, vital sign, ECG, and clinical laboratory testing.
	Secondary Objectives: To characterize the pharmacokinetics of IXT-m200 following a single 3-g intravenous dose of IXT-m200 in healthy participants by measurement of IXT-m200 concentrations.
Endpoints:	Primary Endpoint: • Number of participants with treatment-related AEs assessed by physical examinations and vital sign, AE, ECG, and clinical laboratory testing. Secondary Endpoints: • Time course of IXT-m200 concentrations
Study Population:	Approximately 9 healthy adults will be randomized into the study.
Phase:	1
Description of Sites:	Approximately 1 site in the US will enroll participants
Description of Study Intervention:	IXT-m200 is a high-affinity chimeric anti-METH monoclonal antibody that is well-tolerated in healthy volunteers and in non-intoxicated participants with METH use disorder when administered up to 20 mg/kg (approximately 1.5 g). It will be administered at a dose of 3 g (approximately 40 mg/kg) in this study. IXT-m200 or placebo treatment will be given by intravenous infusion over 30 minutes.
Study Duration:	Approximately 5 months
Participant Duration:	18 weeks

1.2 SCHEMA


Screening Visit
Day -30 to -1
• Informed consent
• Initial evaluations
• Laboratory tests
Inpatient
Days 1 and 2
• Laboratory tests and wellness check
• ECG and pregnancy test
• Blood samples for cytokines, PK, and HACA
• Randomization and dosing
Follow for AEs
Follow-up
Days 8, 15, 22, 29,
36, 43, 64, 85, & 106
• Laboratory tests (Days 8, 28, and 63 only)
• Wellness check
• Blood samples for PK
Final Study Visit
Day 127
• Wellness check
• Pregnancy test
• Blood samples for PK and HACA
Subject
participation
concluded

1.3 SCHEDULE OF ACTIVITIES

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

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

[a] Descriptions of assessments are in Section 8.1.
[b] Study Day -1 is the day prior to the first dose. Study Day 1 is the day of the first dose.
[c] Vital sign measurements will be taken on Day 1 starting with a pre-dose measurement (≤30 min prior), then 0.25, 0.5, 1, 2, and 4 hours (±5 min) after dosing starts, and as needed afterward until normalization. Measurements will be obtained once on each non-dosing day. Each test may be repeated once at each time point if the initial result is out of range.
[d] Laboratory tests require blood and urine sampling for hematology, serum chemistry, and urinalysis. Samples are to be taken at screening, pre-dose and 2-hr post-dose completion (±10 min) on Day 1, and once on Days 2, 8, 29, and 64.
[e] ECGs are to be done pre-dose (up to 2 hr prior) and 30-min post-dose completion (±15 min) on Day 1.
[f] Cytokine samples are to be taken pre-dose (≤60 min prior) on Day 1. If a participant has an infusion reaction, cytokine sampling at 1- and 4-hours post-dose (±10 min) should be performed. If no infusion reaction is observed, pre-dose samples will not be analyzed.
[g] PK samples are to be taken pre-dose (≤30 min prior), then 1, 4, and 8 hr (±10 min) and 24 hr (±30 min) after the start of the infusion on Day 1. All other PK samples are to be collected once each visit.
[h] HACA samples are to be taken pre-dose (≤60 min prior) on Day 1 and once on Day 126.
[i] Doses will be given over 30 min by IV infusion.

2 INTRODUCTION

2.1 BACKGROUND

2.1.1 STUDY AGENT

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

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

2.1.2 NONCLINICAL IXT-M200 EFFECTIVENESS SUMMARY

A significant body of nonclinical work in rats indicates that IXT-m200 may be effective as a treatment for METH use disorders by altering METH CNS effects. The potential human efficacy of IXT-m200 is demonstrated by multiple *in vivo* preclinical studies using the murine version of the antibody, called mAb7F9. The studies and results are summarized in the Investigator's Brochure (IB).

