# METH-OD: A PHASE 2A STUDY OF IXT-M200 IN PATIENTS WITH TOXICITY FROM METHAMPHETAMINE OVERDOSE

**Protocol Number: M200C-2101**

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## SPONSOR APPROVAL AND SIGNATURE PAGE

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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.

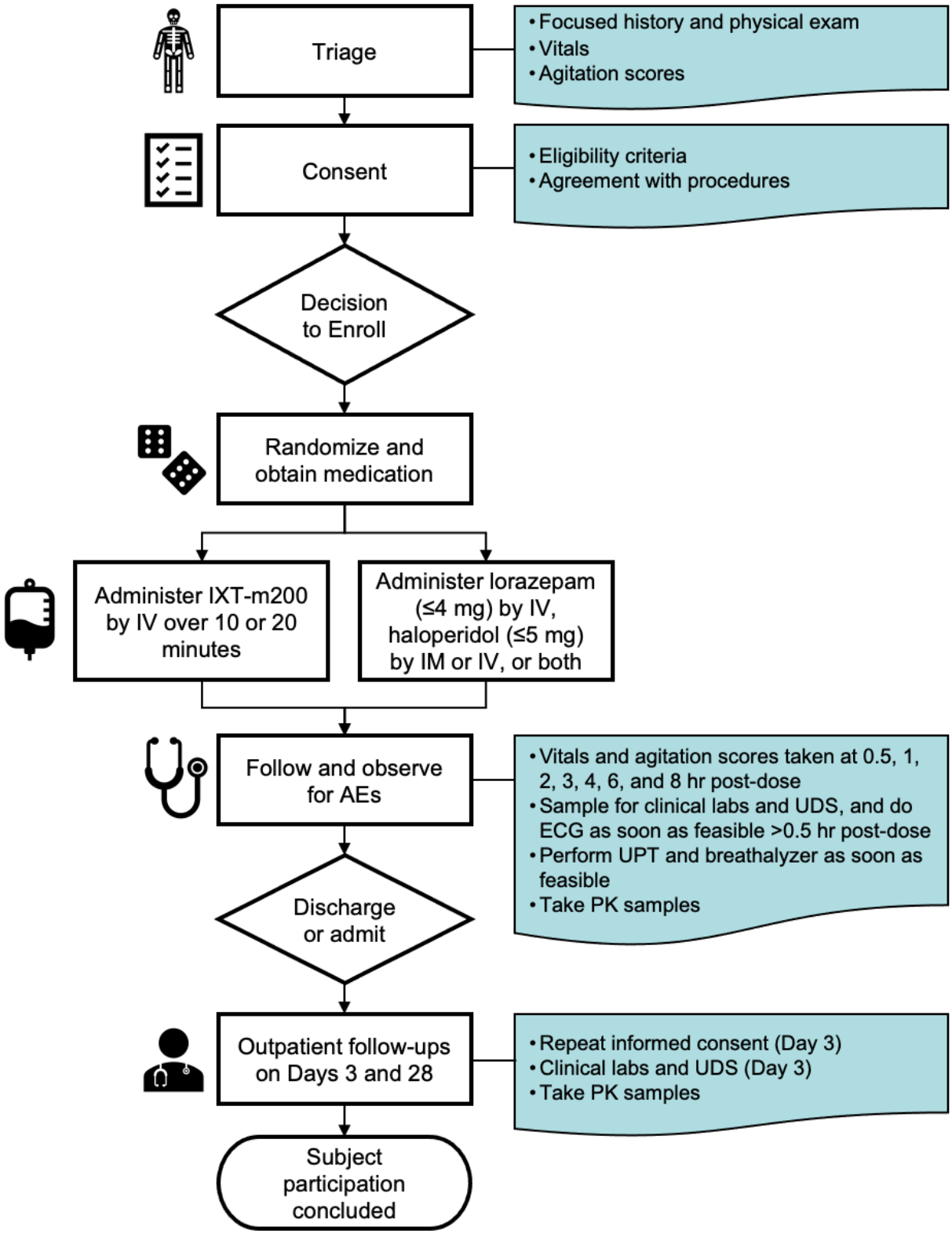
Investigator Signature/Date: _____

# 1. PROTOCOL SUMMARY

## 1.1. SYNOPSIS

| | |
|---|---|
| **Title:** | Meth-OD: A Phase 2a Study of IXT-m200 in Patients with Toxicity from Methamphetamine Overdose |
| **Study Description:** | The proposed study is a randomized, open-label Phase 2a study of IXT-m200 versus treatment-as-usual (TAU) in which patients with mild to moderate methamphetamine (METH) toxicity will be treated with IXT-m200 or lorazepam and/or haloperidol. The hypothesis is that IXT-m200 will be well-tolerated in patients with acute mild to moderate METH toxicity. |
| **Objectives:** | Primary Objective: To evaluate the safety and tolerability of IXT-m200 in patients with mild to moderate METH toxicity.<br>Secondary Objectives: To determine the time course and degree of normalization of agitation and vital signs, and to determine the percentage of participants in each group requiring rescue medications for psychiatric or cardiovascular manifestations of METH intoxication. |
| **Endpoints:** | Primary Endpoint:<br>• Safety and tolerability of IXT-m200 as measured by physical examinations and vital sign, adverse event (AE), electrocardiogram (ECG), and clinical laboratory testing.<br>Secondary Endpoints:<br>• Agitation/sedation scores over time as measured with the ACES (Agitation/Calmness Evaluation Scale);<br>• Vital signs including blood pressure, heart rate and temperature over time;<br>• Need for rescue medications to treat:<br>  ○ agitation, dysphoria, or psychosis (CNS signs/symptoms)<br>  ○ hypertension, tachycardia, or other cardiovascular instability (CV signs/symptoms).<br>Exploratory Endpoints:<br>• Emergency department (ED) length of stay as measured by disposition order time minus triage time, and by disposition order time minus start of treatment time, with log transformation. |
| **Study Population:** | Approximately 24 males and females aged 18-45, presenting to an ED setting with mild to moderate METH toxicity who request treatment for symptoms related to their METH use will be recruited. |
| **Phase:** | 2a |
| **Description of Sites Enrolling Participants:** | Approximately 5 ED sites 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 people with METH use disorder. The total dose will be given over 10 min for the 0.5-g dose and over 20 min for higher doses. Lorazepam is a benzodiazepine that is safe and commonly used to treat agitation and dysphoria in the emergency setting. Haloperidol is commonly used to treat agitation due to psychosis. |
| **Study Duration:** | Approximately one year |
| **Participant Duration:** | 28 days |

## 1.2. SCHEMA


Triage
• Focused history and physical exam
• Vitals
• Agitation scores
Consent
• Eligibility criteria
• Agreement with procedures
Decision to Enroll
Randomize and obtain medication
Administer IXT-m200 by IV over 10 or 20 minutes
Administer lorazepam (≤4 mg) by IV, haloperidol (≤5 mg) by IM or IV, or both
Follow and observe for AEs
• Vitals and agitation scores taken at 0.5, 1, 2, 3, 4, 6, and 8 hr post-dose
• Sample for clinical labs and UDS, and do ECG as soon as feasible >0.5 hr post-dose
• Perform UPT and breathalyzer as soon as feasible
• Take PK samples
Discharge or admit
Outpatient follow-ups on Days 3 and 28
• Repeat informed consent (Day 3)
• Clinical labs and UDS (Day 3)
• Take PK samples
Subject participation concluded

## 1.3. SCHEDULE OF ACTIVITIES (SOA)

| Assessment | Triage | Screening | Dosing and Assessments [f] | | | | | | | | | | | | | Follow-up[a] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study Day | 1 | 1 | 1 | | | | | | | | | | | | Day not specified | 3 (+2) | 28 (±7) |
| Hour | NA | <0 | <0 | 0 | 0.25 | 0.5 | 0.75 | 1 | 1.5 | 2 | 3 | 4 | 6 | 8 | >8, <Discharge from ED | Discharge from ED | NA | NA |
| Focused history and physical exam [b, c] | | X | | | | | | | | | | | | | | | X | X |
| Focused review of systems [b, c] | | X | | | | | | | | | | | | | | X | X | X |
| Medication history | | X | | | | | | | | X | | | | | | | | |
| Detailed and pertinent psychiatric history [c, d] | | X | | | | | | | | | | | | | | | | |
| Vital Signs [c] | | X | X | | | X | | X | | X | X | X | X | X | As needed | X | X | X |
| Agitation score [c] | | X | | X | | X | | X | | X | X | X | X | X | As needed | | | |
| Informed consent and UBACC | | X | | | | | | | | | | | | | | | X | |
| Eligibility criteria | | X | | | | | | | | | | | | | | | | |
| Randomization | | | X | | | | | | | | | | | | | | | |
| PK samples [d] | | | X | | | | | | | | | X | | | | X | X | X |
| Dose administration | | | | X | | | | | | | | | | | | | | |
| Observe for AEs | | | | | X | X | X | X | X | X | X | X | X | X | As needed | X | X | X |
| Assess for rescue meds | | | | | | X | | X | | | | X | | | As needed | X | | |
| Clinical labs and ECG | | | | | | Once, as soon as feasible | | | | | | | | | | | X | |
| UDS, UPT, Breathalyzer | | | Once, as soon as feasible | | | | | | | | | | | | | | | |
| Detailed and pertinent medical history [e] | | | | | | | | | | X | | | | | | | | |
| DSM5 SUD checklist | | | | | | | | | | | | | | | | | X | |
| Drug use assessment and Meth Perception Assessment | | | | | | | | | | | | | | | | | X | X |

AE – adverse event; UDS – urine drug screen; UPT – urine pregnancy test; ECG – electrocardiogram; DSM5 SUD – Diagnostic and Statistical Manual of Mental Disorders 5 for Substance Use Disorders; NA – not applicable; UBACC – UCSD Brief Assessment of Capacity to Consent

[a] If participants do not return for a follow-up visit, a phone call will be attempted to assess any AEs.

[b] Focused history, physical exam and review of systems based on main complaint, related details from other parts of the medical history and physical exam, and eligibility criteria.

[c] Assessments will be obtained as either part of triage or screening, depending on the site. PANSS-EC will be done at screening only; ACES will be done at each time point as marked.

[d] PK samples will be drawn for both IXT-m200 and METH per section 8.2.

[e] Detailed and pertinent history includes pertinent past medical, family and social histories in addition to focused history. Detailed physical exam to be completed if indicated by detailed and pertinent medical history.

[f] Subjects may be discharged at any time point after the 2-hr assessments are completed if the subject is deemed medically eligible; assessments at Day 1, Hours 3-8 may be skipped if discharged. Assessments assigned for the time of discharge from ED should be completed for all subjects.

# 2. INTRODUCTION

## 2.1. STUDY RATIONALE

No direct antagonists have been approved, or even clinically evaluated, for treatment of METH overdose. In fact, no medications have been approved for any form of METH Use Disorder (MUD) [1]. Emergency care providers use a variety of medications to manage patients with METH toxicity based on the primary presenting symptoms and their individual and institutional experience. Mild to moderate agitation and dysphoria may be treated with benzodiazepines or antipsychotic medications [2]. Severe CNS agitation and delirium are treated with combinations of benzodiazepines, antipsychotics, and other sedatives (e.g., ketamine) [2]. The cardiovascular and cerebrovascular effects of METH overdose are treated with combinations of vasodilators, beta and calcium channel blockers, and anti-arrhythmic medications [3]. Altogether, given the lack of targeted therapies, ED management of patients presenting with METH toxicity is symptomatic at best, intended only to reduce and/or mask the acute physiologic effects of METH until it can be cleared by metabolism and excretion. Furthermore, patients with METH toxicity may be hypersomnolent during metabolism of METH and repletion of monoamines and adenosine triphosphate. These sedative effects, especially when combined with sedative effects of benzodiazepines or other sedatives, may delay ED discharge and increase length of stay [4] at best, and may result in compromise of ventilation at worst. **A single pharmacokinetic antagonist medication that results in a calmer, cooperative patient without sedation would offer a clear advantage over current pharmacologic approaches for the management of agitation associated with METH overdose.**

IXT-m200, a chimeric monoclonal antibody (mAb) that binds METH with high affinity, has been evaluated in a Phase 2a study in non-treatment-seeking people who use METH (NCT03336866). Data from multiple studies in rats show that METH effects, such as increased locomotor activity, are quickly reduced following treatment with anti-METH antibodies [5,6].This is accompanied by reductions in brain METH concentrations. Preliminary results from the Phase 2a study in otherwise healthy people with MUD indicate that IXT-m200 greatly reduces METH volume of distribution by sequestering METH in the blood, as expected based on animal data. The antibody also appears to be well-tolerated in healthy people who do and do not use METH. Together, these results suggest that IXT-m200, a specific METH pharmacokinetic (PK) antagonist, could be an effective treatment for METH overdose.

## 2.2. BACKGROUND

**Study Intervention**
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) [7,8].

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 in its active sites in the brain. IXT-m200 may therefore decrease both the CNS and hemodynamic effects of METH [5,6].

**Nonclinical IXT-m200 Effectiveness Summary**
A significant body of nonclinical work in rats indicates that anti-METH antibodies quickly reduce METH effects and brain concentrations after administration. The potential human efficacy of IXT-m200 is

demonstrated by several *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) [5,6,9].

**Nonclinical Safety Summary of the Interaction of IXT-m200 with METH**
A series of nonclinical studies was completed in rats to address the potential for IXT-m200 to exacerbate METH effects, specifically cardiovascular 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) in an effort to overcome the reduction of METH effects by the antibody.

In each of the studies, rats were acclimated over a 14-day period to make them tolerant to high doses of METH, similar to what occurs in people who chronically use METH. 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 at 6 mg/kg spaced 2 hours apart. This binge dosing regimen was repeated on Days 21 and 24 for certain studies and groups.

The studies (GLP toxicology, cardiovascular effects, METH PK, and METH distribution) collected different outcome measurements while using the same METH administration protocol. Results are summarized in the IB. **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.**

**Clinical Research Summary**
A Phase 1 study of the safety of single doses of IXT-m200 in healthy humans has been completed [10]. In this study, 42 subjects (17 females) were dosed in 5 groups (0.2, 0.6, 2, 6, and 20 mg/kg IXT-m200, which are approximately 15 – 1500 mg in an average 75-kg subject), 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/day. 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. 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 investigator heard a single expiratory wheeze. The infusion was stopped and the subject was treated with solumedrol 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 (i.e., 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 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 a range from 0.2 to 20 mg/kg. Therefore, a maximum tolerated dose was not reached.

A Phase 2a study of the effect of IXT-m200 on METH pharmacokinetics and METH pharmacodynamics has been completed in otherwise healthy people who use METH. The primary goals of this study, called

STAMPOUT (Study of Antibody for Methamphetamine Outpatient Therapy, NCT03336866), were to show that IXT-m200 alters the PK of METH and reduces the reinforcing subjective effects that perpetuate METH use. In addition, the safety and tolerability of the effect of single IV doses of IXT-m200 (6 or 20 mg/kg, which were up to 2000 mg) were determined in this population. In STAMPOUT, non-treatment-seeking people who had MUD received a single dose of IXT-m200 followed by weekly METH challenges. Serial blood samples and urine collections were analyzed to determine METH PK changes due to the antibody dose. Drug effects questionnaires were given after METH challenges to quantify the impact of IXT-m200 on the subjective effects of METH.

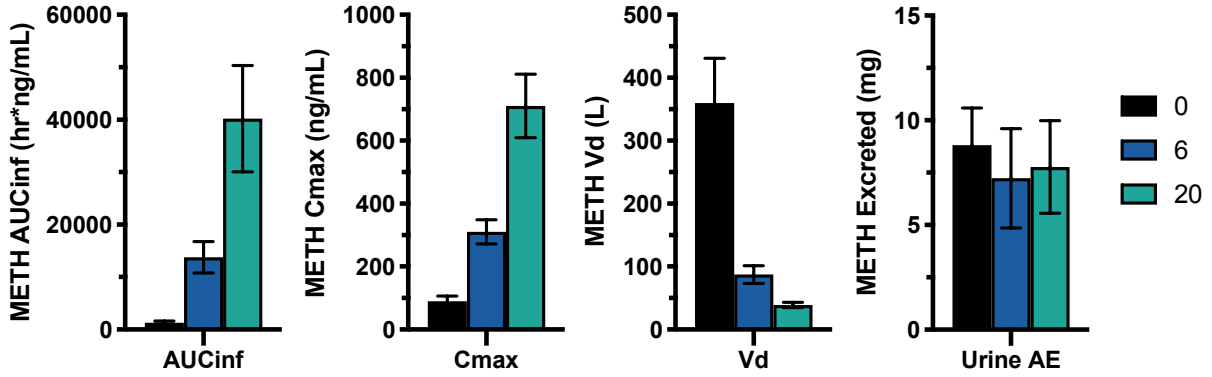



**Figure 1. METH PK data from STAMPOUT interim analysis demonstrate IXT-m200 alters METH distribution.** Area under the curve from time 0 through infinity (AUCinf), maximum METH concentration (Cmax), volume of distribution (Vd), and cumulative urinary excretion over 36 hr (Urine AE) data are plotted as group means ± SD. IXT-m200 (0, 6, or 20 mg/kg, IV) was administered one day prior to METH (30 mg, IV).

In a pre-specified interim analysis of PK and safety data, METH PK parameters were estimated and summarized by treatment group, which showed clear dose-dependent changes in METH disposition in the presence of IXT-m200 (Figure 1). Dose-dependent changes in METH plasma PK parameters, including area under the curve (AUC), maximum concentration (Cmax), and volume of distribution (Vd) were evident at the first METH challenge, and were maintained through the entire inpatient period. These data show that IXT-m200 redistributes METH in a dose-dependent manner. Importantly, METH was excreted in the urine at similar levels across treatment groups, demonstrating that IXT-m200 does not impair renal elimination of METH. There were no SAEs or AEs of greater severity than Grade 2 (mild or moderate only) in STAMPOUT. This includes all events recorded following the dose of IXT-m200 and the subsequent weekly METH challenges. Furthermore, some STAMPOUT participants used METH after release without apparent safety complications, further illustrating the safety of combinations of IXT-m200 and METH. These data suggest that IXT-m200 will be well-tolerated in people who have taken METH prior to treatment in an ED setting.

A second Phase 1 study of single 3-g doses of IXT-m200 in healthy volunteers is ongoing (NCT05027451) with no safety issues identified to date. In this study, 9 healthy volunteers were randomized to 3 g IXT-m200 or placebo at a 7:2 ratio. Each received their dose as a 30-min intravenous infusion, then remained at the study site overnight to complete Day 1 and Day 2 assessments (e.g., electrocardiogram (ECG), laboratory assessments, blood draws, and vital signs). Following discharge on Day 2, participants return to the clinic for follow-up pharmacokinetic (PK) and safety assessments on Day 8, then every 1-3 weeks thereafter until Day 127. Dosing has been completed with > 4 months of safety data collected to date, with no SAEs.