2.1.3 NONCLINICAL SAFETY SUMMARY OF IXT-M200

InterveXion has performed multiple nonclinical safety studies with IXT-m200 which support dosing in humans, and the results of these studies are summarized in the IB. Briefly, a single-dose GLP toxicology study was performed in rats at doses up to 400 mg/kg. No test article-related mortality or evidence of systemic toxicity was observed and no target organs were identified (No Observed Adverse Effect Level (NOAEL) > 400 mg/kg). High titers of anti-IXT-m200 antibodies were detected in the serum of 1 rat each dosed at 50 mg/kg, 150 mg/kg, and 400 mg/kg. Furthermore, a repeat-dose GLP toxicology study was performed in rats using weekly dosing at doses up to 300 mg/kg/week for 26 weeks. No test-article related mortality or evidence of systemic toxicity was observed and no target organs were identified (NOAEL > 300 mg/kg). No animals in this study were confirmed positive for anti-IXT-m200 antibodies.

Additional nonclinical safety studies have also been performed in combination with METH to evaluate the potential interaction of IXT-m200 and METH. Results from these studies are also summarized in the IB, and there were no adverse effects, as measured by cardiovascular parameters or body temperature/activity, attributed to IXT-m200 administration when followed by high doses of METH.

2.1.4 CLINICAL RESEARCH SUMMARY

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

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

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

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

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

56 participants were included in the pharmacokinetic and safety sets, with 20 receiving the placebo, 18 receiving 6 mg/kg IXT-m200, and 18 receiving 20 mg/kg IXT-m200. IXT-m200 was well-tolerated. There were no SAEs and all AEs were grades 1 or 2; all resolved as expected. Importantly, IXT-m200 did not result in substantial hemodynamic changes when compared with METH alone. IXT-m200 met the primary study endpoint, and significantly ($p<0.001$) altered METH AUC and Cmax with all METH challenges, up to 30-fold and 8-fold respectively, without altering METH renal elimination . IXT-m200 decreased METH Vd over 9-fold after the first METH challenge. Though the study was not powered for pharmacodynamic changes, there were favorable trends in DEQ data, suggesting that IXT-m200 has favorable effects on the reinforcing effects of METH use. This study is discussed further in the IB.

2.2 RISK/BENEFIT ASSESSMENT

2.2.1 KNOWN POTENTIAL RISKS

2.2.1.1 GENERAL MAB POTENTIAL RISKS

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®, 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. These are outlined in the IB along with a summary of the nonclinical toxicology studies of IXT-m200 in absence and presence of high-dose METH in rats.

2.2.1.2 SPECIFIC IXT-M200 POTENTIAL RISKS

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

There were 3 adverse events in 2 subjects that were attributed to IXT-m200. A mild infusion reaction (CTCAE v.4.0 Grade 3) and bronchospasm (Grade 2) occurred in the same subject. The symptoms included a brief period of bronchospasm with no drop in oxygen saturation that resolved with stopping the infusion. A separate subject experienced an AE of mild proteinuria (Grade 1). Both subjects were in the same dose group (2 mg/kg IXT-m200).

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

Because 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 participants were confirmed positive for HACA in the Phase 1 study. The development of HACA did not appear to be dose-related.

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

Finally, as in the Phase 1 study, samples from all participants were tested for HACA. Only one participant in each IXT-m200 dose group had notable titers of anti-IXT-m200 antibodies, and the PK of IXT-m200 in these participants did not differ from other participants in the dose group.

2.2.2 KNOWN POTENTIAL BENEFITS

IXT-m200 is an investigational product which has no pharmacologic activity beyond binding METH, and will convey no benefit to participants who do not use METH.

2.2.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The risks of exposing the participants to IXT-m200 are justified to determine its safety at this increased dose level of 3 g.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
Primary	
To evaluate the safety and tolerability of a single 3-g intravenous dose of IXT-m200 in healthy participants.	Number of participants with treatment-related AEs assessed by physical examinations and vital sign, ECG, and clinical laboratory testing.
Secondary	
To characterize the pharmacokinetics of IXT-m200 following a single 3-g intravenous dose of IXT-m200 in healthy participants.	Time course of IXT-m200 concentrations

4 STUDY DESIGN

4.1 OVERALL DESIGN

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

4.2 JUSTIFICATION FOR DOSE

The IXT-m200 dose of 3 g was selected for this study because it is potentially effective in reducing METH effects for several weeks, and will be used in an upcoming repeat-dose Phase 2 clinical study in patients with METH use disorder. Prior to this Phase 2 study, safety and pharmacokinetics of a single 3-g dose in healthy volunteers will be established.

IXT-m200 will be administered via IV infusion over 30 min. This is necessary because it is a protein medication and would be metabolized to inactive components in the gastrointestinal tract if administered orally. The volume that must be given is too large to allow for intramuscular or subcutaneous administration based on the current formulation. This will result in a rate of 40 mg/kg/hr in a 75-kg person, which is significantly lower than doses given during a multiple-dose GLP toxicology study in which the slowest rate for the high dose was 1800 mg/kg/hr.

4.3 END OF STUDY DEFINITION

A participant is considered to have completed the study if s/he has completed all phases of the study including the last visit or last scheduled procedure shown in 1.3. The end of the study is defined as completion of the last visit or procedure in the trial globally.

Participants who have an ongoing AE at the time of study completion will be followed as described in 8.2.5.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Eligible participants will:

1. Be at least 18 years of age at the time of study consent;
2. Be able and willing to read, comprehend, and give Authorization for Use/Disclosure of Health Information (HIPAA) and informed consent;
3. Be healthy, based on the pre-study medical evaluation (medical history and physical exam, vital signs, ECG, and clinical laboratory evaluations);
4. Be willing to comply with study instructions and dosing, agree to make all appointments, and complete the entire course of the study;
5. Be of nonchildbearing potential or agree to use protocol-specified method(s) of birth control throughout study participation;
6. Agree to adhere to Lifestyle Considerations throughout study duration (see section 5.3).

5.2 EXCLUSION CRITERIA

Eligible participants will NOT:

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

5.3 RATIONALE FOR THE SELECTED POPULATION

Phase 1 PK and safety studies have frequently been done in healthy subjects with many chimeric mAbs, including IXT-m200[1]. This study is designed to increase the dose level tested in healthy participants prior to testing in patients that use METH.

5.4 LIFESTYLE CONSIDERATIONS

IXT-m200 may alter the pharmacokinetics of molecules that are structurally similar to METH; therefore, participants should not take drugs such as amphetamine (including Adderall®, Dexedrine®, or Evekeo®) or MDMA (also known as ecstasy) for the duration of study participation.

Participants 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.

Participants 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.

Participants are required to practice an adequate method of birth control, including intrauterine device (IUD); oral, dermal ("patch"), implant or injected contraceptives; tubal ligation; barrier methods with spermicide; or vasectomized partner throughout the study.

5.5 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a short term or temporary medical issue may be rescreened (≥30 days later).

5.6 STRATEGIES FOR RECRUITMENT AND RETENTION

Traditional advertising methods will be utilized to ensure recruitment goals are met. This will be accomplished by using advertising such as print, electronic, and/or digital newspapers, flyers, mailers, billboards, television, radio, online, social networking, and other means of communicating with potential participants that are IRB-approved. The site subject database may also be searched to identify potential participants.

All recruitment materials will refer interested persons to a contact email, website, or telephone number, and they will be approached by a study staff member trained to provide the caller with information about the study and to schedule interested persons for an in-person interview. Participants will undergo an initial screening and those who pass the initial screen will undergo informed consent procedures.

To address retention, we will incorporate standard procedures used in previous Phase 1 trials, which include financial compensation for study participation.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

The study drug, IXT-m200, is a chimeric mAb that binds METH with high affinity. The product contains a murine METH-binding variable region and the constant domains of a human IgG 2κ. This antibody isotype was chosen because of the lower risk of immune response compared to an IgG1 or IgG3. IXT-m200 specifically targets METH and does not rely on binding to any endogenous target for its action.

6.1.2 DOSING AND ADMINISTRATION

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

Participants should lie supine or semi-reclined during dose administration. Each dose will be given with an infusion pump over 30 minutes with a 50-mL saline flush dispensed after each dose to ensure the entire dose is flushed through the infusion set. The study drug infusion start/stop time, infusion rate, infusion volume, whether the infusion was completed, if it was stopped, or stopped and restarted will be recorded.

Participants will be asked to eat a light meal prior to arriving at the study center but not have anything but clear liquids to eat or drink for 1 hour before appointment time. Participants will be offered a light meal after dosing completion.

All study drug doses will be administered in a blinded manner by the Investigator or designee.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Study Drug: All required IXT-m200 vials will be shipped by Sponsor to the study site 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.

Placebo: An unblinded member of the site staff will be responsible for acquiring commercially available normal saline for use as placebo for IXT-m200.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Study Drug: IXT-m200 is formulated as a 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 glass vials with stoppers and flip-off seals. Catalent Pharma Solutions manufactures the formulated active pharmaceutical ingredient.