## 2.3. RISK/BENEFIT ASSESSMENT

### 2.3.1. KNOWN POTENTIAL RISKS

**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.

**Specific IXT-m200 Potential Risks**
During the completed Phase 1 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 frequency, relatedness, or severity of AEs with increased dose or between active- and placebo-treated subjects [10].

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 investigator heard a single expiratory wheeze. The infusion was stopped and the subject was treated with solumedrol 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, 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 subjects were confirmed positive for HACA in the completed Phase 1 study. The development of HACA did not appear to be dose-related [10].

### 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 [7,11], 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.

### 2.3.3. ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The risks of exposing the participants to IXT-m200 are justified to determine its tolerability and effectiveness. IXT-m200 was not associated with significant safety issues in healthy individuals (Phase 1) and in otherwise healthy non-treatment seeking people with MUD (Phase 2a). The general safety of antibody-based medications is outlined above in section 2.3.1 and in the IB. The risks of treatment with IXT-m200 will be minimized by selection of participants who desire treatment for their mild to moderate METH toxicity, but who are not *in extremis*. The risks are further mitigated by the selection of

participants who do not have significant concomitant illness (Section 5.2). Given the mechanism of action and the safety record, IXT-m200 has the potential to be useful in the treatment of METH toxicity, justifying its use.

# 3. OBJECTIVES AND ENDPOINTS

| OBJECTIVES | ENDPOINTS | JUSTIFICATION |
|---|---|---|
| Primary | | |
| *To evaluate the safety and tolerability of IXT-m200 in patients with mild to moderate METH toxicity* | Safety and tolerability of IXT-m200 as measured by physical examinations and vital sign, AE, ECG, and clinical laboratory testing | Safety must be systematically evaluated of IXT-m200 when given to patients with ongoing METH toxicity for the first time |
| Secondary | | |
| *To determine the time course and degree of normalization of agitation and vital signs* | Agitation/sedation scores over time as measured by ACES [12] | Agitation is a significant CNS component of METH toxicity and a cause for hospital admission |
| | Vital signs including blood pressure, heart rate and temperature over time | Elevated or depressed hemodynamics are a component of CV toxicity |
| *To determine the percentage of participants requiring rescue medications for psychiatric or cardiovascular manifestations of METH toxicity* | Need for rescue medications to treat:<br>- agitation, dysphoria, or psychosis (CNS toxicity)<br>- hypertension, tachycardia, or other cardiovascular instability (CV toxicity) | An evaluation of IXT-m200 effects on requirement of rescue medications is needed |
| Tertiary/Exploratory | | |
| *To determine how long patients with METH toxicity stay in the ED* | ED length of stay as measured by disposition order time minus triage time, and as measured by disposition order time minus start of treatment time, with log transformation | Prolonged wait times are associated with a number of negative outcomes, including patient dissatisfaction, increased hospitalization rate, poor quality of care, and increased mortality [13] |

# 4. STUDY DESIGN

## 4.1. OVERALL DESIGN

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

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

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

## 4.2. SCIENTIFIC RATIONALE FOR STUDY DESIGN

Because the participants in this study present requesting treatment for METH toxicity, but because IXT-m200 has not been administered in an acute setting to agitated patients, the open-label TAU comparison offers an early assessment of the utility of IXT-m200 for use to treat METH toxicity. A placebo control is not ethical because these patients present to the ED requesting treatment. The study design also includes rescue medications to ensure that in the event of worsening of the symptoms, which may be due to progression of the intoxication or due to either treatment, the patients may be treated in a timely fashion. The dose escalation in subsequent groups with safety evaluation between cohorts 1 and 2 is designed is ensure that an effective dose is tested.

While lorazepam and haloperidol are commonly used to treat agitation in the ED, there is no consensus on the ideal sedative for acute agitation in the ED [1]. The goal of sedation in the ED is to calm a patient so he/she is not a danger to him/herself or others, and can be more accurately assessed by physicians. METH causes release of monoamines from nerve terminals and blocks their reuptake; chronic and binge METH use severely alters monoamine homeostasis. The adrenergic reserves of METH overdose patients are therefore atypical, making their responses to sedative medications difficult to predict. Even with careful titration of sedatives, patients may experience profound and prolonged somnolence, increasing their length of ED stays [14]. For agitation due to overdose or intoxication, benzodiazepines and/or first-generation antipsychotics, such as haloperidol, are often recommended [2] but sufficient doses of these drugs to reduce agitation may sedate patients for hours. This approach results in at best prolonged ED stays, and at worst the masking of other symptoms (physical or psychiatric) that may need more timely attention.

## 4.3. JUSTIFICATION FOR DOSE

IXT-m200 will be given via IV administration because this will provide immediate effects and provide for reliable pharmacokinetic analysis. The IXT-m200 doses selected for this study may include the range tested in Phase 1 (0.2 to 20 mg/kg or 3-g) and Phase 2a (6 and 20 mg/kg) studies of IXT-m200. Converting doses for a 75-kg person shows that the 0.5-g dose = 6.67 mg/kg and a 1.5-g dose = 20 mg/kg. 2-g doses have been given to participants weighing 100 kg without complication in the Phase 2a study and 3-g doses were given to all active participants (n=7) in the second Phase 1 study. Importantly, it is not necessary to reduce METH brain concentrations to “zero” to demonstrate a clinically useful effect in this

study, so we do not anticipate that markedly higher doses will be required. Rather, the pharmacological goal is to redistribute enough METH from the CNS into the systemic circulation so that symptoms are reduced sufficiently to allow patients to be discharged or referred for further treatment. In rodent studies, IXT-m200 acutely reduces CNS effects when present in a ratio of less than 30 molecules of METH per mAb binding site [15]. Given that there is no way to predict body burden or previous METH intake by people presenting to an ED, this study uses unit doses (e.g., 0.5 and 2 g) to facilitate dosing, establish safety, and determine dose response for agitation.

The rate of IXT-m200 administration is justified to obtain rapid resolution of symptoms of METH toxicity, commensurate with that obtained by lorazepam and/or haloperidol. The infusion rate for the 0.5-g dose is 33 mg/kg/hr (assuming a 75-kg person) and those for the 2-g doses are 80 mg/kg/hr. In prior studies, the highest infusion rate was 80 mg/kg/hr. Importantly, the infusion rates in two GLP toxicology studies greatly exceed the proposed rates for this study. In the first, rats were given 200 mg/kg/hr for a total single dose of 400 mg/kg, and in a second completed study, 300 mg/kg was given in 10 min or less each week for six months for a repeating rate of 1800 mg/kg/hr. There were no reported safety issues with these infusion rates in rats. Furthermore, it appears unlikely that there have been infusion rate-related AEs in human studies.

### 4.4. 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 the Schedule of Activities (SoA; section 1.3). Participants with an ongoing AE at the time of study completion will be followed until the event resolves, the Sponsor and the investigator agree that further follow-up is not medically necessary, or until they are lost to follow-up.

The end of the study is defined as completion of the last visit or procedure shown in the SoA.

## 5. STUDY POPULATION

### 5.1. DESCRIPTION OF AND RATIONALE FOR THE SELECTED POPULATION

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

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

Criteria for diagnosing METH toxicity are adapted from the DSM-5 criteria for stimulant intoxication and include:

- Recent (last 24 hour) use of methamphetamine or amphetamine
- Clinically significant problematic behavioral or psychological changes
    - e.g., euphoria or affective blunting; changes in sociability; hypervigilance; interpersonal sensitivity; anxiety, tension or anger; stereotyped behaviors; impaired judgement that developed during or shortly after METH use
- Two or more of the following
    - Bradycardia or tachycardia (<40 or >100 beats per minute)
    - Hypertension or hypotension (>140/90 or < 90/60)
    - Pupillary dilatation
    - Perspiration or chills
    - Nausea or vomiting
    - Psychomotor agitation or retardation
    - Muscular weakness, respiratory depression, chest pain, or cardiac arrhythmias
    - Confusion, seizures, dyskinesias, dystonias, or coma
- The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder

## 5.2. INCLUSION CRITERIA

Eligible participants will:

1. Be aged 18 to 45 years, inclusive;
2. Present to the ED with METH toxicity as defined in protocol;
3. Have a PANSS-EC score of 14-28, inclusive;
4. Have or agrees to have an intravenous (IV) line placed;
5. Give a history of METH use in the past 24 hours, with participant or observer attribution of symptoms to METH, or have a positive METH drug screen;
6. Be accompanied or readily represented by a legally authorized representative (surrogate) who can consent to participation on behalf of the participant if participant is found not able to consent for themselves using the UCSD Brief Assessment of Capacity to Consent (UBACC); and
7. Consent or assent to participation in the study.

## 5.3. EXCLUSION CRITERIA

Eligible participants will NOT:

1. Present with concomitant opioid overdose requiring ventilatory support;
2. Be self-reported to be pregnant or lactating;
3. Be considered to have significant concomitant medical illness or trauma, or symptoms of severe METH toxicity including
    a. sepsis or febrile illness;
    b. myocardial infarction, cardiac decompensation or arrhythmias including tachycardia that is not sinus; severe hypertension (>180/110 mmHg); inadequately treated hypertension on chronic medication; history of vasculitis;
    c. coma, stroke or severe head injury; new or ongoing seizure activity
    d. acute pulmonary decompensation or severe chronic obstructive pulmonary disease;

e. any hepatic impairment and/or acute hepatitis or renal impairment due to concomitant medical illness; or
f. current, or history of, neuroleptic malignant syndrome;

4. Be considered to be at imminent risk of suicide or have disqualifying answers to the following two questions. Disqualifying answers would be 1b2 or 2b.

    1. In the past 30 days, have you considered killing yourself?
        a) No
        b) Yes – if Yes, how often?
            B1) Not often (twice or less)
            b2) Somewhat often (more than twice)

    2. In the past year, have you attempted to kill yourself?
        a) No
        b) Yes

5. Be considered to be at imminent risk of injury or danger to self, others or property;
6. Have a history of severe allergy (rash, hives, breathing difficulty, etc.) to both lorazepam and haloperidol, or known hypersensitivity or infusion reaction to any antibody medications; or
7. Be judged by the treating ED physician, investigator, or Sponsor (or designee) to be inappropriate for the study, including people whom the investigator determines cannot reasonably be consulted for assent to participation.

## 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.

Subjects 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 and until 90 days after receiving the dose of study drug.

## 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 SAEs.

All participants who consent but fail screening will be referred to treatment in the ED outside of the study per the recommendation of the screening physician. Subjects may be rescreened at any future presentation to the ED.

## 5.6. STRATEGIES FOR RECRUITMENT AND RETENTION

### 5.6.1. STRATEGIES FOR RECRUITMENT

Generally speaking, recruitment strategies are based on appropriate site selection (sufficient numbers of potential participants) and education of ED staff to look for possible participants.

The recruitment of vulnerable participants is necessary because the study is designed to determine if IXT-m200 is well-tolerated and works to reverse METH toxicity in an emergency setting. While people under the influence of METH and other drugs may be vulnerable because they may lack full consent capacity, participants will still provide assent, and their legally authorized representative will provide consent at the time of the study start if the participant is found lacking the capacity to consent for themselves using the UBACC assessment. No participant will be enrolled in the study who does not provide consent or assent. On Day 3, when participants return for their first follow-up visit, informed consent will be obtained, or repeated, from them.

Participants will be compensated based on local precedent, which may be different at each site.

### 5.6.2. STRATEGIES FOR RETENTION AND FOLLOW-UP

Retention strategies are based on education of the participant and discussion of the importance of follow-up to good health. Specifically, this includes the opportunity to follow up on any medical findings from the ED stay, and to further discuss opportunities for treatment for MUD if the person desires.

Phone calls, text messages, and emails will be sent as reminders to the participants to follow up. Transportation will be provided if needed to the follow-up visits, and referral for treatment of psychiatric and medical issues will be arranged.

# 6. STUDY INTERVENTION

## 6.1. STUDY INTERVENTION ADMINISTRATION

### 6.1.1. STUDY INTERVENTION DESCRIPTION

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.

The mechanism of action of IXT-m200 is via high-affinity binding to METH, which either prevents METH from reaching its sites of action in the CNS, or removes it from those sites of action [7,8]. Because anti-METH antibody medications significantly alter the distribution and tissue concentration of METH, their mechanism of action is PK antagonism. IXT-m200 was developed from a murine anti-METH

antibody and preclinical studies have shown that both the murine and chimeric antibodies bind METH and alter its PK in a similar way [7,8,16]. Further information on IXT-m200 may be found in the IB.

### 6.1.2. DOSING AND ADMINISTRATION

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

## 6.2. PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

### 6.2.1. ACQUISITION AND ACCOUNTABILITY

Study Intervention: Sponsor will provide the required number of vials of IXT-m200. 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.

The investigator at each site will be responsible for acquiring commercially available TAU and rescue medications for use in the study.

### 6.2.2. FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Study Intervention: 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 glass vials with stoppers and flip-off seals. Catalent Pharma Solutions manufactures the formulated active pharmaceutical ingredient. The University of Iowa Pharmaceuticals produces the vialed drug product.

Labels will be similar to the following:

InterveXion Therapeutics®
Anti-methamphetamine IXT-m200
18.5-21.5 mg/mL
Manufactured: DD MMM YYYY
UIP Lot: XXXIXXXX
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

### 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

The appropriate total dose of IXT-m200 will be prepared for IV administration. No dilution of the drug product is required. For calculation purposes, the concentration of the drug product is 20 mg/mL.

| Dose level (g) | Volume to be dosed (mL) |
|---|---|
| 0.5 | 25 |
| 2 | 100 |

TAU and rescue medications: These are obtained and provided by the local pharmacy in appropriate doses and delivery devices. Lorazepam will be given by slow IV push as the participant tolerates. Haloperidol is given via an intramuscular injection in the deltoid or gluteal muscles or by slow IV push as tolerated.

## 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 in cohorts 1 and 2 will be randomized to IXT-m200 or TAU after consenting to participate. Those who qualify will be randomized at a 4:1 ratio. Randomization codes will be generated by the randomization statistician and will be implemented by interactive voice/web response system (IXRS). This will be the same system for all sites so that there is no site bias to dosing. Participants will be randomized in the order they are enrolled. Participants in cohort 3 will receive TAU.

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

## 6.4. STUDY INTERVENTION COMPLIANCE

IXT-m200 and TAU are administered by the IV or IM routes by qualified personnel. Compliance with dosing will be verified by reference to the eCRF documentation of dosing.

## 6.5. CONCOMITANT THERAPY AND RISK MITIGATION PLAN

All concomitant medications (i.e., those given in the ED, prescription medications, over-the-counter medications, non-prescription medications, and supplements) taken during study participation will be recorded on the eCRF.

### 6.5.1. RESCUE MEDICINES

Lorazepam or haloperidol will be used as first-line rescue medications in all participants, regardless of treatment assignment, for agitation or dysphoria (lorazepam) or psychosis (haloperidol) [2,14,17]. If further rescue medications are needed, the choice and doses of the rescue medications will be at the discretion of the treating ED physician. To allow time for maximum effects of the initial treatments to evolve, rescue medications should not be given for 30 min after initiation of IXT-m200 or TAU dosing; however, timing is ultimately at the discretion of the treating physician.

Hypertension or tachycardia may be treated at the discretion of the treating physician with labetalol, hydralazine, or other similar approaches. Other cardiovascular instability (e.g., hypotension with blood pressure less than approximately 80/50 mmHg or less than approximately 90/60 mmHg with symptoms of dizziness, near syncope, or nausea, for example) will be treated initially with a fluid bolus[14]. If hypotension persists, it will be treated with incremental doses of the direct acting vasopressors phenylephrine, norepinephrine, or dopamine (starting at alpha adrenergic doses >10 µg/kg/min), or other appropriate medications at the discretion of the treating ED physician.

### 6.5.2. RISK MITIGATION

The following risk mitigation strategies have been designed based on other studies in people who use METH, on the problems posed specifically by enrolling participants in an emergency setting, on the clinical pharmacology of METH, and on the known pharmacology of IXT-m200:

1. Selection of a specific participant group. As stipulated in the protocol, participants who are relatively healthy with no significant medical or surgical illness will be recruited.
2. IXT-m200 dosing. IXT-m200 will be administered in escalating dose groups so that the lowest IXT-m200 dose (0.5 g) will be evaluated before the higher doses, in subsequent cohorts. This will allow determination of the effects of IXT-m200 at a low predicted effective IXT-m200 dose, before effects are assessed following a high predicted effective IXT-m200 dose.
3. Treatment in an Emergency Department. A crash cart will be available in the ED and personnel trained in CPR are always available in the ED setting. Oxygen and emergency ventilation equipment are immediately available. Normal saline will be used as the IV fluid and fluid boluses can be administered if any hypotension is seen. In the event of serious medical complications, a code may be called.
4. Frequent safety review. A formal safety review will be done between cohorts, and at any point needed based on the severity of AEs. This would include Grade 3 AEs related to worsening of METH effects in the presence of IXT-m200.

All of the study sites are EDs and therefore have all medications that might be needed to treat mAb toxicity, which may manifest as hypotension and bradycardia or tachycardia; bronchospasm with or without hypoxemia; or flushing, pruritis, and urticaria. Hospital-maintained crash carts, and oxygen and emergency ventilation equipment (Ambubags) are always available. Advanced Cardiovascular Life Support-certified providers and code teams are always available to treat life-threatening events.

# 7. STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

## 7.1. DISCONTINUATION OF STUDY INTERVENTION

The criteria outlined in section 8.3.3.1 will be used to categorize the severity of all AEs.
Enrollment and study drug administration will be immediately paused if any 1 of the following events occurs, unless the event was clearly unrelated to study drug administration, or the event is an expected sequelae of untreated METH toxicity:

- Three (3) participants experience a Grade 3 AE.
- Two (2) participants experience a Grade 3 AE related to increased agitation, aggression, or anxiety.
- One (1) participant experiences a Grade 4 AE.
- A death occurs.

Expected sequelae of untreated METH toxicity which will not be considered grounds for a study pause include:

- Hypertension/tachycardia
- Euphoria
- Agitation
- Insomnia
- Anxiety
- Seizures
- Mania/aggression

Worsening of any of the above following administration of study drug will be considered an AE and subject to the rules for study pause above.

If any of the pause conditions are met, the Sponsor, in consultation with the investigator and Medical Monitor, will suspend enrollment until a full safety review by both the Sponsor and DSMB is performed. A decision to reinitiate enrollment will be made following relevant consultation with the appropriate authorities based on the results of the safety review.

## 7.2. PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants may be withdrawn from the study at any time before IXT-m200 administration for reasons including the following:

- at their own request or at the request of their legally authorized representative,
- the participant meets an exclusion criterion (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 participant,
- if, in the investigator's opinion, continuation in the study would be detrimental to the participant's well-being, or
- at the specific request of InterveXion (Sponsor) or clinical site.

Once participants receive IXT-m200, every reasonable effort will be made to have them attend the Day 3 and 28 follow-up appointments.

In all cases, the reason for withdrawal must be recorded in the electronic Case Report Form (eCRF) 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 discontinue from further participation in the study, the research staff will cease further contact attempts.

Participants who consent and are randomized but do not receive the study intervention may be replaced and will not be included in any data set.

Participants who consent and are randomized and do receive the study intervention, but leave the ED prior to medical discharge and/or are not positive for METH by UDS or blood testing will be included in the safety set and ITT. Additional subjects may be recruited to ensure that both cohorts 1 and 2 contain 8 subjects dosed with IXT-m200 and 2 subjects dosed with TAU who complete the protocol through discharge from the ED and are positive for METH based on UDS or blood testing.

Participants will not be replaced if they complete through discharge from the ED, but do not return for Day 3 or 28 visits.

### 7.3. LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if s/he fails to return for the Day 3 and 28 scheduled visits 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 as soon as possible and 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. EFFICACY ASSESSMENTS

Study procedures to evaluate agitation include:

- The PANSS-EC (Positive and Negative Syndrome Scale – Excited Component) is used commonly as an assessment tool for clinical studies of pharmacotherapy for agitation. It includes 5 items (excitement, poor impulse control, tension, hostility, and uncooperativeness) which are each rated from 1 (absent) to 7 (extremely severe). A score of 14-28 is consistent with clinically significant psychomotor agitation of mild to moderate severity [18–20]. It will be administered only at screening as part of eligibility determination.
- The ACES (Agitation-Calmness Evaluation Scale) is a single-item, 9-point scale to differentiate agitated, calm, and sleep states. It has been used to assess the effects of pharmacotherapy on

agitation [12]. This assessment will be performed at all time points marked in the Schedule of Activities table to determine the impact of IXT-m200 versus TAU on agitation.
- Vital sign measurements over time including heart rate, blood pressure, temperature.
- Need for rescue medications to treat CNS symptoms of agitation, dysphoria, or psychosis; and CV symptoms of hypertension, tachycardia, or other cardiovascular instability.

## 8.2. SAFETY AND OTHER ASSESSMENTS

UCSD Brief Assessment of Capacity to Consent (UBACC)
- A 10-item list of questions focused on understanding and appreciation of the description of the research study [21]. This assessment will be used to screen potential participants for the capacity to consent for themselves. A score of 20 will be required to be eligible to consent without an LAR.

Safety evaluations include the following:

Medical and Medication Histories
- Medical history: A focused medical history will be obtained at triage/screening by interview and any available medical records. A detailed and pertinent medical history will be obtained after IXT-m200 dosing or TAU is complete and the participant is cooperative.
- Medication history: A medication history will be obtained at triage/screening by interview and any available medical records. This will be reviewed and supplemented if needed after IXT-m200 or TAU dosing is complete and the participant is cooperative. The medication history will be reviewed at the 2 scheduled study visits.

Physical Examination, Vital Sign Measurement, Height, and Weight
- A focused physical examination (excluding rectal/genital and breast examination) will be performed at triage/screening. The physical examination may consist of vital signs and an examination of the following: general appearance, neurological, skin, head, eyes, ears, nose, throat, neck, chest, heart, abdomen, and extremities.
    - A detailed physical examination (excluding rectal/genital and breast examination) will be performed after IXT-m200 or TAU dosing is complete and the patient is cooperative.
    - Focused exams will be performed during the two follow-up appointments and as otherwise necessary.
- Vital sign measurements (heart rate, blood pressures [systolic and diastolic], respiratory rate, temperature [oral], and pulse oximetry readings) will be obtained. Measurements will be taken at triage and screening, and as outlined in the Schedule of Activities table.
- Height and weight will be obtained on Day 1 after dosing with IXT-m200 or TAU.

Evaluations of Drug and Alcohol Use
- DSM-5 criteria will be used at the Day 3 follow-up visit to assess for Substance Use Disorders (including METH, opioids, alcohol, nicotine, marijuana, etc.).
- Qualitative urine drug screen (UDS; including amphetamines, MDMA, barbiturates, benzodiazepines, cocaine, opiates, THC, and phencyclidine) and alcohol breath testing will be performed once. This testing may be done before or after initial treatment so that the agitation may be treated as quickly as possible.
- Administer standard drug assessment of METH and other drug use since last visit on Days 3 and 28
- The METH Perceptions Assessment is the following list of questions intended to determine whether IXT-m200 affects how subjects perceive subsequent doses of METH.

- 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?*" Answer: 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

Psychiatric Evaluation

- A detailed and pertinent psychiatric history will be obtained at triage/screening evaluating for (but not limited to) the following: major current depression, psychosis, bipolar illness, organic brain disorder, or dementia, which would make study compliance difficult in the opinion of the investigator.
- Subjects will be queried about their history of suicide attempts and suicide ideation by the following two questions and any others the investigator deems necessary.

1. In the past 30 days, have you considered killing yourself?
   a) No
   b) Yes - if Yes, how often?
      b1) Not often (twice or less)
      b2) Somewhat often (more than twice)
2. In the past year, have you attempted to kill yourself?
   a) No
   b) Yes

Disqualifying answers would be 1b2 or 2b.

Electrocardiogram

- An electrocardiogram (ECG; 12-lead) will be recorded after IXT-m200 or TAU dosing is complete and the participant is cooperative. Standard ECG parameters including heart rate, QRS, 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).

Biological Specimen and Laboratory Evaluations

- Blood samples will be taken for analysis of IXT-m200 in serum on Day 1 (pre-dose, 4 hours after dosing, and at discharge), Day 3, and Day 28 from subjects who were randomized to receive IXT-m200 only.
- Blood samples will be taken for analysis of METH and amphetamine in plasma on Day 1 (pre-dose, 4 hours after dosing, and at discharge).
- Blood will be taken for clinical laboratory studies which will include complete blood count, blood urea nitrogen/creatinine, serum glucose, electrolytes, liver function tests (AST, ALT, gamma-glutamyl transferase, alkaline phosphatase, total and direct bilirubin), and creatinine phosphokinase. These tests will be performed on Day 1 after dosing is completed and repeated on Day 3.
- Urine samples will be taken for UDS, urinalysis, and urine pregnancy tests. These tests will be performed on Day 1; results are not required prior to dosing.

## 8.3. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

### 8.3.1. DEFINITION OF ADVERSE EVENTS (AE)

An **AE** is any untoward medical occurrence in a participant administered IXT-m200 or TAU, 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 IXT-m200 or TAU, whether or not related to IXT-m200 or TAU.

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, TAU, 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".

### 8.3.2. DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An SAE is an AE that at any dose:

- results in death;
- is life-threatening;
- requires admission to the hospital;
- 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 participant 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 in the view of the PI require medical or surgical intervention to prevent one of the other outcomes listed above. These will also usually be considered serious.

### 8.3.3. CLASSIFICATION OF AN ADVERSE EVENT

#### 8.3.3.1 SEVERITY OF EVENT

The general approach outlined by the Club Phase 1 working group [22] 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.

Regarding vital sign AEs, Section 6.5.1 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 ($O_2$ saturation < 93% on oxygen) occurs and requires medications, this will constitute a Grade 3 reaction, and will be documented as such.

#### 8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All 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.

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 to the study drug;
- 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.

#### 8.3.3.3. 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 or for the participant's underlying medical condition.

### 8.3.4. 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, 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.

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.

### 8.3.5. ADVERSE EVENT REPORTING

All AEs (whether serious or nonserious) that occur after the participant has been randomized must be documented on the appropriate pages of the eCRF. 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, until a satisfactory explanation is found or the investigator 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 Sponsor, Medical Monitor and DSMB between cohorts. If an investigator decides it necessary, AEs may be reviewed at any time by consultation with the investigator, Medical Monitor, and Sponsor.

### 8.3.6. 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 Medical Monitor and Sponsor within 24 hours of site awareness.
- Other SAEs regardless of relationship, will be submitted to the Medical Monitor and Sponsor within 48 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until the investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the Medical Monitor or 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 Sponsor will be responsible for notifying the 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 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.

### 8.3.7. REPORTING EVENTS TO PARTICIPANTS

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

### 8.3.8. EVENTS OF SPECIAL INTEREST

As a dose-escalation safety trial, safety will be monitored closely and dose escalation will occur only when available safety data warrant. On the other hand, the proposed trial by nature involves a population in significant duress, sufficient to merit a visit to the ED and meet the required eligibility criteria, and these participants will display a range of expected AEs due to their concomitant METH toxicity.

To balance these important requirements of trial conduct and patient protection, the study will capture any AEs underway at the time of presentation to the ED that can be attributed to METH toxicity. These include:

- Hypertension/tachycardia
- Euphoria
- Agitation
- Insomnia
- Anxiety
- Seizures
- Mania/aggression

These AEs will not be considered as study participation-related, and will not be included in consideration of dose escalation or study stopping criteria, unless they newly emerge or worsen after administration of investigational product. If they worsen, and reach sufficient severity, they will be considered as a part of the trial stopping criteria.

### 8.3.9. REPORTING OF PREGNANCY

If a participant is found to be pregnant after they have received IXT-m200 and before day 28, they should complete the study, with no further IXT-m200 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.

## 8.4. UNANTICIPATED PROBLEMS

### 8.4.1. 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.

### 8.4.2. 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 subject protections. The primary consideration in making these judgments is the need to take timely action to prevent avoidable harms to other participants.

### 8.4.3. 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.

The statistical evaluation will be performed using SAS® software version 9.4 or higher (SAS Institute, Cary, NC). All data will be listed, and summary tables will be provided. Summary statistics will be summarized and presented by treatment group, i.e., dose level of IXT-m200 and TAU, whereby the TAU patients from all cohorts will be pooled. For continuous variables, data will be summarized with the number of subjects (N), mean, standard deviation, median, minimum, and maximum by treatment group. For categorical variables, data will be tabulated with the number and proportion of subjects for each category by treatment group.

### 9.1. STATISTICAL HYPOTHESES

This is a descriptive study for evaluation of safety and tolerability as the primary objective. Descriptive summaries will be performed for tabulation and comparison of safety and efficacy endpoints. Descriptive statistical tests will be applied for the pairwise statistical comparison of efficacy endpoints in IXT-m200 dose levels versus TAU using a two-sided alpha level of 5%.

### 9.2. SAMPLE SIZE DETERMINATION

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

## 9.3. POPULATIONS FOR ANALYSES

The enrolled population will include all patients who sign the informed consent.

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

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

The Full Analysis Set (FAS) population will include those in the ITT population who receive any dose of study drug and were positive for methamphetamine by UDS or blood testing during the ED stay. The treatment group assignment in this population will be defined by the randomized treatment. This population will be used for the analysis of efficacy.

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

The PK Population will include all subjects for whom a PK concentration is available post-dose.

## 9.4. STATISTICAL ANALYSES

### 9.4.1. GENERAL APPROACH

This is a descriptive study for evaluation of safety and tolerability as the primary objective. The comparison of safety endpoints and of efficacy endpoints between the treatment groups will be performed using descriptive summaries and descriptive confidence intervals (CI) and statistical tests.

### 9.4.2. ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Not applicable.

### 9.4.3. ANALYSIS OF THE SECONDARY ENDPOINT(S)

Summary tables with descriptive statistics for actual values and changes from baseline will be provided for the ACES score for each scheduled timepoint by treatment group. Descriptive pairwise t-tests will be performed for the comparison of the changes from baseline of each IXT-m200 dose versus TAU. The time course of actual ACES scores and of change from baseline ACES scores will be presented by treatment group in a figure using mean values and 95% CIs.

The time to normalization of agitation using ACES will be defined as the time until the ACES score climbs to ≥4 the first time, in subjects for which the score remains in the range of 4-6 for the remaining time points. If the ACES score rises to the range of 7-9 during the ED stay, then normalization will be

defined as the time until the score is reduced to within the range of 4-6 following the end of the sedated period. This time will be presented by Kaplan-Meier estimates and figure by treatment group, and will be pairwise compared between each IXT-m200 dose versus TAU by the logrank test.

The time course of actual values of vital sign parameters and of changes from baseline will be presented by treatment group in a figure using mean values and 95% CIs. A shift table of post-baseline vital sign parameter values compared to baseline values will be provided by treatment group presenting the number and percentage of subjects below normal range / within normal range / above normal range. The time to normalization (i.e., returning to normal range) of vital sign parameters is defined as the first time the vital sign parameter is in normal range and remains in normal range for the remaining time-points. This time will be presented by Kaplan-Meier estimates and figure by treatment group, and will be pairwise compared between each IXT-m200 dose versus TAU by the logrank test.

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

PK concentrations of IXT-m200 and METH will be summarized by timepoint and by treatment group. Additionally, change from baseline of METH concentration will be summarized for each post-dose timepoint by treatment group. The change from baseline in METH concentration will be presented graphically.

### 9.4.4. SAFETY ANALYSES

All reported AEs will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA). The incidence of treatment-emergent AEs (TEAEs; events with onset dates on or after the administration of the study drug) will be included in incidence tables. Events with missing onset dates will be included as treatment-emergent. If a subject experiences more than one occurrence of the same AE, the occurrence with the greatest severity and the closest association with the study drug will be used in the summary tables. An overall summary by treatment group, overall IXT-m200 and total will be presented with the number and percentage of subjects experiencing any TEAE, any TEAE by severity, any related TEAE, any serious AE (SAE), any related SAE, any AESI, and any TEAE leading to death. Summary tables by system organ class and preferred term will be provided for treatment group, overall IXT-m200 and total for TEAEs, TEAEs by maximum severity, TEAEs by maximum relationship to study treatment, treatment-related TEAEs, serious TEAEs, and AESIs. All AEs will be listed by patient, along with information regarding onset, duration, relationship and severity to study drug, action taken with study drug, treatment of event, and outcome.

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

Physical examination results will be presented by number and percentage of patients in each category and scheduled time point by treatment group, overall IXT-m200 and total.

Clinical laboratory data (continuous parameters) will be summarized using descriptive statistics for each scheduled assessment time point by treatment group. Categorical laboratory data and urinary drug screen results will be presented by number and percentage of patients in each category and scheduled time point

by treatment group. Additionally, for laboratory data, frequency tables with number and percentage of patients of scheduled time point will be provided using the categories above/within/below normal range.

Extent of exposure will be summarized by a frequency table of number and percentage of patients by treatment group who received the total amount of the planned infusion, and who received the infusion partly.

#### 9.4.5. BASELINE DESCRIPTIVE STATISTICS

Demographic and baseline characteristics will be summarized by treatment group, overall IXT-m200 and total.

#### 9.4.6. PLANNED INTERIM ANALYSES

No interim analyses are planned.

#### 9.4.7. EXPLORATORY ANALYSES

The duration of the stay in the ED, calculated as starting from triage time and also as starting from treatment start time, will be summarized by descriptive statistics by treatment group and overall IXT-m200. The descriptive pairwise comparison of IXT-m200 dose levels versus TAU will be performed by a t-test using log-transformed durations.

# 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/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

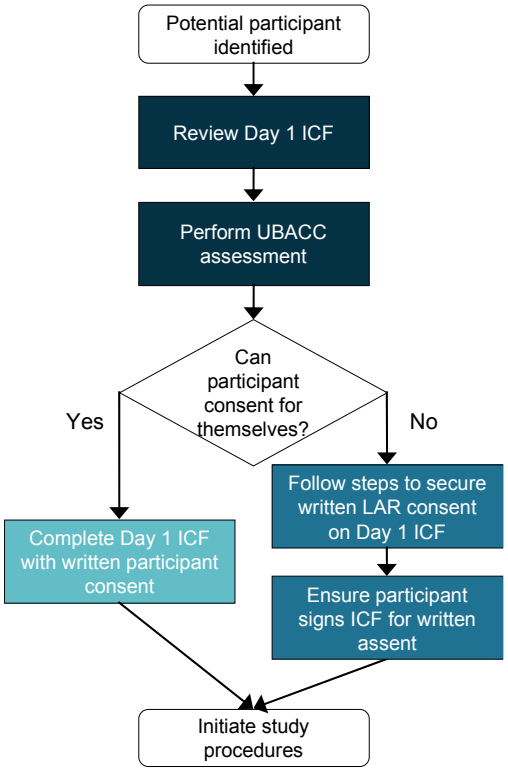
Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and if required, a legally authorized representative (LAR; surrogate or substitute decision maker) and written documentation of informed consent and/or assent from the participant is required prior to starting the screening process, and subsequently administering study intervention.

### 10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Given that METH use can cause agitation, delirium, and psychosis, only people who are found able to consent for themselves using the UBACC, or for whom a LAR who can consent for the participant can be identified will be recruited. The LAR may provide consent in accordance with local regulations, as described in 0.

Specifics will vary depending the clinical site, but patients identified with symptoms of METH toxicity will be approached by the investigator or designated and trained study personnel about participation in the study. Patients will be asked if they would like to participate in the study and if they have a LAR to provide consent for them. If the answer is yes to both questions, or they are found able to give consent for themselves, informed consent will be sought using IRB-approved consent forms and processes. No one will participate without providing written consent or assent by signature of the participant recorded on the ICF.

The process for consent is outlined in the following figure.




Written informed consent, or reconsent, from the participant will be obtained before any procedures are conducted on Day 3.

#### 10.1.1.2.1 LAR CONSENT PROCEDURES

The following steps will be conducted to obtain consent from the LAR on Day 1, when a subject is found unable to consent for themselves by using the UBACC:

1. The informed consent form (ICF) will be sent to the potential LAR by email, fax, or other electronic means.
2. The person obtaining consent will connect with the LAR by phone, video, or other means and will confirm they are speaking with the correct individual.
    a. The conversation requires a witness to be present starting with Step 2, preferably a member of the site staff so that signatures can be easily obtained.
3. The date and version number of the consent will be confirmed between the person obtaining consent and the LAR.
4. The consenting process will proceed as usual with the person obtaining consent verbally going over the informed consent and answering any questions.
5. The person obtaining consent will ask for verbal informed consent to conduct screening assessments.
6. The person obtaining consent will document the conversation in the subject file or progress notes recording at a minimum:
    a. Date and time of the conversation
    b. How it occurred (e.g., telephone or video conference)
    c. Name of the witness and any other participants
    d. Confirmation that the LAR received the ICF
    e. Confirmation of verbal informed consent to conduct screening
7. The LAR will sign the ICF. This may be documented in many ways, including:
    a. The LAR may print the ICF, sign it and return a scan or picture of the form electronically. The LAR must be informed that there is a small risk of email being intercepted in route.
    b. The LAR may use an electronic signature. Some options include:
        i. Adobe Sign
        ii. Apple Pen
        iii. DocuSign
8. Documentation of the LAR signature must be received, and all other steps in the informed consent process completed, prior to any therapeutic intervention.
9. The final ICF must be filed in the designated investigator/research file location and a copy given to the LAR and participant.