Labels will be similar to the following:

InterveXion Therapeutics®
Anti-methamphetamine IXT-m200
18.5-21.5 mg/mL
Manufactured: DD MMM YYYY
DP Lot: XXXXXXX
Catalent Lot: XXXXX
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

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

Only unblinded study staff will have access to the labeled study drugs.

6.2.3 PRODUCT STORAGE AND STABILITY

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.

6.2.4 PREPARATION

An unblinded staff member (e.g., pharmacist) will prepare the study drugs for administration. The appropriate amount of IXT-m200 should be administered over 30 min. Since IXT-m200 is a clear solution, it will appear similar to saline placebo.

Placebo: Normal saline requires no preparation prior to administration.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Each potential participant will be assigned a unique number in the screening process (screening number). This number will be used to identify the participant throughout the study.

Participants who qualify will be randomized on Day 1 to 3 g IXT-m200 or placebo (7:2).

Unblinding of treatment assignment during the study is discouraged and should occur only if it is absolutely necessary for the Investigator, Sponsor, or participant to know what he or she received for safety reasons. If the Sponsor or the Investigator deems identification of the study drug to the participant as necessary for the purpose of providing urgent care, the pharmacy will inform the Investigator of the assignment, who will notify the Sponsor and participant. The process of unblinding will be appropriately documented in the Investigator file. The date and reason for the unblinding must be recorded. When

possible, the Sponsor should be notified prior to unblinding; otherwise, they must be notified within 24 hours after unblinding.

6.4 STUDY INTERVENTION COMPLIANCE

Study drug is administered by intravenous infusion by qualified personnel who are blinded to the treatment assignment of the participant. Compliance with dosing will be verified by reference to the CRF documentation of dosing.

6.5 CONCOMITANT THERAPY

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

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

The criteria outlined in section 8.2.3.1 will be used to categorize the severity of all AEs. The Sponsor, in consultation with the Investigator, will suspend enrollment until a full safety review is performed if any 1 of the following events occurs, unless the event was clearly unrelated to study drug administration:

- Two (2) participants experience a Grade 3 AE; or,
- One (1) participant experiences a Grade 4 AE; or,
- A death occurs.

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

A decision to reinitiate enrollment will be made by the Sponsor following any necessary consultation with the appropriate authorities based on the results of the safety review. All other study procedures will continue per protocol during any study pause.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants who withdraw consent for future study visits (following early termination assessments) will be considered ‘withdrawn’. Participants are free to withdraw at any time upon request; they will be asked to complete early termination assessments as soon as possible.

Participants that receive less than the complete single dose of study drug but agree to continue participation in other study procedures and assessments will be considered ‘discontinued’. Participants are free to discontinue at any time during dosing upon request. Participants will be encouraged to complete study visits and assessments, even if they elect to discontinue study drug administration. In this case, all study activities will be completed per protocol with the exception of dose administration.

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

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

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

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

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for the final scheduled visit, including an early term visit, and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 SAFETY AND OTHER ASSESSMENTS

Assessments are to be performed at the time points described in the Schedule of Activities (1.3).

8.1.1 ELIGIBILITY CRITERIA

- Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria checklist should be used to assess participants for Substance Use Disorders (including METH, opioids, alcohol, nicotine, marijuana, etc.)

- Urine drug screen to include illicit substances (barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, MDMA, METH, or amphetamine) on Day 1 (a positive test for tetrahydrocannabinol may be acceptable if the subject is not intoxicated at the discretion of the Investigator).

8.1.2 MEDICAL AND MEDICATION HISTORY

- A complete medical history will be obtained by interview and any available medical records at screening. Interim medical history will be obtained at all subsequent time points.
- A complete medication history will be obtained by interview and any available medical records at screening, with particular attention to any medications taken in the previous 12 months. The medication history, including concomitant medications, will be updated at all subsequent visits.

8.1.3 VITAL SIGNS

- Vital sign measurements (heart rate, blood pressures [systolic and diastolic], respiratory rate, temperature [oral], and pulse oximetry readings) will be obtained after the participant has been resting for at least 5 minutes.