### 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, the DSMB, 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 subjects 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. Investigators are subject to subsection 301(d) of the Public Health Service Act.

### 10.1.4. FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored as described in the Statistical Considerations (Section 9) and Data Handling (Section 10.1.9) sections of this protocol. 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 | Medical Monitor |
|---|---|
| W. Brooks Gentry, MD | Patrick Keenan, MD |
| InterveXion Therapeutics, LLC | Syneos Health |
| 4301 W. Markham St. #831 | 5707 Southwest Parkway Bldg 2, Suite 200 |
| Little Rock, AR 72205 | Austin, TX 78735 |
| 501 320 7601 | O: 737 484 3018, C: 512 806 4429 |
| gentrywilliamb@uams.edu | patrick.keenan@syneoshealth.com |

### 10.1.6. SAFETY OVERSIGHT

Safety oversight will be under the direction of a DSMB composed of individuals with the appropriate expertise, likely including clinical trial oversight, monoclonal antibody and methamphetamine clinical pharmacology, acute care medicine (cardiovascular and/or emergency), psychiatry or behavioral medicine, statistics, and a patient advocate or representative. Members of the DSMB will be independent from the study conduct and free of conflict of interest, or measures will be enacted to minimize real or perceived conflicts of interest. The DSMB will meet at the conclusion of cohort 1 to assess safety data and intermittently as necessary. 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.

Cohort escalation review will be performed by the Sponsor, Medical Monitor, and DSMB between cohorts 1 and 2 and the next group will not start until after completion of this review. This review will be scheduled to occur approximately two weeks after the last enrollee in the cohort has completed the Day 3 visit so that all Day 3 data available are considered. Safety data to be reviewed include vital signs, ECG, AEs, clinical laboratory values (serum and urine), and UDS.

### 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 or by electronic means of viewing both records, 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).

Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what

level of detail monitoring will be performed, and the distribution of monitoring reports. 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

Each 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/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 eCRF(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 adverse events (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 investigator and the IRB
- Composition of the IRB or other applicable statement
- Record of all significant communications between the investigator 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 eCRFs and of documentation of corrections for all participants
- 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 investigator 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.

### 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 sites 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 subject'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 |
| ACES | Agitation/Calmness Evaluation Scale |
| ALT | Alanine Aminotransferase |
| AST | Aspartate Aminotransferase |
| AUC | Area Under the Curve |
| AUCinf | Area Under the Curve from Time 0 Through Infinity |
| CFR | Code of Federal Regulations |
| CI | Confidence Interval |
| Cmax | Maximum Concentration |
| CMP | Clinical Monitoring Plan |
| CNS | Central Nervous System |
| COC | Certificate of Confidentiality |
| CONSORT | Consolidated Standards of Reporting Trials |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CV | Cardiovascular |
| DHHS | Department of Health and Human Services |
| DSM5 | Diagnostic and Statistical Manual of Mental Disorders 5 |
| DSM5 SUD | Diagnostic and Statistical Manual of Mental Disorders 5 for Substance Use Disorders |
| DSMB | Data and Safety Monitoring Board |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Forms |
| ED | Emergency Department |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practices |
| HACA | Human Anti-Chimeric Antibody |
| IB | Investigator's Brochure |
| ICH | International Conference on Harmonisation |
| IgG | Immunoglobulin G |
| IND | Investigational New Drug Application |
| IRB | Institutional Review Board |
| ITT | Intention-To-Treat |
| IV | Intravenous |
| IXRS | Interactive Voice/Web Response System |
| LAR | Legally Authorized Representative |
| mAb | Monoclonal Antibody |
| MedDRA | Medical Dictionary for Regulatory Activities |
| METH | Methamphetamine |
| MUD | Methamphetamine Use Disorder |
| N | Number |
| NA | Not Applicable |
| NCT | National Clinical Trial |
| NIH | National Institutes of Health |
| NIDA | National Institute on Drug Abuse |
| OHRP | Office for Human Research Protections |

| | |
|---|---|
| PANSS-EC | Positive and Negative Syndrome Scale – Excited Component |
| PI | Principal Investigator |
| PK | Pharmacokinetic |
| PP | Per-Protocol |
| QC | Quality Control |
| SA | Self-Administration |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SoA | Schedule of Activities |
| SOP | Standard Operating Procedure |
| STAMPOUT | Study of Antibody for Methamphetamine Outpatient Therapy, NCT03336866 |
| TAU | Treatment As Usual |
| TEAE | Treatment-Emergent Adverse Event |
| UBACC | UCSD Brief Assessment of Capacity to Consent |
| UDS | Urine Drug Screen |
| UPT | Urine Pregnancy Test |
| Urine AE | Cumulative Urinary Excretion |
| US | United States |
| $V_d$ | Volume of Distribution |
| WBC | White Blood Cell |

## 10.3. PROTOCOL AMENDMENT HISTORY

| Version/Date | Description of Change | Brief Rationale |
|---|---|---|
| V2 23Mar2021 | Updates throughout to allow dosing of haloperidol up to 5 mg by IM or IV | TAU may include 5 mg haloperidol. IV dosing option added to allow physicians the choice. |
| | 1.3 Clarified SOA to match section 8 for UDS. | Clarification updates only. |
| | 5.2 Updated inclusion criteria 3 with upper bound of 25 for PANSS-EC score. | To ensure that severely METH intoxicated patients are not enrolled. |
| | 6.5.1 Added dopamine (and other medications) as option for rescue medication for hypotension at specified starting dose. | To include additional rescue medications. |
| | 7.1 Added study halting rule for two Grade 3 AEs related to agitation, aggression, or anxiety. | Increased METH toxicity signs could indicate treatment failure. It is important to pause the study for review in the case of toxicity-related AEs. |
| | 8.2 Changed Day 3 clinical labs from 'repeat if needed' to 'required'. | It is likely that the Day 1 lab results would not be available in order to determine necessity of repeat lab data by Day 3. |
| | 10.1.1.2 Clarified consent process. | To note that a box will be checked if LAR consent is obtained by phone. |
| | 12.9.1 Added DSMB member names and affiliations. | To add names and affiliations. |
| V3 15Nov2021 | 1.2 Updated schema. | To remove references to time frames. |
| | 1.3 Added collection of ACES score at time 0 and broadened the window for collection of UDS, UPT, and breathalyzer. | To ensure an ACES score is captured proximate to dosing initiation and to allow UDS, UPT, and breathalyzer to occur before or after dosing. |
| | 5.2 Revised inclusion criteria 3 to increase the upper limit of the PANSS-EC assessment to 28. | To more accurately reflect moderate severity agitation, which could include a score of "4" on all 7 dimensions. |
| | 5.2 Revised inclusion criteria 5 to include a positive METH drug screen. | To allow a positive METH drug screen rather than participant or observer attribution of symptoms to METH use. |
| | 5.3 Revised exclusion criteria 1 to remove the exclusion of those requiring naloxone treatment. | Removed as unnecessary. |
| | 5.3 Revised exclusion criteria 3c to remove the | Removed as unnecessary. |

| Version/Date | Description of Change | Brief Rationale |
|---|---|---|
| | exclusion of agitation requiring restraint. | |
| | 5.3 Revised exclusion criteria 4 to include suicidality questions asked and modify the time frame of the questions asked. | To include the specific questions to be asked and the disqualification criteria in the list with other criteria. The time frames for reported suicidal ideation and suicide attempt were reduced to allow those with adolescent or >1 year ago suicide attempts to enroll. It is considered that participants who have not attempted suicide again in the past year and have also not been thinking much about it in the past month are stable enough for study enrollment. |
| | 6.2.3 Removed the frozen IP storage option. | To clarify the preferred storage condition of refrigerated. |
| | 7.2 Clarified recruitment of additional subjects. | To clarify that additional subjects may, not will, be recruited to complete the cohorts with those testing positive for METH. |
| | 8.1 Updated the rationale for the PANSS-EC range. | To clarify the change to inclusion criteria 3. |
| | 8.2 Updated the Evaluations of Drug and Alcohol Use to remove propoxyphene and change time frame for UDS and breathalyzer | To remove propoxyphene testing as unnecessary and broaden the time frame for collecting UDS and breathalyzer tests to before or after dosing. |
| | 8.2 Updated the Psychiatric Evaluation section to modify the time frame used for questions about suicide attempts and ideation. | The time frames for reported suicidal ideation and suicide attempt were reduced to allow those with adolescent or >1 year ago suicide attempts to enroll. It is considered that participants who have not attempted suicide again in the past year and have also not been thinking much about it in the past month are stable enough for study enrollment. Removed reference to IXT Suicidal Ideation Questionnaire as unnecessary. |
| | 8.2 Added bilirubin to laboratory evaluations | Test was previously omitted. |
| | 8.2 Changed time frame for UDS, urinalysis, and UPT | To broaden the time frame for collecting urine samples to before or after dosing. |
| | 8.3.2 Clarified wording to define a medically important event classified as an SAE. | To clarify the definition of a medically important event that should be considered an SAE. |
| | 8.3.6 Reduced the time frame of reporting of SAEs to Sponsor and Medical Monitor that are not life threatening to 48 hours. | To allow time for reporting to NIDA by 72 hours post-event occurrence. |
| | 9.4.3 Removed requirement for two consecutive time points following a return to | To allow subjects to be discharged faster rather than waiting on an additional time point after a return to normal. |

| Version/Date | Description of Change | Brief Rationale |
|---|---|---|
| | normal for the ACES assessment. | |
| | 9.4.3 Removed requirement to report ratio of IXT-m200 to METH. | Removed as unnecessary. |
| | 10.1.1.2 Clarified consent process by adding wording from Protocol Clarification Letter dated 07 April 2021. | Removed unnecessary wording and added section 10.1.1.2.1 describing IRB-approved consent procedures for LAR. |
| | 10.1.7 Added option for electronic SDV as needed. | To clarify that SDV could be done via electronic means if necessary and possible, and not only during an on-site visit. |
| V4 09Mar2022 | Updates throughout to change dose level for cohort 2 to 2-g doses | To update the dose level for cohort 2 to 2-g doses. Dose levels for cohorts 3 and 4 will be updated by future amendment. |
| | 1.3 Inserted UBACC in SOA | To note that the UBACC should be performed along with Informed Consent processes |
| | 2.2 Noted that the STAMPOUT study was complete and a Phase 1 study is ongoing | To provide updated background information in support of the protocol change. |
| | 4.1 Updated table of cohort dose levels | To update the dose levels for cohorts 2-4. |
| | 4.3 Updated dose levels and added supporting information | To remove unnecessary dose information for 1- and 1.5-g doses, and provide calculated dose administration rates that are supportive of the protocol change. |
| | 5.2 Added phrase to IC#6 | To allow an exception to the requirement for an LAR if the participant is capable of consenting for themselves as determined by the UBACC |
| | 5.2 Added consent or to IC#7 | To clarify that participants must consent or assent, the choice of which will depend on whether they have the capacity to consent for themselves |
| | 5.3 Adjusted EC#6 wording | To allow participants with an allergy to one of the two TAU medications to participate, so long as they are not allergic to both |
| | 5.6.1 Updated phrasing for consistency | To note that a LAR is required only if a participant is found unable to consent for themselves |
| | 6.2.4 Removed 1- and 1.5-g doses | To remove reference to doses that are now unplanned |
| | 8.2 Added description of the UBACC | To provide a description of the UBACC and clarify its use |
| | 9.4.6 Revised the purpose of the Interim Analysis | To change the purpose of the Interim Analysis slightly by determining the appropriate cohorts 3 and 4 doses rather than confirming their pre-specified levels are appropriate. |

| Version/Date | Description of Change | Brief Rationale |
|---|---|---|
| | 10.1.1 Updated Informed Consent process | Entire section updated to allow participants to consent for themselves if found to have the capacity to consent by the UBACC. If unable to consent, a LAR may be used for consent along with the written assent of the participant. All participants are to provide consent, again if they originally consented for themselves, on Day 3. |
| | 10.1.3 Added Investigator responsibility | To specify that Investigators have certain responsibilities due to the Certificate of Confidentiality. |
| V5 22Aug2022 | 1.1 Updated number of anticipated participants | Changed number from 40 to 24 in order to complete the study with equal number of participants in the low, high, and TAU groups. |
| | 4.1 Updated number of anticipated participants, number of cohorts, and timing of DSMB reviews | Changed number from 40 to 24 participants, reduced the number of cohorts required, and the timing of DSMB meetings. |
| | 4.2 Removed comment that lowest effective dose would be identified | Intermediate doses have been removed from the protocol, thus the lowest effective dose may not be identified |
| | 6.2 Clarified randomization | Required update to match cohort dose revisions |
| | 6.3 Clarified randomization | Required update to match cohort dose revisions |
| | 7.2 Updated replacement of participant | Required update to match cohort dose revisions |
| | 9 Removed reference to 4 cohorts | Required update to match cohort dose revisions |
| | 9.2 Clarified number of TAU patients needed is 8 | Required update to match cohort dose revisions |
| | 9.4.6 Removed plan for interim analysis | An interim analysis is no longer necessary following cohort 2 as the treatment for cohort 3 is TAU. |
| | 10.1.6 Updated DSMB meeting schedule | Required update to match cohort dose revisions |

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## 12 DATA AND SAFETY MONITORING PLAN

**U01 DA 053043 (PD/PI: Gentry, William B. and Stevens, Misty)**

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

**Protocol Number: M200C-2101**

**Medical Monitor: Patrick Keenan, MD**

**August 22, 2022**

This Data and Safety Monitoring Plan (DSMP) is forward looking and may not be amended in real time to reflect changes in study status, participant enrollment, etc. In the event of a conflict between the DSMP and the clinical protocol, the current clinical protocol shall be followed.

# 12.1. SUMMARY OF THE PROTOCOL

## 12.1.1. STUDY DESIGN

Refer to protocol section 4 for further details.

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

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

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

The next page shows the Schedule of Activities.

| Assessment | Triage | Screening | Dosing and Assessments [f] | | | | | | | | | | | | | Follow-up[a] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study Day | 1 | 1 | 1 | | | | | | | | | | | | Day not specified | 3 (+2) | 28 (±7) |
| Hour | NA | <0 | <0 | 0 | 0.25 | 0.5 | 0.75 | 1 | 1.5 | 2 | 3 | 4 | 6 | 8 | >8, <Discharge from ED | Discharge from ED | NA | NA |
| Focused history and physical exam [b, c] | | X | | | | | | | | | | | | | | | X | X |
| Focused review of systems [b, c] | | X | | | | | | | | | | | | | | X | X | X |
| Medication history | | X | | | | | | | | X | | | | | | | | |
| Detailed and pertinent psychiatric history [c, d] | | X | | | | | | | | | | | | | | | | |
| Vital Signs [c] | | X | X | | | X | | X | | X | X | X | X | X | As needed | X | X | X |
| Agitation score [c] | | X | | X | | X | | X | | X | X | X | X | X | As needed | | | |
| Informed consent and UBACC | | X | | | | | | | | | | | | | | | X | |
| Eligibility criteria | | X | | | | | | | | | | | | | | | | |
| Randomization | | | X | | | | | | | | | | | | | | | |
| PK samples [d] | | | X | | | | | | | | | X | | | | X | X | X |
| Dose administration | | | | X | | | | | | | | | | | | | | |
| Observe for AEs | | | | | X | X | X | X | X | X | X | X | X | X | As needed | X | X | X |
| Assess for rescue meds | | | | | | X | | X | | | | X | | | As needed | X | | |
| Clinical labs and ECG | | | | | | Once, as soon as feasible | | | | | | | | | | | X | |
| UDS, UPT, Breathalyzer | | | Once, as soon as feasible | | | | | | | | | | | | | | | |
| Detailed and pertinent medical history [e] | | | | | | | | | | X | | | | | | | | |
| DSM5 SUD checklist | | | | | | | | | | | | | | | | | X | |
| Drug use assessment and Meth Perception Assessment | | | | | | | | | | | | | | | | | X | X |

AE – adverse event; UDS – urine drug screen; UPT – urine pregnancy test; ECG – electrocardiogram; DSM5 SUD – Diagnostic and Statistical Manual of Mental Disorders 5 for Substance Use Disorders; NA – not applicable; UBACC – UCSD Brief Assessment of Capacity to Consent

[a] If participants do not return for a follow-up visit, a phone call will be attempted to assess any AEs.

[b] Focused history, physical exam and review of systems based on main complaint, related details from other parts of the medical history and physical exam, and eligibility criteria.

[c] Assessments will be obtained as either part of triage or screening, depending on the site. PANSS-EC will be done at screening only; ACES will be done at each time point as marked.

[d] PK samples will be drawn for both IXT-m200 and METH per section 8.2.

[e] Detailed and pertinent history includes pertinent past medical, family and social histories in addition to focused history. Detailed physical exam to be completed if indicated by detailed and pertinent medical history.

[f] Subjects may be discharged at any time point after the 2-hr assessments are completed if the subject is deemed medically eligible; assessments at Day 1, Hours 3-8 may be skipped if discharged. Assessments assigned for the time of discharge from ED should be completed for all subjects.

### 12.1.2. PRIMARY AND SECONDARY OBJECTIVES AND OUTCOME MEASURES

Refer to protocol section 3.

| OBJECTIVES | ENDPOINTS | JUSTIFICATION |
|---|---|---|
| Primary | | |
| *To evaluate the safety and tolerability of IXT-m200 in patients with mild to moderate METH toxicity* | Safety and tolerability of IXT-m200 as measured by physical examinations and vital sign, AE, ECG, and clinical laboratory testing | Safety must be systematically evaluated of IXT-m200 when given to patients with ongoing METH toxicity for the first time |
| Secondary | | |
| *To determine the time course and degree of normalization of agitation and vital signs* | Agitation/sedation scores over time as measured by ACES [12] | Agitation is a significant CNS component of METH toxicity and a cause for hospital admission |
| | Vital signs including blood pressure, heart rate and temperature over time | Elevated or depressed hemodynamics are a component of CV toxicity |
| *To determine the percentage of participants requiring rescue medications for psychiatric or cardiovascular manifestations of METH toxicity* | Need for rescue medications to treat:<br>- agitation, dysphoria, or psychosis (CNS toxicity)<br>- hypertension, tachycardia, or other cardiovascular instability (CV toxicity) | An evaluation of IXT-m200 effects on requirement of rescue medications is needed |
| Tertiary/Exploratory | | |
| *To determine how long patients with METH toxicity stay in the ED* | ED length of stay as measured by disposition order time minus triage time, and as measured by disposition order time minus start of treatment time, with log transformation | Prolonged wait times are associated with a number of negative outcomes, including patient dissatisfaction, increased hospitalization rate, poor quality of care, and increased mortality [13] |

### 12.1.3. INCLUSION CRITERIA

Refer to protocol section 5.2.

Eligible participants will:

1. Be aged 18 to 45 years, inclusive;
2. Present to the ED with METH toxicity as defined in protocol;
3. Have a PANSS-EC score of 14-28, inclusive;
4. Have or agrees to have an intravenous (IV) line placed;
5. Give a history of METH use in the past 24 hours, with participant or observer attribution of symptoms to METH or have a positive METH drug screen;
6. Be accompanied or readily represented by a legally authorized representative (surrogate) who can consent to participation on behalf of the participant if participant is found not able to consent for themselves using the UCSD Brief Assessment of Capacity to Consent (UBACC); and
7. Consent or assent to participation in the study.

### 12.1.4. EXCLUSION CRITERIA

Refer to protocol section 5.3.

Eligible participants will NOT:

1. Present with concomitant opioid overdose requiring ventilatory support;
2. Be self-reported to be pregnant or lactating;
3. Be considered to have significant concomitant medical illness or trauma, or symptoms of severe METH toxicity including
    a. sepsis or febrile illness;
    b. myocardial infarction, cardiac decompensation or arrhythmias including tachycardia that is not sinus; severe hypertension (>180/110 mmHg); inadequately treated hypertension on chronic medication; history of vasculitis
    c. coma, stroke or severe head injury; new or ongoing seizure activity
    d. acute pulmonary decompensation or severe chronic obstructive pulmonary disease;
    e. any hepatic impairment and/or acute hepatitis or renal impairment due to concomitant medical illness; or
    f. current, or history of, neuroleptic malignant syndrome
4. Be considered to be at imminent risk of suicide or have disqualifying answers to the following two questions. Disqualifying answers would be 1b2 or 2b.

    1. In the past 30 days, have you considered killing yourself?
       a) No
       b) Yes - if Yes, how often?
          b1) Not often (twice or less)
          b2) Somewhat often (more than twice)

    2. In the past year, have you attempted to kill yourself?
       a) No
       b) Yes

5. Be considered to be at imminent risk of injury or danger to self, others or property;
6. Have a history of severe allergy (rash, hives, breathing difficulty, etc.), to both lorazepam and haloperidol, or known hypersensitivity or infusion reaction to any antibody medications; or
7. Be judged by the treating ED physician, investigator, or Sponsor (or designee) to be inappropriate for the study, including people whom the investigator determines cannot reasonably be consulted for assent to participation.

### 12.1.5. POWER CALCULATION AND SAMPLE SIZE

Refer to protocol section 9 and the SAP for further detail on statistical analysis.

Because Meth-OD is mainly a safety study, the sample size for this study is not based on statistical hypotheses. The number of participants within each dose group was chosen based on feasibility, as well as historical experience with initial safety and tolerability trials. From the perspective of tolerability assessment, the probability that a given adverse event would not be observed in a group of participants administered an assigned dose was analyzed for various true population incidence rates was computed (Table 1).

**Table 1. Probability of Not Observing an Adverse Event for Various True Incidence Rates**

| | Probability of Not Observing an AE in Varying Group Sizes | | | | | |
|---|---|---|---|---|---|---|
| **True incidence rate** | **4 subjects** | **6 subjects** | **8 subjects** | **9 subjects** | **12 subjects** | **18 subjects** |
| 0.10 | 0.66 | 0.53 | 0.43 | 0.387 | 0.28 | 0.150 |
| 0.20 | 0.41 | 0.26 | 0.17 | 0.134 | 0.069 | 0.018 |
| 0.30 | 0.24 | 0.12 | 0.058 | 0.040 | 0.014 | 0.002 |
| 0.40 | 0.13 | 0.047 | 0.017 | 0.010 | 0.002 | < 0.001 |
| 0.50 | 0.063 | 0.016 | 0.004 | 0.002 | < 0.001 | < 0.001 |

The probability of not observing an AE under each sample size and true incidence rate scenario was calculated using an exact test for binomial proportion assuming a two-sided Type I error (alpha) of 0.05 and near-zero null proportion of 0.000001. The values reported in the table are the Type 2 error. Analyses were conducted in SAS® 9.4.

Based on the nature of this study, the proposed sample size of 8 participants in each IXT-m200-containing treatment group adequately allows for the detection of clinically meaningful rates of adverse events with the probability of not observing an AE for true incidence rates.

## 12.2. TRIAL MANAGEMENT

### 12.2.1. PARTICIPATING CLINICS

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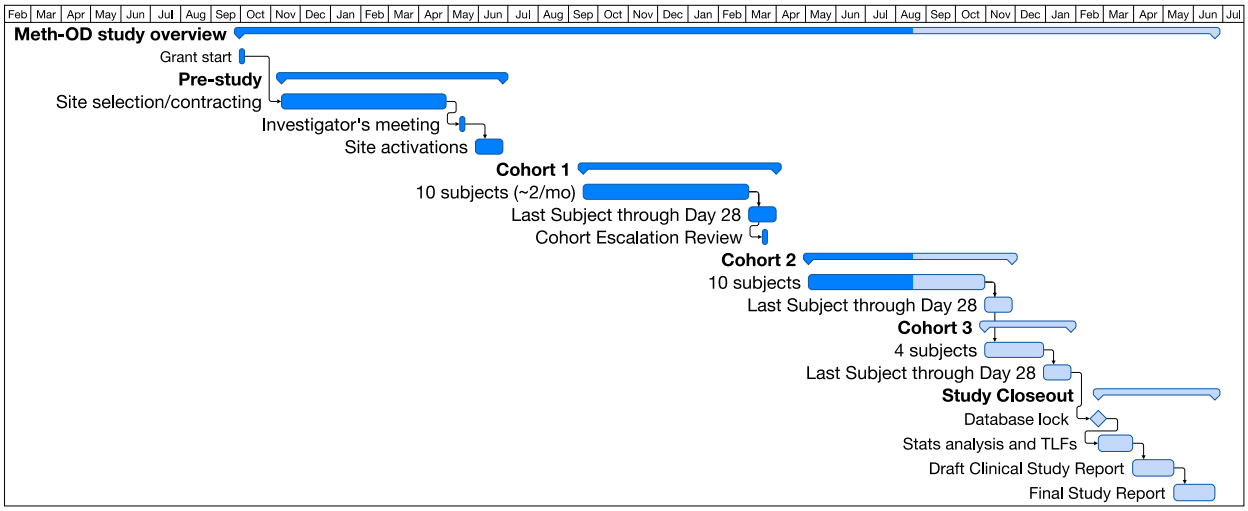
## 12.2.2. PLANNED ENROLLMENT TIMETABLE




## 12.2.3. TARGET POPULATION DISTRIBUTION

| TARGETED/PLANNED ENROLLMENT: Number of Participants | | | | | |
|---|---|---|---|---|---|
| | Not Hispanic or Latino | | Hispanic or Latino | | |
| Racial Categories | Female | Male | Female | Male | Total |
| American Indian/ Alaska Native | 0 | 1 | 0 | 0 | 1 |
| Asian | 0 | 1 | 0 | 0 | 1 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 | 0 | 0 |
| Black or African American | 1 | 2 | 0 | 0 | 3 |
| White | 4 | 7 | 1 | 3 | 15 |
| More than One Race | 1 | 1 | 1 | 1 | 4 |
| Total | 6 | 12 | 2 | 4 | 24 |

## 12.3. DATA MANAGEMENT AND ANALYSIS

### 12.3.1. DATA ACQUISITION AND TRANSMISSION

Refer to protocol section 10.1.9.1.

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 eCRF(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 adverse events (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.

### 12.3.2. DATA ENTRY METHODS

All data will be collected on source documents and then entered in the eCRFs.

### 12.3.3. DATA SECURITY AND PLAN FOR PROTECTING CONFIDENTIALITY

Refer to protocol section 10.1.3.

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 subjects 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.

#### 12.3.4. DATA ANALYSIS PLAN

Refer to protocol section 9 for further details.

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.

## 12.4. QUALITY ASSURANCE AND QUALITY CONTROL

#### 12.4.1. PROCEDURES IN PLACE TO ENSURE THE VALIDITY AND INTEGRITY OF THE DATA

Refer to protocol section 10.1.8.

Each 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/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.

#### 12.4.2. PROCEDURES TO GUARANTEE THE ACCURACY AND COMPLETENESS OF THE DATA DURING DATA COLLECTION, ENTRY, TRANSMISSION, AND ANALYSIS

Refer to protocol section 10.1.7.

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 or by electronic means of viewing both records, 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).

Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports. 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.

## 12.5. REGULATORY ISSUES

### 12.5.1. REPORTING OF SAES

Refer to protocol section 8.3.6.

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 Medical Monitor and Sponsor within 24 hours of site awareness.
- Other SAEs regardless of relationship, will be submitted to the Medical Monitor and Sponsor within 48 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until the investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the Medical Monitor or 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 Sponsor will be responsible for notifying the 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) and Project Scientist (PS) 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.

### 12.5.2. REPORTING OF IRB ACTIONS TO NIDA

InterveXion will be responsible for reporting IRB actions to the NIDA PO.

### 12.5.3. REPORT OF CHANGES OR AMENDMENTS TO THE PROTOCOL

InterveXion will be responsible for reports of protocol changes or amendments to the NIDA PO and PS and the FDA. Significant protocol changes will be approved by NIDA prior to implementation, unless there is an immediate safety concern for participants.

## 12.6. TRIAL SAFETY

### 12.6.1. POTENTIAL RISKS AND BENEFITS FOR PARTICIPANTS

Refer to protocol section 2.3.

**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.

**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 subjects 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 subjects [10].

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 investigator heard a single expiratory wheeze. The infusion was stopped and the subject was treated with solumedrol 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, 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 subjects were confirmed positive for HACA in the Phase 1 study. The development of HACA did not appear to be dose-related [10].

IXT-m200 is an investigational product and may convey no benefit to patients. Based on nonclinical studies in rodents [7,11], 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.

### 12.6.2. RISK MITIGATION PLAN

Refer to protocol section 6.5.2.

The following risk mitigation strategies have been designed based on other studies in people who use METH, on the problems posed specifically by enrolling participants in an emergency setting, on the clinical pharmacology of METH, and on the known pharmacology of IXT-m200:

1. Selection of a specific participant group. As stipulated in the protocol, participants who are relatively healthy with no significant medical or surgical illness will be recruited.
2. IXT-m200 dosing. IXT-m200 will be administered in escalating dose groups so that the lowest IXT-m200 dose (0.5 g) will be evaluated before the higher doses), in subsequent cohorts. This will allow determination of the effects of IXT-m200 at a low predicted effective IXT-m200 dose, before effects are assessed following a high predicted effective IXT-m200 dose.
3. Treatment in an Emergency Department. A crash cart will be available in the ED and personnel trained in CPR are always available in the ED setting. Oxygen and emergency ventilation equipment are immediately available. Normal saline will be used as the IV fluid and fluid boluses can be administered if any hypotension is seen. In the event of serious medical complications, a code may be called.
4. Frequent safety review. A formal safety review will be done between cohorts, and at any point needed based on the severity of AEs. This would include Grade 3 AE's related to worsening of METH effects in the presence of IXT-m200.

All of the study sites are EDs and therefore have all medications that might be needed to treat mAb toxicity, which may manifest as hypotension and bradycardia or tachycardia; bronchospasm with or without hypoxemia; or flushing, pruritis, and urticaria. Hospital-maintained crash carts, and oxygen and emergency ventilation equipment (Ambubags) are always available. Advanced Cardiovascular Life Support-certified providers and code teams are always available to treat life-threatening events.

### 12.6.3. TRIAL STOPPING RULES

Refer to protocol section 7.1.

Enrollment and study drug administration will be immediately paused if any 1 of the following events occurs, unless the event was clearly unrelated to study drug administration, or the event is an expected sequelae of untreated METH toxicity:

- Three (3) participants experience a Grade 3 AE.
- Two (2) participants experience a Grade 3 AE related to increased agitation, aggression, or anxiety.
- One (1) participant experiences a Grade 4 AE.
- A death occurs.

Expected sequelae of untreated METH toxicity which will not be considered grounds for a study pause include:

- Hypertension/tachycardia
- Euphoria

- Agitation
- Insomnia
- Anxiety
- Seizures
- Mania/aggression

Worsening of any of the above following administration of study drug will be considered an AE and subject to the rules for study pause above.

If any of the pause conditions are met, the Sponsor, in consultation with the investigator and Medical Monitor, will suspend enrollment until a full safety review by both the Sponsor and DSMB is performed. A decision to reinitiate enrollment will be made following relevant consultation with the appropriate authorities based on the results of the safety review.

Also refer to protocol section 10.1.2.

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, the DSMB, 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.

### 12.6.4. PROCESS OF AE/SAE COLLECTION, ASSESSMENT, AND REPORTING

Refer to protocol section 8.3.

All AEs (whether serious or nonserious) that occur after the participant has been randomized must be documented on the appropriate pages of the eCRF. 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, until a satisfactory explanation is found or the investigator 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 Sponsor, Medical Monitor and DSMB between cohorts. If an investigator decides it necessary, AEs may be reviewed at any time by consultation with the investigator, Medical Monitor, and Sponsor.

Refer to DSMP section 12.5.1 for details on SAEs.

#### 12.6.5. AE/SAE FOLLOW-UP PLAN

Refer to DSMP section 12.6.4.

## 12.7. TRIAL EFFICACY

#### 12.7.1. PLANS FOR INTERIM ANALYSIS OF EFFICACY DATA

Refer to protocol section 9.4.6.

No interim analyses are planned.

## 12.8. DSM PLAN ADMINISTRATION

#### 12.8.1. RESPONSIBILITY FOR DATA AND SAFETY MONITORING

Refer to protocol section 10.1.6.

Safety oversight will be under the direction of a DSMB composed of individuals with the appropriate expertise, likely including clinical trial oversight, monoclonal antibody and methamphetamine clinical pharmacology, acute care medicine (cardiovascular and/or emergency), psychiatry or behavioral medicine, statistics, and a patient advocate or representative. Members of the DSMB will be independent from the study conduct and free of conflict of interest, or measures will be enacted to minimize real or perceived conflicts of interest. The DSMB will meet at the conclusion of cohort 1 to assess safety data and intermittently as necessary. 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.

Cohort escalation review will be performed by the Sponsor, Medical Monitor, and DSMB between cohorts 1 and 2 and the next group will not start until after completion of this review. This review will be scheduled to occur approximately two weeks after the last enrollee in the cohort has completed the Day 3 visit so that all Day 3 data available are considered. Safety data to be reviewed include vital signs, ECG, AEs, clinical laboratory values (serum and urine), and UDS.

#### 12.8.2. PERSONS RESPONSIBLE FOR MONITORING THE TRIAL

Safety monitoring will be the responsibility of the investigators, Medical Monitor and the DSMB. Each investigator and the Medical Monitor will provide recommendations to the Sponsor based on their perspectives. The Sponsor, by the actions of its Chief Medical Officer, W. Brooks Gentry, will then determine whether cohort enrollment should continue or if changes should be made.

### 12.8.3. DISCLOSURE OF ANY CONFLICT OF INTEREST IN THE DSM

Employees at the selected trial sites have no financial interests in InterveXion, and therefore the monitoring done at the study sites and by the clinical monitor will not be conflicted. As described above, the DSMB will be recruited to have no serious conflicts of interest and any unavoidable conflicts will be properly disclosed.

Dr. Gentry maintains an active conflict management plan with UAMS. A component of this plan is that human studies related to InterveXion are to be performed by a contract research organization (CRO) in which safety can be assessed by the CRO. Dr. Gentry is not involved in any way with subject recruitment or with the day-to-day management of the trial. All safety decisions will be made with the input of the investigator, Medical Monitor, and DSMB.

InterveXion also maintains records on conflicts for its investigators.

### 12.8.4. FREQUENCY OF DSM

Refer to DSMP section 12.4.2 for clinical monitoring frequency and section 12.8.1 for DSMB meeting frequency.

### 12.8.5. CONTENT OF DSM REPORT

Content of DSM report *(to be submitted to NIDA PO and PS annually at the same time as the RPPR is due)*

- Brief description of the trial and progress
- Enrollment update and baseline sociodemographic characteristics
- Retention and disposition of study participants (active, completed, and terminated/withdrawn)
- Regulatory Issues (amendment, deviations, IRB report, QA issues)
- AEs and SAEs listings

## 12.9. DSM BOARD PLAN

### 12.9.1. MEMBERS AND AFFILIATION

- Keith Coffee, MD (Chair) – Medical and Scientific Operations, Peachtree Bioresearch Solutions
- Lauren Whiteside, MD – Dept of Emergency Medicine, University of Washington
- Travis Rieder, PhD – Berman Institute of Bioethics, Johns Hopkins University
- Lukas Makris, PhD – Statistical Consultant, Stathmi, Inc.
- Theodore Treese, MD, MBA – Psychiatrist and Principal Investigator, Adaptive Clinical Research, Inc.

### 12.9.2. CONFLICT OF INTEREST

Refer to DSMP section 12.8.1.

### 12.9.3. FREQUENCY OF MEETINGS

Refer to DSMP section 12.8.1.

### 12.9.4. PROTECTION OF CONFIDENTIALITY

The DSMB members will be required to sign confidentiality agreements prior to participation.

### 12.9.5. MONITORING ACTIVITIES (INITIAL AND ONGOING STUDY REVIEW)

The Board will meet to review the protocol, monitor recruitment, adverse events, data quality, and overall study performance. Details of the monitoring activities will be outlined in the DSMB Charter.

### 12.9.6. COMMUNICATION PLAN TO IRB, NIDA, AND FDA

The DSMB's recommendations following interim reviews will be reported to InterveXion as Sponsor. If the recommendation is other than that the study should continue as designed, and if study changes are made as a result, InterveXion will promptly report to the IRB, NIDA, and FDA if necessary, according to applicable regulations and ICH Guidance.


# METH-OD: A PHASE 2A STUDY OF IXT-M200 IN PATIENTS WITH TOXICITY FROM METHAMPHETAMINE OVERDOSE

**Protocol Number: M200C-2101**

**National Clinical Trial (NCT) Identified Number: NCT04715230**

**IND Sponsor: InterveXion Therapeutics, LLC**

**Funded by: NIH/NIDA U01 DA053043**

**Version Number: 5**

**22 Aug 2022**

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## SPONSOR APPROVAL AND SIGNATURE PAGE

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

Misty Stevens, Ph.D., M.B.A.
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.