8.1.4 PHYSICAL EXAM

- Physical examination (excluding rectal/genital and breast examination) will consist of an examination of the following: general appearance, neurological, skin, head, eyes, ears, nose, throat, neck, lymph nodes, chest, heart, abdomen, and extremities.
- Targeted physical exams will include heart, lungs, abdomen, skin, and site of injection. Additional areas may be targeted if AEs or other complaints require appropriate and more detailed exams.
- Height and weight will be recorded at screening; weight will be recorded at subsequent visits.

8.1.5 PSYCHIATRIC EVALUATION

- A psychiatric history will be obtained at screening evaluating for (but not limited to) the following: major current depression, psychosis, bipolar illness, organic brain disorder, anorexia nervosa or bulimia disorder or dementia, which require ongoing medication or which would make study compliance difficult in the opinion of the Investigator.

8.1.6 PREGNANCY TEST

- Urine pregnancy tests will be performed on all females at designated visits.

8.1.7 LABORATORY TESTS

The below laboratory tests will be centrally assessed:

- 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.
- 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.

8.1.8 ELECTROCARDIOGRAMS

- Electrocardiograms (12-lead) will be recorded after the participants have been supine for 5 minutes. Standard ECG parameters including heart rate, 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.
- Confirmed ECG anomalies will be referred for appropriate medical follow-up.

8.1.9 BLOOD FOR PK/HACA AND CYTOKINES

- PK of IXT-m200: A validated enzyme linked immunosorbent assay procedure will be used to quantitate IXT-m200 in serum samples. Approximately 1 mL per sample is required.
- HACA: A validated electrochemiluminescent procedure has been developed to quantitate HACA in serum samples. Approximately 1 mL per sample is required. These samples may be analyzed after the completion of this study.
- Cytokine panel to include at a minimum IL-6, IL-8, and TNFα levels will be determined only if any study drug infusion reaction occurs.

8.2 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.2.1 DEFINITION OF ADVERSE EVENTS (AE)

An AE is any untoward medical occurrence in a person administered study drug, whether or not considered intervention-related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not related to the IXT-m200 dose.

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".

8.2.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An SAE is an AE that at any dose:

- results in death;
- is life-threatening;
- requires 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 person 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 person or may require intervention to prevent one of the other outcomes listed above. These will also usually be considered serious.

8.2.3 CLASSIFICATION OF AN ADVERSE EVENT

8.2.3.1 SEVERITY OF EVENT

The general approach outlined by the Club Phase 1 working group in the British Journal of Clinical Pharmacology[2] will be used to categorize the severity of all AEs. The stopping rules outlined in Section 7.1 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.

For example, 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 (SaO2 < 93% on oxygen) occurs and requires medications, this will constitute a Grade 3 reaction, and will be documented as such.

8.2.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

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 participant's clinical state.

POSSIBLY – The AE:

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

UNLIKELY – The AE:

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

UNRELATED – The AE:

- is definitely produced by the participant's clinical state or by other modes of therapy administered to the participant.

8.2.3.3 EXPECTEDNESS

The Sponsor 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.

8.2.4 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, during engagement of the participant with the smartphone app, 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 CRF. 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.

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 Investigator will record all reportable events with start dates occurring any time after informed consent is obtained until 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.

8.2.5 ADVERSE EVENT REPORTING

All AEs (whether serious or nonserious) that occur after the participant has been randomized into a treatment group must be documented on the appropriate pages of the CRF. For all AEs, the Investigator 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 participants 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 to a maximum of 30 days following the end of study visit. Should the AE result in death, a full pathologist's report should be supplied, if possible.

8.2.6 SERIOUS ADVERSE EVENT REPORTING

The Investigator 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 Sponsor within 24 hours of site awareness.
- Other SAEs regardless of relationship, will be submitted to the 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 Sponsor and should be provided as soon as possible.

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.

The study Sponsor will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. In addition, the Sponsor must notify FDA and all participating Investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

The NIDA Project Officer (PO) 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).

8.2.7 REPORTING EVENTS TO PARTICIPANTS

It is not anticipated that safety updates, including AEs or SAEs, will be reported to study participants.

8.2.8 EVENTS OF SPECIAL INTEREST

Not applicable.

8.2.9 REPORTING OF PREGNANCY

If a participant is found to be pregnant after they have received study drug, they should complete the study, with no further study drug doses administered, and be followed to determine the outcome of the pregnancy if the participant 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.