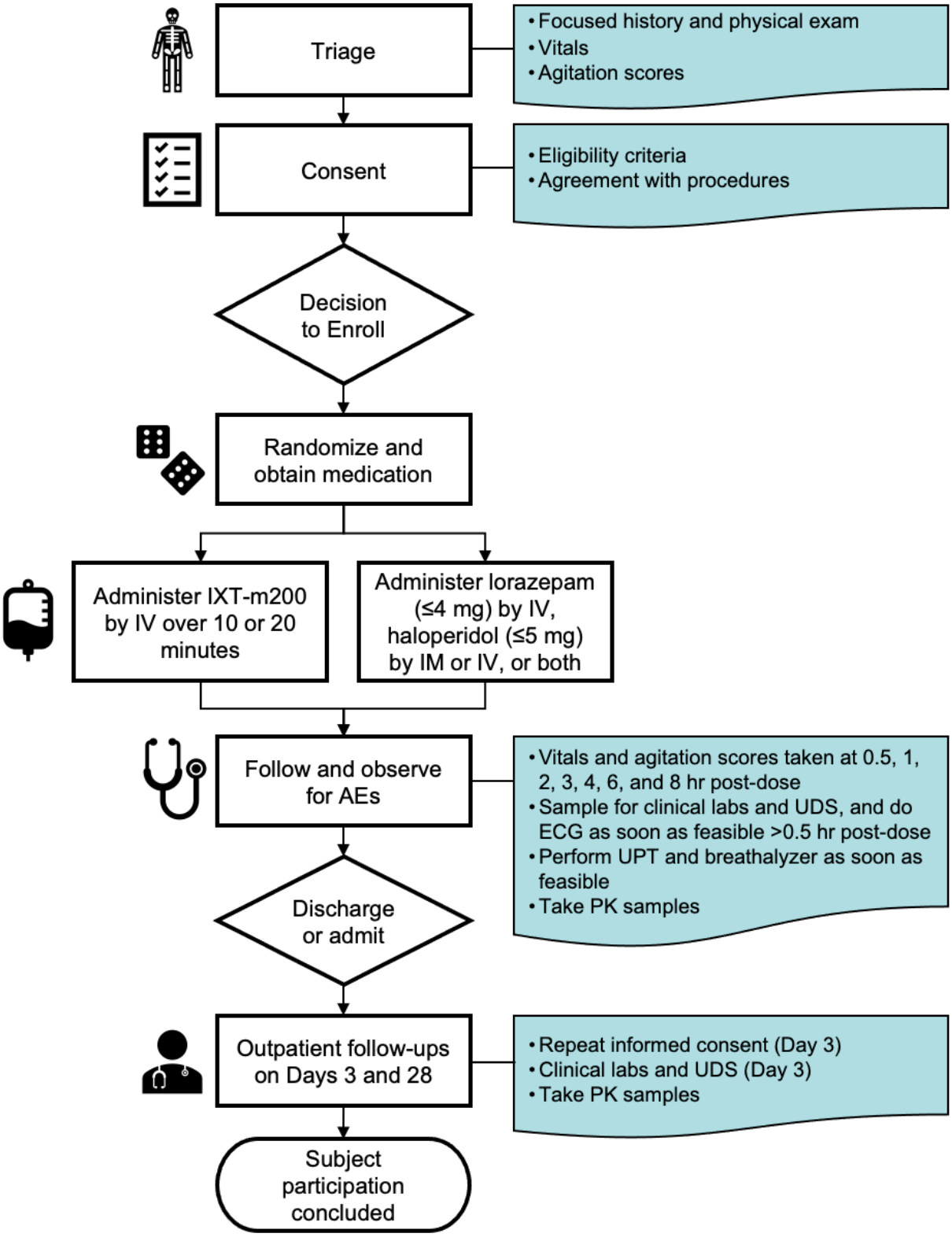
Investigator Signature/Date: _____

# 1. PROTOCOL SUMMARY

## 1.1. SYNOPSIS

| | |
|---|---|
| **Title:** | Meth-OD: A Phase 2a Study of IXT-m200 in Patients with Toxicity from Methamphetamine Overdose |
| **Study Description:** | The proposed study is a randomized, open-label Phase 2a study of IXT-m200 versus treatment-as-usual (TAU) in which patients with mild to moderate methamphetamine (METH) toxicity will be treated with IXT-m200 or lorazepam and/or haloperidol. The hypothesis is that IXT-m200 will be well-tolerated in patients with acute mild to moderate METH toxicity. |
| **Objectives:** | Primary Objective: To evaluate the safety and tolerability of IXT-m200 in patients with mild to moderate METH toxicity.<br>Secondary Objectives: To determine the time course and degree of normalization of agitation and vital signs, and to determine the percentage of participants in each group requiring rescue medications for psychiatric or cardiovascular manifestations of METH intoxication. |
| **Endpoints:** | Primary Endpoint:<br>• Safety and tolerability of IXT-m200 as measured by physical examinations and vital sign, adverse event (AE), electrocardiogram (ECG), and clinical laboratory testing.<br>Secondary Endpoints:<br>• Agitation/sedation scores over time as measured with the ACES (Agitation/Calmness Evaluation Scale);<br>• Vital signs including blood pressure, heart rate and temperature over time;<br>• Need for rescue medications to treat:<br>  ○ agitation, dysphoria, or psychosis (CNS signs/symptoms)<br>  ○ hypertension, tachycardia, or other cardiovascular instability (CV signs/symptoms).<br>Exploratory Endpoints:<br>• Emergency department (ED) length of stay as measured by disposition order time minus triage time, and by disposition order time minus start of treatment time, with log transformation. |
| **Study Population:** | Approximately ~~40~~ 24 males and females aged 18-45, presenting to an ED setting with mild to moderate METH toxicity who request treatment for symptoms related to their METH use will be recruited. |
| **Phase:** | 2a |
| **Description of Sites Enrolling Participants:** | Approximately 5 ED sites 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 people with METH use disorder. The total dose will be given over 10 min for the 0.5-g dose and over 20 min for higher doses. Lorazepam is a benzodiazepine that is safe and commonly used to treat agitation and dysphoria in the emergency setting. Haloperidol is commonly used to treat agitation due to psychosis. |
| **Study Duration:** | Approximately one year |
| **Participant Duration:** | 28 days |

## 1.2. SCHEMA


Triage
• Focused history and physical exam
• Vitals
• Agitation scores
Consent
• Eligibility criteria
• Agreement with procedures
Decision to Enroll
Randomize and obtain medication
Administer IXT-m200 by IV over 10 or 20 minutes
Administer lorazepam (≤4 mg) by IV, haloperidol (≤5 mg) by IM or IV, or both
Follow and observe for AEs
• Vitals and agitation scores taken at 0.5, 1, 2, 3, 4, 6, and 8 hr post-dose
• Sample for clinical labs and UDS, and do ECG as soon as feasible >0.5 hr post-dose
• Perform UPT and breathalyzer as soon as feasible
• Take PK samples
Discharge or admit
Outpatient follow-ups on Days 3 and 28
• Repeat informed consent (Day 3)
• Clinical labs and UDS (Day 3)
• Take PK samples
Subject participation concluded

## 1.3. SCHEDULE OF ACTIVITIES (SOA)

| Assessment | Triage | Screening | Dosing and Assessments [f] | | | | | | | | | | | | | Follow-up[a] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study Day | 1 | 1 | 1 | | | | | | | | | | | | Day not specified | 3 (+2) | 28 (±7) |
| Hour | NA | <0 | <0 | 0 | 0.25 | 0.5 | 0.75 | 1 | 1.5 | 2 | 3 | 4 | 6 | 8 | >8, <Discharge from ED | Discharge from ED | NA | NA |
| Focused history and physical exam [b, c] | | X | | | | | | | | | | | | | | | X | X |
| Focused review of systems [b, c] | | X | | | | | | | | | | | | | | X | X | X |
| Medication history | | X | | | | | | | | X | | | | | | | | |
| Detailed and pertinent psychiatric history [c, d] | | X | | | | | | | | | | | | | | | | |
| Vital Signs [c] | | X | X | | | X | | X | | X | X | X | X | X | As needed | X | X | X |
| Agitation score [c] | | X | | X | | X | | X | | X | X | X | X | X | As needed | | | |
| Informed consent and UBACC | | X | | | | | | | | | | | | | | | X | |
| Eligibility criteria | | X | | | | | | | | | | | | | | | | |
| Randomization | | | X | | | | | | | | | | | | | | | |
| PK samples [d] | | | X | | | | | | | | | X | | | | X | X | X |
| Dose administration | | | | X | | | | | | | | | | | | | | |
| Observe for AEs | | | | | X | X | X | X | X | X | X | X | X | X | As needed | X | X | X |
| Assess for rescue meds | | | | | | X | | X | | | | X | | | As needed | X | | |
| Clinical labs and ECG | | | | | | Once, as soon as feasible | | | | | | | | | | | X | |
| UDS, UPT, Breathalyzer | | | Once, as soon as feasible | | | | | | | | | | | | | | | |
| Detailed and pertinent medical history [e] | | | | | | | | | | X | | | | | | | | |
| DSM5 SUD checklist | | | | | | | | | | | | | | | | | X | |
| Drug use assessment and Meth Perception Assessment | | | | | | | | | | | | | | | | | X | X |

AE – adverse event; UDS – urine drug screen; UPT – urine pregnancy test; ECG – electrocardiogram; DSM5 SUD – Diagnostic and Statistical Manual of Mental Disorders 5 for Substance Use Disorders; NA – not applicable; UBACC – UCSD Brief Assessment of Capacity to Consent

[a] If participants do not return for a follow-up visit, a phone call will be attempted to assess any AEs.

[b] Focused history, physical exam and review of systems based on main complaint, related details from other parts of the medical history and physical exam, and eligibility criteria.

[c] Assessments will be obtained as either part of triage or screening, depending on the site. PANSS-EC will be done at screening only; ACES will be done at each time point as marked.

[d] PK samples will be drawn for both IXT-m200 and METH per section 8.2.

[e] Detailed and pertinent history includes pertinent past medical, family and social histories in addition to focused history. Detailed physical exam to be completed if indicated by detailed and pertinent medical history.

[f] Subjects may be discharged at any time point after the 2-hr assessments are completed if the subject is deemed medically eligible; assessments at Day 1, Hours 3-8 may be skipped if discharged. Assessments assigned for the time of discharge from ED should be completed for all subjects.

# 2. INTRODUCTION

## 2.1. STUDY RATIONALE

No direct antagonists have been approved, or even clinically evaluated, for treatment of METH overdose. In fact, no medications have been approved for any form of METH Use Disorder (MUD) [1]. Emergency care providers use a variety of medications to manage patients with METH toxicity based on the primary presenting symptoms and their individual and institutional experience. Mild to moderate agitation and dysphoria may be treated with benzodiazepines or antipsychotic medications [2]. Severe CNS agitation and delirium are treated with combinations of benzodiazepines, antipsychotics, and other sedatives (e.g., ketamine) [2]. The cardiovascular and cerebrovascular effects of METH overdose are treated with combinations of vasodilators, beta and calcium channel blockers, and anti-arrhythmic medications [3]. Altogether, given the lack of targeted therapies, ED management of patients presenting with METH toxicity is symptomatic at best, intended only to reduce and/or mask the acute physiologic effects of METH until it can be cleared by metabolism and excretion. Furthermore, patients with METH toxicity may be hypersomnolent during metabolism of METH and repletion of monoamines and adenosine triphosphate. These sedative effects, especially when combined with sedative effects of benzodiazepines or other sedatives, may delay ED discharge and increase length of stay [4] at best, and may result in compromise of ventilation at worst. **A single pharmacokinetic antagonist medication that results in a calmer, cooperative patient without sedation would offer a clear advantage over current pharmacologic approaches for the management of agitation associated with METH overdose.**

IXT-m200, a chimeric monoclonal antibody (mAb) that binds METH with high affinity, has been evaluated in a Phase 2a study in non-treatment-seeking people who use METH (NCT03336866). Data from multiple studies in rats show that METH effects, such as increased locomotor activity, are quickly reduced following treatment with anti-METH antibodies [5,6].This is accompanied by reductions in brain METH concentrations. Preliminary results from the Phase 2a study in otherwise healthy people with MUD indicate that IXT-m200 greatly reduces METH volume of distribution by sequestering METH in the blood, as expected based on animal data. The antibody also appears to be well-tolerated in healthy people who do and do not use METH. Together, these results suggest that IXT-m200, a specific METH pharmacokinetic (PK) antagonist, could be an effective treatment for METH overdose.

## 2.2. BACKGROUND

**Study Intervention**
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) [7,8].

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 in its active sites in the brain. IXT-m200 may therefore decrease both the CNS and hemodynamic effects of METH [5,6].

**Nonclinical IXT-m200 Effectiveness Summary**
A significant body of nonclinical work in rats indicates that anti-METH antibodies quickly reduce METH effects and brain concentrations after administration. The potential human efficacy of IXT-m200 is

demonstrated by several *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) [5,6,9].

**Nonclinical Safety Summary of the Interaction of IXT-m200 with METH**
A series of nonclinical studies was completed in rats to address the potential for IXT-m200 to exacerbate METH effects, specifically cardiovascular 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) in an effort to overcome the reduction of METH effects by the antibody.

In each of the studies, rats were acclimated over a 14-day period to make them tolerant to high doses of METH, similar to what occurs in people who chronically use METH. 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 at 6 mg/kg spaced 2 hours apart. This binge dosing regimen was repeated on Days 21 and 24 for certain studies and groups.

The studies (GLP toxicology, cardiovascular effects, METH PK, and METH distribution) collected different outcome measurements while using the same METH administration protocol. Results are summarized in the IB. **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.**

**Clinical Research Summary**
A Phase 1 study of the safety of single doses of IXT-m200 in healthy humans has been completed [10]. In this study, 42 subjects (17 females) were dosed in 5 groups (0.2, 0.6, 2, 6, and 20 mg/kg IXT-m200, which are approximately 15 – 1500 mg in an average 75-kg subject), 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/day. 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. 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 investigator heard a single expiratory wheeze. The infusion was stopped and the subject was treated with solumedrol 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 (i.e., 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 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 a range from 0.2 to 20 mg/kg. Therefore, a maximum tolerated dose was not reached.

A Phase 2a study of the effect of IXT-m200 on METH pharmacokinetics and METH pharmacodynamics has been completed in otherwise healthy people who use METH. The primary goals of this study, called

STAMPOUT (Study of Antibody for Methamphetamine Outpatient Therapy, NCT03336866), were to show that IXT-m200 alters the PK of METH and reduces the reinforcing subjective effects that perpetuate METH use. In addition, the safety and tolerability of the effect of single IV doses of IXT-m200 (6 or 20 mg/kg, which were up to 2000 mg) were determined in this population. In STAMPOUT, non-treatment-seeking people who had MUD received a single dose of IXT-m200 followed by weekly METH challenges. Serial blood samples and urine collections were analyzed to determine METH PK changes due to the antibody dose. Drug effects questionnaires were given after METH challenges to quantify the impact of IXT-m200 on the subjective effects of METH.

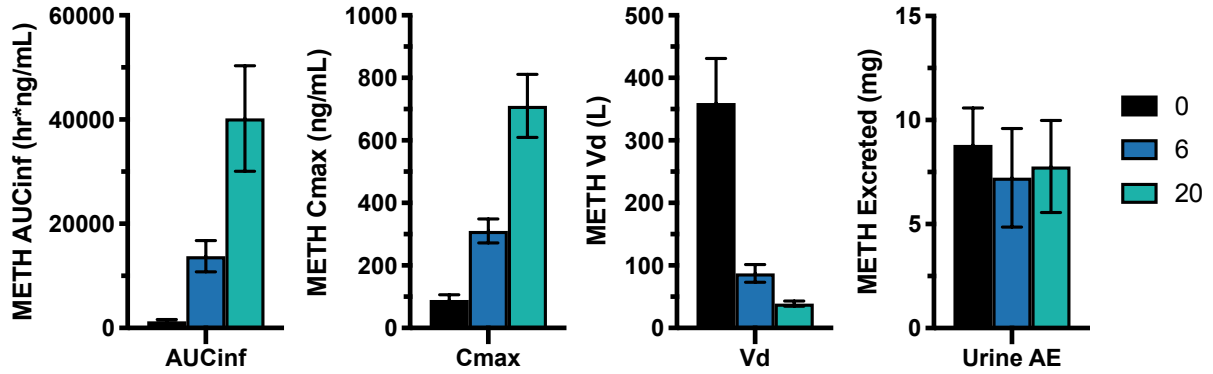



**Figure 1. METH PK data from STAMPOUT interim analysis demonstrate IXT-m200 alters METH distribution.** Area under the curve from time 0 through infinity (AUCinf), maximum METH concentration (Cmax), volume of distribution (Vd), and cumulative urinary excretion over 36 hr (Urine AE) data are plotted as group means ± SD. IXT-m200 (0, 6, or 20 mg/kg, IV) was administered one day prior to METH (30 mg, IV).

In a pre-specified interim analysis of PK and safety data, METH PK parameters were estimated and summarized by treatment group, which showed clear dose-dependent changes in METH disposition in the presence of IXT-m200 (Figure 1). Dose-dependent changes in METH plasma PK parameters, including area under the curve (AUC), maximum concentration (Cmax), and volume of distribution (Vd) were evident at the first METH challenge, and were maintained through the entire inpatient period. These data show that IXT-m200 redistributes METH in a dose-dependent manner. Importantly, METH was excreted in the urine at similar levels across treatment groups, demonstrating that IXT-m200 does not impair renal elimination of METH. There were no SAEs or AEs of greater severity than Grade 2 (mild or moderate only) in STAMPOUT. This includes all events recorded following the dose of IXT-m200 and the subsequent weekly METH challenges. Furthermore, some STAMPOUT participants used METH after release without apparent safety complications, further illustrating the safety of combinations of IXT-m200 and METH. These data suggest that IXT-m200 will be well-tolerated in people who have taken METH prior to treatment in an ED setting.

A second Phase 1 study of single 3-g doses of IXT-m200 in healthy volunteers is ongoing (NCT05027451) with no safety issues identified to date. In this study, 9 healthy volunteers were randomized to 3 g IXT-m200 or placebo at a 7:2 ratio. Each received their dose as a 30-min intravenous infusion, then remained at the study site overnight to complete Day 1 and Day 2 assessments (e.g., electrocardiogram (ECG), laboratory assessments, blood draws, and vital signs). Following discharge on Day 2, participants return to the clinic for follow-up pharmacokinetic (PK) and safety assessments on Day 8, then every 1-3 weeks thereafter until Day 127. Dosing has been completed with > 4 months of safety data collected to date, with no SAEs.

## 2.3. RISK/BENEFIT ASSESSMENT

### 2.3.1. KNOWN POTENTIAL RISKS

**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.

**Specific IXT-m200 Potential Risks**
During the completed Phase 1 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 frequency, relatedness, or severity of AEs with increased dose or between active- and placebo-treated subjects [10].

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 investigator heard a single expiratory wheeze. The infusion was stopped and the subject was treated with solumedrol 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, 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 subjects were confirmed positive for HACA in the completed Phase 1 study. The development of HACA did not appear to be dose-related [10].

### 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 [7,11], 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.

### 2.3.3. ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The risks of exposing the participants to IXT-m200 are justified to determine its tolerability and effectiveness. IXT-m200 was not associated with significant safety issues in healthy individuals (Phase 1) and in otherwise healthy non-treatment seeking people with MUD (Phase 2a). The general safety of antibody-based medications is outlined above in section 2.3.1 and in the IB. The risks of treatment with IXT-m200 will be minimized by selection of participants who desire treatment for their mild to moderate METH toxicity, but who are not *in extremis*. The risks are further mitigated by the selection of

participants who do not have significant concomitant illness (Section 5.2). Given the mechanism of action and the safety record, IXT-m200 has the potential to be useful in the treatment of METH toxicity, justifying its use.

# 3. OBJECTIVES AND ENDPOINTS

| OBJECTIVES | ENDPOINTS | JUSTIFICATION |
|---|---|---|
| Primary | | |
| *To evaluate the safety and tolerability of IXT-m200 in patients with mild to moderate METH toxicity* | Safety and tolerability of IXT-m200 as measured by physical examinations and vital sign, AE, ECG, and clinical laboratory testing | Safety must be systematically evaluated of IXT-m200 when given to patients with ongoing METH toxicity for the first time |
| Secondary | | |
| *To determine the time course and degree of normalization of agitation and vital signs* | Agitation/sedation scores over time as measured by ACES [12] | Agitation is a significant CNS component of METH toxicity and a cause for hospital admission |
| | Vital signs including blood pressure, heart rate and temperature over time | Elevated or depressed hemodynamics are a component of CV toxicity |
| *To determine the percentage of participants requiring rescue medications for psychiatric or cardiovascular manifestations of METH toxicity* | Need for rescue medications to treat:<br>- agitation, dysphoria, or psychosis (CNS toxicity)<br>- hypertension, tachycardia, or other cardiovascular instability (CV toxicity) | An evaluation of IXT-m200 effects on requirement of rescue medications is needed |
| Tertiary/Exploratory | | |
| *To determine how long patients with METH toxicity stay in the ED* | ED length of stay as measured by disposition order time minus triage time, and as measured by disposition order time minus start of treatment time, with log transformation | Prolonged wait times are associated with a number of negative outcomes, including patient dissatisfaction, increased hospitalization rate, poor quality of care, and increased mortality [13] |

# 4. STUDY DESIGN

## 4.1. OVERALL DESIGN

The hypothesis of this multisite Phase 2a study is that IXT-m200 will be well-tolerated in patients with acute mild to moderate METH toxicity. A randomized, open label design will be used in which one dose of IXT-m200 will be compared to treatment-as-usual (TAU). Approximately ~~40~~ 24 participants will be enrolled in ~~4~~ 3 cohorts. A dose escalation approach will be used so that progressively higher IXT-m200 doses will be evaluated in each of the first two cohorts. In conjunction with safety monitoring, this design assures the opportunity to observe early safety findings before any participants are exposed to the next higher dose. The randomization ratio for IXT-m200 versus TAU is defined as 4:1 for each of cohorts 1 and 2, with up to an additional 4 TAU participants in cohort 3 so that the number of participants receiving TAU equals the number receiving each dose of IXT-m200 at the end of the study.

| Cohort | IXT-m200 dose (g) | IXT-m200:TAU subject numbers |
|---|---|---|
| 1 | 0.5 | 8:2 |
| 2 | 2 | 8:2 |
| 3 | ~~To be determined by amendment; ≤3~~0 | ~~8~~0:~~2~~4 |
| ~~4~~ | ~~To be determined by amendment; ≤3~~ | ~~8:2~~ |

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

## 4.2. SCIENTIFIC RATIONALE FOR STUDY DESIGN

Because the participants in this study present requesting treatment for METH toxicity, but because IXT-m200 has not been administered in an acute setting to agitated patients, the open-label TAU comparison offers an early assessment of the utility of IXT-m200 for use to treat METH toxicity. A placebo control is not ethical because these patients present to the ED requesting treatment. The study design also includes rescue medications to ensure that in the event of worsening of the symptoms, which may be due to progression of the intoxication or due to either treatment, the patients may be treated in a timely fashion. The dose escalation in subsequent groups with safety evaluation between cohorts 1 and 2 is designed is ensure that an effective dose is tested~~, and to identify the lowest effective dose of mAb~~.

While lorazepam and haloperidol are commonly used to treat agitation in the ED, there is no consensus on the ideal sedative for acute agitation in the ED [1]. The goal of sedation in the ED is to calm a patient so he/she is not a danger to him/herself or others, and can be more accurately assessed by physicians. METH causes release of monoamines from nerve terminals and blocks their reuptake; chronic and binge METH use severely alters monoamine homeostasis. The adrenergic reserves of METH overdose patients are therefore atypical, making their responses to sedative medications difficult to predict. Even with careful titration of sedatives, patients may experience profound and prolonged somnolence, increasing their length of ED stays [14]. For agitation due to overdose or intoxication, benzodiazepines and/or first-generation antipsychotics, such as haloperidol, are often recommended [2] but sufficient doses of these drugs to reduce agitation may sedate patients for hours. This approach results in at best prolonged ED stays, and at worst the masking of other symptoms (physical or psychiatric) that may need more timely attention.

## 4.3. JUSTIFICATION FOR DOSE

IXT-m200 will be given via IV administration because this will provide immediate effects and provide for reliable pharmacokinetic analysis. The IXT-m200 doses selected for this study may include the range tested in Phase 1 (0.2 to 20 mg/kg or 3-g) and Phase 2a (6 and 20 mg/kg) studies of IXT-m200. Converting doses for a 75-kg person shows that the 0.5-g dose = 6.67 mg/kg and a 1.5-g dose = 20 mg/kg. 2-g doses have been given to participants weighing 100 kg without complication in the Phase 2a study and 3-g doses were given to all active participants (n=7) in the second Phase 1 study. Importantly, it is not

necessary to reduce METH brain concentrations to "zero" to demonstrate a clinically useful effect in this study, so we do not anticipate that markedly higher doses will be required. Rather, the pharmacological goal is to redistribute enough METH from the CNS into the systemic circulation so that symptoms are reduced sufficiently to allow patients to be discharged or referred for further treatment. In rodent studies, IXT-m200 acutely reduces CNS effects when present in a ratio of less than 30 molecules of METH per mAb binding site [15]. Given that there is no way to predict body burden or previous METH intake by people presenting to an ED, this study uses unit doses (e.g., 0.5 and 2 g) to facilitate dosing, establish safety, and determine dose response for agitation.

The rate of IXT-m200 administration is justified to obtain rapid resolution of symptoms of METH toxicity, commensurate with that obtained by lorazepam and/or haloperidol. The infusion rate for the 0.5-g dose is 33 mg/kg/hr (assuming a 75-kg person) and those for the 2-g doses are 80 mg/kg/hr. In prior studies, the highest infusion rate was 80 mg/kg/hr. Importantly, the infusion rates in two GLP toxicology studies greatly exceed the proposed rates for this study. In the first, rats were given 200 mg/kg/hr for a total single dose of 400 mg/kg, and in a second completed study, 300 mg/kg was given in 10 min or less each week for six months for a repeating rate of 1800 mg/kg/hr. There were no reported safety issues with these infusion rates in rats. Furthermore, it appears unlikely that there have been infusion rate-related AEs in human studies.

### 4.4. 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 the Schedule of Activities (SoA; section 1.3). Participants with an ongoing AE at the time of study completion will be followed until the event resolves, the Sponsor and the investigator agree that further follow-up is not medically necessary, or until they are lost to follow-up.

The end of the study is defined as completion of the last visit or procedure shown in the SoA.

## 5. STUDY POPULATION

### 5.1. DESCRIPTION OF AND RATIONALE FOR THE SELECTED POPULATION

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

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

Criteria for diagnosing METH toxicity are adapted from the DSM-5 criteria for stimulant intoxication and include:

- Recent (last 24 hour) use of methamphetamine or amphetamine
- Clinically significant problematic behavioral or psychological changes
    - e.g., euphoria or affective blunting; changes in sociability; hypervigilance; interpersonal sensitivity; anxiety, tension or anger; stereotyped behaviors; impaired judgement that developed during or shortly after METH use
- Two or more of the following
    - Bradycardia or tachycardia (<40 or >100 beats per minute)
    - Hypertension or hypotension (>140/90 or < 90/60)
    - Pupillary dilatation
    - Perspiration or chills
    - Nausea or vomiting
    - Psychomotor agitation or retardation
    - Muscular weakness, respiratory depression, chest pain, or cardiac arrhythmias
    - Confusion, seizures, dyskinesias, dystonias, or coma
- The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder

## 5.2. INCLUSION CRITERIA

Eligible participants will:

1. Be aged 18 to 45 years, inclusive;
2. Present to the ED with METH toxicity as defined in protocol;
3. Have a PANSS-EC score of 14-28, inclusive;
4. Have or agrees to have an intravenous (IV) line placed;
5. Give a history of METH use in the past 24 hours, with participant or observer attribution of symptoms to METH, or have a positive METH drug screen;
6. Be accompanied or readily represented by a legally authorized representative (surrogate) who can consent to participation on behalf of the participant if participant is found not able to consent for themselves using the UCSD Brief Assessment of Capacity to Consent (UBACC); and
7. Consent or assent to participation in the study.

## 5.3. EXCLUSION CRITERIA

Eligible participants will NOT:

1. Present with concomitant opioid overdose requiring ventilatory support;
2. Be self-reported to be pregnant or lactating;
3. Be considered to have significant concomitant medical illness or trauma, or symptoms of severe METH toxicity including
    a. sepsis or febrile illness;
    b. myocardial infarction, cardiac decompensation or arrhythmias including tachycardia that is not sinus; severe hypertension (>180/110 mmHg); inadequately treated hypertension on chronic medication; history of vasculitis;
    c. coma, stroke or severe head injury; new or ongoing seizure activity
    d. acute pulmonary decompensation or severe chronic obstructive pulmonary disease;

e. any hepatic impairment and/or acute hepatitis or renal impairment due to concomitant medical illness; or
f. current, or history of, neuroleptic malignant syndrome;

4. Be considered to be at imminent risk of suicide or have disqualifying answers to the following two questions. Disqualifying answers would be 1b2 or 2b.

    1. In the past 30 days, have you considered killing yourself?
       a) No
       b) Yes – if Yes, how often?
          B1) Not often (twice or less)
          b2) Somewhat often (more than twice)

    2. In the past year, have you attempted to kill yourself?
       a) No
       b) Yes

5. Be considered to be at imminent risk of injury or danger to self, others or property;
6. Have a history of severe allergy (rash, hives, breathing difficulty, etc.) to both lorazepam and haloperidol, or known hypersensitivity or infusion reaction to any antibody medications; or
7. Be judged by the treating ED physician, investigator, or Sponsor (or designee) to be inappropriate for the study, including people whom the investigator determines cannot reasonably be consulted for assent to participation.

## 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.

Subjects 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 and until 90 days after receiving the dose of study drug.

## 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 SAEs.

All participants who consent but fail screening will be referred to treatment in the ED outside of the study per the recommendation of the screening physician. Subjects may be rescreened at any future presentation to the ED.

## 5.6. STRATEGIES FOR RECRUITMENT AND RETENTION

### 5.6.1. STRATEGIES FOR RECRUITMENT

Generally speaking, recruitment strategies are based on appropriate site selection (sufficient numbers of potential participants) and education of ED staff to look for possible participants.

The recruitment of vulnerable participants is necessary because the study is designed to determine if IXT-m200 is well-tolerated and works to reverse METH toxicity in an emergency setting. While people under the influence of METH and other drugs may be vulnerable because they may lack full consent capacity, participants will still provide assent, and their legally authorized representative will provide consent at the time of the study start if the participant is found lacking the capacity to consent for themselves using the UBACC assessment. No participant will be enrolled in the study who does not provide consent or assent. On Day 3, when participants return for their first follow-up visit, informed consent will be obtained, or repeated, from them.

Participants will be compensated based on local precedent, which may be different at each site.

### 5.6.2. STRATEGIES FOR RETENTION AND FOLLOW-UP

Retention strategies are based on education of the participant and discussion of the importance of follow-up to good health. Specifically, this includes the opportunity to follow up on any medical findings from the ED stay, and to further discuss opportunities for treatment for MUD if the person desires.

Phone calls, text messages, and emails will be sent as reminders to the participants to follow up. Transportation will be provided if needed to the follow-up visits, and referral for treatment of psychiatric and medical issues will be arranged.

# 6. STUDY INTERVENTION

## 6.1. STUDY INTERVENTION ADMINISTRATION

### 6.1.1. STUDY INTERVENTION DESCRIPTION

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.

The mechanism of action of IXT-m200 is via high-affinity binding to METH, which either prevents METH from reaching its sites of action in the CNS, or removes it from those sites of action [7,8]. Because anti-METH antibody medications significantly alter the distribution and tissue concentration of METH, their mechanism of action is PK antagonism. IXT-m200 was developed from a murine anti-METH

antibody and preclinical studies have shown that both the murine and chimeric antibodies bind METH and alter its PK in a similar way [7,8,16]. Further information on IXT-m200 may be found in the IB.

### 6.1.2. DOSING AND ADMINISTRATION

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

## 6.2. PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

### 6.2.1. ACQUISITION AND ACCOUNTABILITY

Study Intervention: Sponsor will provide the required number of vials of IXT-m200. 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.

The investigator at each site will be responsible for acquiring commercially available TAU and rescue medications for use in the study.

### 6.2.2. FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Study Intervention: 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 glass vials with stoppers and flip-off seals. Catalent Pharma Solutions manufactures the formulated active pharmaceutical ingredient. The University of Iowa Pharmaceuticals produces the vialed drug product.

Labels will be similar to the following:

InterveXion Therapeutics®
Anti-methamphetamine IXT-m200
18.5-21.5 mg/mL
Manufactured: DD MMM YYYY
UIP Lot: XXXIXXXX
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

### 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

The appropriate total dose of IXT-m200 will be prepared for IV administration. No dilution of the drug product is required. For calculation purposes, the concentration of the drug product is 20 mg/mL.

| Dose level (g) | Volume to be dosed (mL) |
|---|---|
| 0.5 | 25 |
| 2 | 100 |

TAU and rescue medications: These are obtained and provided by the local pharmacy in appropriate doses and delivery devices. Lorazepam will be given by slow IV push as the participant tolerates. Haloperidol is given via an intramuscular injection in the deltoid or gluteal muscles or by slow IV push as tolerated.

## 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 in ~~each~~ cohorts 1 and 2 will be randomized to IXT-m200 or TAU after consenting to participate. Those who qualify will be randomized at a 4:1 ratio. Randomization codes will be generated by the randomization statistician and will be implemented by interactive voice/web response system (IXRS). This will be the same system for all sites so that there is no site bias to dosing. Participants will be randomized in the order they are enrolled. Participants in cohort 3 will receive TAU.

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

## 6.4. STUDY INTERVENTION COMPLIANCE

IXT-m200 and TAU are administered by the IV or IM routes by qualified personnel. Compliance with dosing will be verified by reference to the eCRF documentation of dosing.

## 6.5. CONCOMITANT THERAPY AND RISK MITIGATION PLAN

All concomitant medications (i.e., those given in the ED, prescription medications, over-the-counter medications, non-prescription medications, and supplements) taken during study participation will be recorded on the eCRF.

### 6.5.1. RESCUE MEDICINES

Lorazepam or haloperidol will be used as first-line rescue medications in all participants, regardless of treatment assignment, for agitation or dysphoria (lorazepam) or psychosis (haloperidol) [2,14,17]. If further rescue medications are needed, the choice and doses of the rescue medications will be at the discretion of the treating ED physician. To allow time for maximum effects of the initial treatments to evolve, rescue medications should not be given for 30 min after initiation of IXT-m200 or TAU dosing; however, timing is ultimately at the discretion of the treating physician.

Hypertension or tachycardia may be treated at the discretion of the treating physician with labetalol, hydralazine, or other similar approaches. Other cardiovascular instability (e.g., hypotension with blood pressure less than approximately 80/50 mmHg or less than approximately 90/60 mmHg with symptoms of dizziness, near syncope, or nausea, for example) will be treated initially with a fluid bolus[14]. If hypotension persists, it will be treated with incremental doses of the direct acting vasopressors phenylephrine, norepinephrine, or dopamine (starting at alpha adrenergic doses >10 µg/kg/min), or other appropriate medications at the discretion of the treating ED physician.

### 6.5.2. RISK MITIGATION

The following risk mitigation strategies have been designed based on other studies in people who use METH, on the problems posed specifically by enrolling participants in an emergency setting, on the clinical pharmacology of METH, and on the known pharmacology of IXT-m200:

1. Selection of a specific participant group. As stipulated in the protocol, participants who are relatively healthy with no significant medical or surgical illness will be recruited.
2. IXT-m200 dosing. IXT-m200 will be administered in escalating dose groups so that the lowest IXT-m200 dose (0.5 g) will be evaluated before the higher doses, in subsequent cohorts. This will allow determination of the effects of IXT-m200 at a low predicted effective IXT-m200 dose, before effects are assessed following a high predicted effective IXT-m200 dose.
3. Treatment in an Emergency Department. A crash cart will be available in the ED and personnel trained in CPR are always available in the ED setting. Oxygen and emergency ventilation equipment are immediately available. Normal saline will be used as the IV fluid and fluid boluses can be administered if any hypotension is seen. In the event of serious medical complications, a code may be called.
4. Frequent safety review. A formal safety review will be done between cohorts, and at any point needed based on the severity of AEs. This would include Grade 3 AEs related to worsening of METH effects in the presence of IXT-m200.

All of the study sites are EDs and therefore have all medications that might be needed to treat mAb toxicity, which may manifest as hypotension and bradycardia or tachycardia; bronchospasm with or without hypoxemia; or flushing, pruritis, and urticaria. Hospital-maintained crash carts, and oxygen and emergency ventilation equipment (Ambubags) are always available. Advanced Cardiovascular Life Support-certified providers and code teams are always available to treat life-threatening events.

# 7. STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

## 7.1. DISCONTINUATION OF STUDY INTERVENTION

The criteria outlined in section 8.3.3.1 will be used to categorize the severity of all AEs.
Enrollment and study drug administration will be immediately paused if any 1 of the following events occurs, unless the event was clearly unrelated to study drug administration, or the event is an expected sequelae of untreated METH toxicity:

- Three (3) participants experience a Grade 3 AE.
- Two (2) participants experience a Grade 3 AE related to increased agitation, aggression, or anxiety.
- One (1) participant experiences a Grade 4 AE.
- A death occurs.

Expected sequelae of untreated METH toxicity which will not be considered grounds for a study pause include:

- Hypertension/tachycardia
- Euphoria
- Agitation
- Insomnia
- Anxiety
- Seizures
- Mania/aggression

Worsening of any of the above following administration of study drug will be considered an AE and subject to the rules for study pause above.

If any of the pause conditions are met, the Sponsor, in consultation with the investigator and Medical Monitor, will suspend enrollment until a full safety review by both the Sponsor and DSMB is performed. A decision to reinitiate enrollment will be made following relevant consultation with the appropriate authorities based on the results of the safety review.