8.3 UNANTICIPATED PROBLEMS

8.3.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

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.

8.3.2 UNANTICIPATED PROBLEM REPORTING

Investigators will adhere to the following guidelines for prompt reporting:

- Unanticipated problems that are SAEs should be reported to the IRB within 1 week of the Investigator becoming aware of the event.

- Any other unanticipated problem should be reported to the IRB within 2 weeks of the Investigator becoming aware of the problem.

All unanticipated problems should be reported by the Sponsor to the supporting Department of Health and Human Services (DHHS) agency head (or designee), and Office for Human Research Protections (OHRP) within one month of the IRB's receipt of the report of the problem from the Investigator.

In some cases, the requirement for prompt reporting may be met by submitting a preliminary report to the IRB, the supporting DHHS agency head (or designee), and OHRP, with a follow-up report submitted at a later date when more information is available. Determining the appropriate time frame for reporting a particular unanticipated problem requires careful judgment by persons knowledgeable about human participant protections. The primary consideration in making these judgments is the need to take timely action to prevent avoidable harms to other participants.

8.3.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

It is not expected that unanticipated problems will be reported to study participants, although appropriate study-related actions may be undertaken if determined necessary.

9 STATISTICAL CONSIDERATIONS

A statistical analysis plan (SAP) will be prepared after the protocol is approved. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. The SAP will serve as a complement to the protocol and supersedes it in case of differences.

9.1 STATISTICAL HYPOTHESES

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

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

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

9.2 SAMPLE SIZE DETERMINATION

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

9.3 POPULATIONS FOR ANALYSES

The study analysis populations will consist of:

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

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

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

The results of this study will be reported using summary tables, figures, and data listings. All summaries will be by treatment group.

9.4.2 SAFETY ANALYSES

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

9.4.3 BASELINE DESCRIPTIVE STATISTICS

Demographic and baseline characteristics (age, sex, race, ethnicity, body weight, height, and BMI) will be summarized by treatment group using descriptive statistics for the Safety population.

9.4.4 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Participant-level listings will include collected data by treatment group and timepoint.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting the screening process, and subsequently administering study intervention. Other information may be provided to potential participants to help describe the nature and objectives of the study and clinical research in general, including access to web-based material describing the study. All such participant-facing information will be approved in advance by the study's IRB.

10.1.1.2 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. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The Investigator or designee 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 advisors or think about it prior to agreeing to participate. The participant will sign the Informed Consent Form (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.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated at the sole discretion of the Sponsor. Written notification, documenting the reason for study suspension or termination, will be provided by the Sponsor to Investigators, NIDA, and, if necessary, FDA. Investigators will notify participants and the IRB. Sponsor will provide the reason(s) for the termination or suspension. Participants will be contacted, as applicable, and informed of changes to the study visit schedule.

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

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

- Determination of futility.

At the discretion of the Sponsor, if temporarily suspended, the Study may resume once any relevant concerns have been addressed.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant 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 participants. All personal details of participants 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 any applicable state laws governing the individual study sites. The study participants' contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, institutional policies, or Sponsor requirements.

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, IRB or regulatory agencies may inspect any documents maintained by the Investigator, such as available medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

Certificate of Confidentiality (COC): To further protect the privacy of study participants, a COC is granted by the National Institutes of Health (NIH) to all awardees conducting research that collects or uses identifiable, sensitive information. 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.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored as described above. After the study is completed, the de-identified, archived data will be maintained as long as regulations require, and will be made available by the Sponsor for use by other researchers including those outside of the study via a data sharing agreement.

Blood and urine specimens remaining after clinical safety assessments are performed will be stored only until the clinical study report is completed.

Blood specimens remaining after PK assessments are performed will be stored for at least 12 months for future drug metabolism and PK analysis if needed.

No genetic analysis will be performed.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Sponsor Contact	Principal Investigator
W. Brooks Gentry, MD	Magdy L Shenouda, MD
InterveXion Therapeutics, LLC	Clinilabs
4301 W. Markham St. #831	4 Industrial Way West, 2nd Floor
Little Rock, AR 72205	Eatontown, NJ 07724
501-320-7601	212-994-4569
gentrywilliamb@uams.edu	mshenouda@clinilabs.com

10.1.6 SAFETY OVERSIGHT

As a Phase 1 study specifically designed to determine safety of a single 3-g dose of IXT-m200, robust evaluation of safety parameters and safety oversight will be conducted. The clinical site has been selected based on its track record as a Phase 1 safety unit, with all available resources for detection and management of any observed adverse events during the study. The Investigator will directly monitor participant safety and make real-time recommendations for any necessary interventions or study modifications to the Sponsor's Medical Liaison.

10.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of study participants 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).

Data at clinical sites will be monitored by one or more Study Monitors. Throughout the course of the study, the Study Monitor will make frequent contact with the Investigator. 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 participant's medical records including verification of informed consent). This will require direct access to all original records for each participant (e.g., clinic charts).

The Study Monitor will also perform drug accountability checks and will request to perform a review of the Investigator's 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 Investigator, 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 Investigator will permit inspection of the study files by authorized representatives of the Sponsor or regulatory agencies.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

The clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation, and completion. Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification and resolution.

Following written Standard Operating Procedures (SOPs), the Study Monitor will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, GCP, and other applicable regulatory requirements.

The investigational site will provide direct access to all source data/documents and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at each site under the supervision of the site Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Data recorded in the CRF(s) derived from source documents should be consistent with the data recorded on the source documents. Hardcopies of any source document(s) used for recording data for each participant enrolled in the study will be filed at the investigative site to be reviewed by the Study Monitor for accuracy.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into a 21 CFR Part 11-compliant data capture system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.9.2 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 Investigator:

- Signed ICFs for all participants
- Screening log (if applicable), and enrollment log
- Record of official communications between the site and the IRB
- Composition of the IRB or other applicable statement
- Record of all significant communications between the site and Sponsor
- List of sub-Investigators and other appropriately qualified persons to whom the Investigator 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 participants
- Drug accountability records
- Record of any body fluids or tissue samples retained

- All other source documents (medical 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 Investigator is unable to continue to store the study records, s/he must contact the Sponsor to make alternative arrangements. Details of these arrangements should be documented.

10.1.10 PROTOCOL DEVIATIONS

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

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 site to use continuous vigilance to identify and report deviations in a timely manner. The Investigator will document and explain any deviation from the approved protocol in the study source documents and notify the Sponsor. Protocol deviations may need to be sent to the reviewing IRB, depending on the nature of the deviation and the IRB guidelines. The Investigators and study staff are responsible for knowing and adhering to the IRB requirements.

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 participant's rights, safety, or well-being. Deviations will be categorized by type and will be reviewed on an ongoing basis.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will comply with the 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.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at www.clinicaltrials.gov, and results information from this trial will be submitted to www.clinicaltrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

10.1.12 CONFLICT OF INTEREST POLICY

Any 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 Sponsor has established policies and procedures to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMI	Body Mass Index
CFR	Code of Federal Regulations
CI	Confidence Interval
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine Phosphokinase
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DHHS	Department of Health and Human Services
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG	Electrocardiogram
ET	Early termination visit
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
HACA	Human Anti-Chimeric Antibodies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICF	Informed Consent Form
IgG	Immunoglobulin G
IND	Investigational New Drug Application
IRB	Institutional Review Board
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
METH	Methamphetamine
MDA	Methylenedioxyamphetamine
MDMA	MethylenedioxyMETH
NIH	National Institutes of Health
NIDA	National Institute on Drug Abuse
NOAEL	No Observed Adverse Effect Level
OHRP	Office for Human Research Protections
PK	Pharmacokinetics
PO	Program Officer
QC	Quality Control
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAETRS	Serious Adverse Event Tracking and Reporting System
SAP	Statistical Analysis Plan

SOC	System Organ Class
SOP	Standard Operating Procedure
STAMPOUT	Study of Antibody for Methamphetamine Outpatient Therapy
UP	Unanticipated Problem
US	United States
Vd	Volume of Distribution
WBC	White Blood Cell

10.3 PROTOCOL AMENDMENT HISTORY

Version - Date	Description of Change	Brief Rationale
1 - 25 Aug 2021	Not applicable	New protocol

11 REFERENCES

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

2. Sibille M, Patat A, Caplain H, Donazzolo Y. A safety grading scale to support dose escalation and define stopping rules for healthy subject first-entry-into-man studies. Br J Clin Pharmacol 2010; 70:736–48.