## 7.2. PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants may be withdrawn from the study at any time before IXT-m200 administration for reasons including the following:

- at their own request or at the request of their legally authorized representative,
- the participant meets an exclusion criterion (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 participant,
- if, in the investigator's opinion, continuation in the study would be detrimental to the participant's well-being, or
- at the specific request of InterveXion (Sponsor) or clinical site.

Once participants receive IXT-m200, every reasonable effort will be made to have them attend the Day 3 and 28 follow-up appointments.

In all cases, the reason for withdrawal must be recorded in the electronic Case Report Form (eCRF) 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 discontinue from further participation in the study, the research staff will cease further contact attempts.

Participants who consent and are randomized but do not receive the study intervention may be replaced and will not be included in any data set.

Participants who consent and are randomized and do receive the study intervention, but leave the ED prior to medical discharge and/or are not positive for METH by UDS or blood testing will be included in the safety set and ITT. Additional subjects may be recruited to ensure that ~~each~~ both cohorts 1 and 2 contain~~s~~ 8 subjects dosed with IXT-m200 and 2 subjects dosed with TAU who complete the protocol through discharge from the ED and are positive for METH based on UDS or blood testing.

Participants will not be replaced if they complete through discharge from the ED, but do not return for Day 3 or 28 visits.

### 7.3. LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if s/he fails to return for the Day 3 and 28 scheduled visits 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 as soon as possible and 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. EFFICACY ASSESSMENTS

Study procedures to evaluate agitation include:

- The PANSS-EC (Positive and Negative Syndrome Scale – Excited Component) is used commonly as an assessment tool for clinical studies of pharmacotherapy for agitation. It includes 5 items (excitement, poor impulse control, tension, hostility, and uncooperativeness) which are each rated from 1 (absent) to 7 (extremely severe). A score of 14-28 is consistent with clinically significant psychomotor agitation of mild to moderate severity [18–20]. It will be administered only at screening as part of eligibility determination.
- The ACES (Agitation-Calmness Evaluation Scale) is a single-item, 9-point scale to differentiate agitated, calm, and sleep states. It has been used to assess the effects of pharmacotherapy on

agitation [12]. This assessment will be performed at all time points marked in the Schedule of Activities table to determine the impact of IXT-m200 versus TAU on agitation.
- Vital sign measurements over time including heart rate, blood pressure, temperature.
- Need for rescue medications to treat CNS symptoms of agitation, dysphoria, or psychosis; and CV symptoms of hypertension, tachycardia, or other cardiovascular instability.

## 8.2. SAFETY AND OTHER ASSESSMENTS

UCSD Brief Assessment of Capacity to Consent (UBACC)
- A 10-item list of questions focused on understanding and appreciation of the description of the research study [21]. This assessment will be used to screen potential participants for the capacity to consent for themselves. A score of 20 will be required to be eligible to consent without an LAR.

Safety evaluations include the following:

Medical and Medication Histories
- Medical history: A focused medical history will be obtained at triage/screening by interview and any available medical records. A detailed and pertinent medical history will be obtained after IXT-m200 dosing or TAU is complete and the participant is cooperative.
- Medication history: A medication history will be obtained at triage/screening by interview and any available medical records. This will be reviewed and supplemented if needed after IXT-m200 or TAU dosing is complete and the participant is cooperative. The medication history will be reviewed at the 2 scheduled study visits.

Physical Examination, Vital Sign Measurement, Height, and Weight
- A focused physical examination (excluding rectal/genital and breast examination) will be performed at triage/screening. The physical examination may consist of vital signs and an examination of the following: general appearance, neurological, skin, head, eyes, ears, nose, throat, neck, chest, heart, abdomen, and extremities.
    - A detailed physical examination (excluding rectal/genital and breast examination) will be performed after IXT-m200 or TAU dosing is complete and the patient is cooperative.
    - Focused exams will be performed during the two follow-up appointments and as otherwise necessary.
- Vital sign measurements (heart rate, blood pressures [systolic and diastolic], respiratory rate, temperature [oral], and pulse oximetry readings) will be obtained. Measurements will be taken at triage and screening, and as outlined in the Schedule of Activities table.
- Height and weight will be obtained on Day 1 after dosing with IXT-m200 or TAU.

Evaluations of Drug and Alcohol Use
- DSM-5 criteria will be used at the Day 3 follow-up visit to assess for Substance Use Disorders (including METH, opioids, alcohol, nicotine, marijuana, etc.).
- Qualitative urine drug screen (UDS; including amphetamines, MDMA, barbiturates, benzodiazepines, cocaine, opiates, THC, and phencyclidine) and alcohol breath testing will be performed once. This testing may be done before or after initial treatment so that the agitation may be treated as quickly as possible.
- Administer standard drug assessment of METH and other drug use since last visit on Days 3 and 28
- The METH Perceptions Assessment is the following list of questions intended to determine whether IXT-m200 affects how subjects perceive subsequent doses of METH.

- 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?*" Answer: 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

Psychiatric Evaluation

- A detailed and pertinent psychiatric history will be obtained at triage/screening evaluating for (but not limited to) the following: major current depression, psychosis, bipolar illness, organic brain disorder, or dementia, which would make study compliance difficult in the opinion of the investigator.
- Subjects will be queried about their history of suicide attempts and suicide ideation by the following two questions and any others the investigator deems necessary.

1. In the past 30 days, have you considered killing yourself?
   a) No
   b) Yes - if Yes, how often?
      b1) Not often (twice or less)
      b2) Somewhat often (more than twice)
2. In the past year, have you attempted to kill yourself?
   a) No
   b) Yes

Disqualifying answers would be 1b2 or 2b.

Electrocardiogram

- An electrocardiogram (ECG; 12-lead) will be recorded after IXT-m200 or TAU dosing is complete and the participant is cooperative. Standard ECG parameters including heart rate, QRS, 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).

Biological Specimen and Laboratory Evaluations

- Blood samples will be taken for analysis of IXT-m200 in serum on Day 1 (pre-dose, 4 hours after dosing, and at discharge), Day 3, and Day 28 from subjects who were randomized to receive IXT-m200 only.
- Blood samples will be taken for analysis of METH and amphetamine in plasma on Day 1 (pre-dose, 4 hours after dosing, and at discharge).
- Blood will be taken for clinical laboratory studies which will include complete blood count, blood urea nitrogen/creatinine, serum glucose, electrolytes, liver function tests (AST, ALT, gamma-glutamyl transferase, alkaline phosphatase, total and direct bilirubin), and creatinine phosphokinase. These tests will be performed on Day 1 after dosing is completed and repeated on Day 3.
- Urine samples will be taken for UDS, urinalysis, and urine pregnancy tests. These tests will be performed on Day 1; results are not required prior to dosing.

## 8.3. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

### 8.3.1. DEFINITION OF ADVERSE EVENTS (AE)

An **AE** is any untoward medical occurrence in a participant administered IXT-m200 or TAU, 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 IXT-m200 or TAU, whether or not related to IXT-m200 or TAU.

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, TAU, 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".

### 8.3.2. DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An SAE is an AE that at any dose:

- results in death;
- is life-threatening;
- requires admission to the hospital;
- 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 participant 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 in the view of the PI require medical or surgical intervention to prevent one of the other outcomes listed above. These will also usually be considered serious.

### 8.3.3. CLASSIFICATION OF AN ADVERSE EVENT

#### 8.3.3.1 SEVERITY OF EVENT

The general approach outlined by the Club Phase 1 working group [22] 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.

Regarding vital sign AEs, Section 6.5.1 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 ($O_2$ saturation < 93% on oxygen) occurs and requires medications, this will constitute a Grade 3 reaction, and will be documented as such.

#### 8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All 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.

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 to the study drug;
- 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.

#### 8.3.3.3. 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 or for the participant's underlying medical condition.

### 8.3.4. 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, 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.

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.

### 8.3.5. ADVERSE EVENT REPORTING

All AEs (whether serious or nonserious) that occur after the participant has been randomized must be documented on the appropriate pages of the eCRF. 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, until a satisfactory explanation is found or the investigator 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 Sponsor, Medical Monitor and DSMB between cohorts. If an investigator decides it necessary, AEs may be reviewed at any time by consultation with the investigator, Medical Monitor, and Sponsor.

### 8.3.6. 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 Medical Monitor and Sponsor within 24 hours of site awareness.
- Other SAEs regardless of relationship, will be submitted to the Medical Monitor and Sponsor within 48 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until the investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the Medical Monitor or 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 Sponsor will be responsible for notifying the 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 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.

### 8.3.7. REPORTING EVENTS TO PARTICIPANTS

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

### 8.3.8. EVENTS OF SPECIAL INTEREST

As a dose-escalation safety trial, safety will be monitored closely and dose escalation will occur only when available safety data warrant. On the other hand, the proposed trial by nature involves a population in significant duress, sufficient to merit a visit to the ED and meet the required eligibility criteria, and these participants will display a range of expected AEs due to their concomitant METH toxicity.

To balance these important requirements of trial conduct and patient protection, the study will capture any AEs underway at the time of presentation to the ED that can be attributed to METH toxicity. These include:

- Hypertension/tachycardia
- Euphoria
- Agitation
- Insomnia
- Anxiety
- Seizures
- Mania/aggression

These AEs will not be considered as study participation-related, and will not be included in consideration of dose escalation or study stopping criteria, unless they newly emerge or worsen after administration of investigational product. If they worsen, and reach sufficient severity, they will be considered as a part of the trial stopping criteria.

### 8.3.9. REPORTING OF PREGNANCY

If a participant is found to be pregnant after they have received IXT-m200 and before day 28, they should complete the study, with no further IXT-m200 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.

## 8.4. UNANTICIPATED PROBLEMS

### 8.4.1. 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.

### 8.4.2. 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 subject protections. The primary consideration in making these judgments is the need to take timely action to prevent avoidable harms to other participants.

### 8.4.3. 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.

The statistical evaluation will be performed using SAS® software version 9.4 or higher (SAS Institute, Cary, NC). All data will be listed, and summary tables will be provided. Summary statistics will be summarized and presented by treatment group, i.e., dose level of IXT-m200 and TAU, whereby the TAU patients from all ~~4~~ cohorts will be pooled. For continuous variables, data will be summarized with the number of subjects (N), mean, standard deviation, median, minimum, and maximum by treatment group. For categorical variables, data will be tabulated with the number and proportion of subjects for each category by treatment group.

### 9.1. STATISTICAL HYPOTHESES

This is a descriptive study for evaluation of safety and tolerability as the primary objective. Descriptive summaries will be performed for tabulation and comparison of safety and efficacy endpoints. Descriptive statistical tests will be applied for the pairwise statistical comparison of efficacy endpoints in IXT-m200 dose levels versus TAU using a two-sided alpha level of 5%.

### 9.2. SAMPLE SIZE DETERMINATION

No formal sample size estimation has been performed. A sample size of 8 IXT-m200 and <u>approximately</u> ~~2~~<u>28</u> TAU patients ~~per dose cohort~~ is considered adequate to assess the safety and tolerability of IXT-m200 compared to TAU. Data from TAU patients from each cohort will be pooled for summaries.

## 9.3. POPULATIONS FOR ANALYSES

The enrolled population will include all patients who sign the informed consent.

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

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

The Full Analysis Set (FAS) population will include those in the ITT population who receive any dose of study drug and were positive for methamphetamine by UDS or blood testing during the ED stay. The treatment group assignment in this population will be defined by the randomized treatment. This population will be used for the analysis of efficacy.

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

The PK Population will include all subjects for whom a PK concentration is available post-dose.

## 9.4. STATISTICAL ANALYSES

### 9.4.1. GENERAL APPROACH

This is a descriptive study for evaluation of safety and tolerability as the primary objective. The comparison of safety endpoints and of efficacy endpoints between the treatment groups will be performed using descriptive summaries and descriptive confidence intervals (CI) and statistical tests.

### 9.4.2. ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Not applicable.

### 9.4.3. ANALYSIS OF THE SECONDARY ENDPOINT(S)

Summary tables with descriptive statistics for actual values and changes from baseline will be provided for the ACES score for each scheduled timepoint by treatment group. Descriptive pairwise t-tests will be performed for the comparison of the changes from baseline of each IXT-m200 dose versus TAU. The time course of actual ACES scores and of change from baseline ACES scores will be presented by treatment group in a figure using mean values and 95% CIs.

The time to normalization of agitation using ACES will be defined as the time until the ACES score climbs to ≥4 the first time, in subjects for which the score remains in the range of 4-6 for the remaining time points. If the ACES score rises to the range of 7-9 during the ED stay, then normalization will be

defined as the time until the score is reduced to within the range of 4-6 following the end of the sedated period. This time will be presented by Kaplan-Meier estimates and figure by treatment group, and will be pairwise compared between each IXT-m200 dose versus TAU by the logrank test.

The time course of actual values of vital sign parameters and of changes from baseline will be presented by treatment group in a figure using mean values and 95% CIs. A shift table of post-baseline vital sign parameter values compared to baseline values will be provided by treatment group presenting the number and percentage of subjects below normal range / within normal range / above normal range. The time to normalization (i.e., returning to normal range) of vital sign parameters is defined as the first time the vital sign parameter is in normal range and remains in normal range for the remaining time-points. This time will be presented by Kaplan-Meier estimates and figure by treatment group, and will be pairwise compared between each IXT-m200 dose versus TAU by the logrank test.

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

PK concentrations of IXT-m200 and METH will be summarized by timepoint and by treatment group. Additionally, change from baseline of METH concentration will be summarized for each post-dose timepoint by treatment group. The change from baseline in METH concentration will be presented graphically.

### 9.4.4. SAFETY ANALYSES

All reported AEs will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA). The incidence of treatment-emergent AEs (TEAEs; events with onset dates on or after the administration of the study drug) will be included in incidence tables. Events with missing onset dates will be included as treatment-emergent. If a subject experiences more than one occurrence of the same AE, the occurrence with the greatest severity and the closest association with the study drug will be used in the summary tables. An overall summary by treatment group, overall IXT-m200 and total will be presented with the number and percentage of subjects experiencing any TEAE, any TEAE by severity, any related TEAE, any serious AE (SAE), any related SAE, any AESI, and any TEAE leading to death. Summary tables by system organ class and preferred term will be provided for treatment group, overall IXT-m200 and total for TEAEs, TEAEs by maximum severity, TEAEs by maximum relationship to study treatment, treatment-related TEAEs, serious TEAEs, and AESIs. All AEs will be listed by patient, along with information regarding onset, duration, relationship and severity to study drug, action taken with study drug, treatment of event, and outcome.

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

Physical examination results will be presented by number and percentage of patients in each category and scheduled time point by treatment group, overall IXT-m200 and total.

Clinical laboratory data (continuous parameters) will be summarized using descriptive statistics for each scheduled assessment time point by treatment group. Categorical laboratory data and urinary drug screen results will be presented by number and percentage of patients in each category and scheduled time point

by treatment group. Additionally, for laboratory data, frequency tables with number and percentage of patients of scheduled time point will be provided using the categories above/within/below normal range.

Extent of exposure will be summarized by a frequency table of number and percentage of patients by treatment group who received the total amount of the planned infusion, and who received the infusion partly.

#### 9.4.5. BASELINE DESCRIPTIVE STATISTICS

Demographic and baseline characteristics will be summarized by treatment group, overall IXT-m200 and total.

#### 9.4.6. PLANNED INTERIM ANALYSES

~~Between cohorts 2 and 3, a review of the efficacy data, i.e., all secondary endpoints, will be undertaken to determine the dose levels for cohorts 3 and 4. The Medical Monitor and DSMB will provide their recommendations to the Sponsor for a final decision.~~

~~A protocol amendment will incorporate the adjustments. Further details will be provided in the DSMB Charter and the SAP.~~No interim analyses are planned.

#### 9.4.7. EXPLORATORY ANALYSES

The duration of the stay in the ED, calculated as starting from triage time and also as starting from treatment start time, will be summarized by descriptive statistics by treatment group and overall IXT-m200. The descriptive pairwise comparison of IXT-m200 dose levels versus TAU will be performed by a t-test using log-transformed durations.

# 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/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

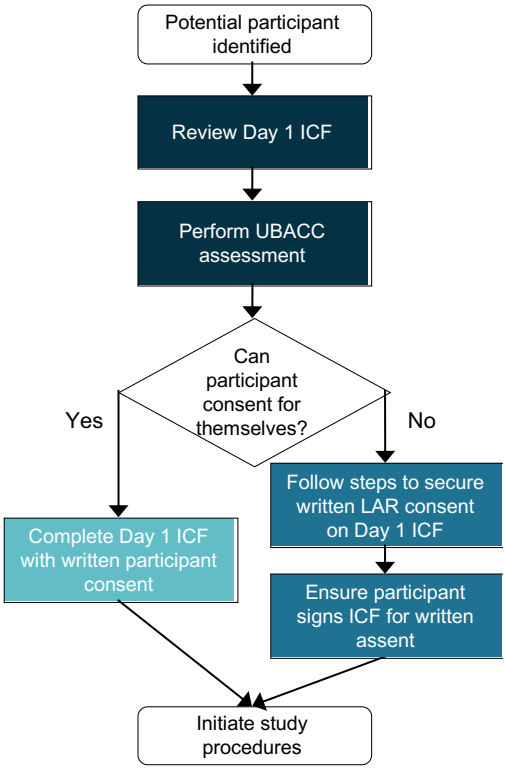
Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and if required, a legally authorized representative (LAR; surrogate or substitute decision maker) and written documentation of informed consent and/or assent from the participant is required prior to starting the screening process, and subsequently administering study intervention.

#### 10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Given that METH use can cause agitation, delirium, and psychosis, only people who are found able to consent for themselves using the UBACC, or for whom a LAR who can consent for the participant can be identified will be recruited. The LAR may provide consent in accordance with local regulations, as described in 0.

Specifics will vary depending the clinical site, but patients identified with symptoms of METH toxicity will be approached by the investigator or designated and trained study personnel about participation in the study. Patients will be asked if they would like to participate in the study and if they have a LAR to provide consent for them. If the answer is yes to both questions, or they are found able to give consent for themselves, informed consent will be sought using IRB-approved consent forms and processes. No one will participate without providing written consent or assent by signature of the participant recorded on the ICF.

The process for consent is outlined in the following figure.




Written informed consent, or reconsent, from the participant will be obtained before any procedures are conducted on Day 3.

#### 10.1.1.2.1 LAR CONSENT PROCEDURES

The following steps will be conducted to obtain consent from the LAR on Day 1, when a subject is found unable to consent for themselves by using the UBACC:

1. The informed consent form (ICF) will be sent to the potential LAR by email, fax, or other electronic means.
2. The person obtaining consent will connect with the LAR by phone, video, or other means and will confirm they are speaking with the correct individual.
    a. The conversation requires a witness to be present starting with Step 2, preferably a member of the site staff so that signatures can be easily obtained.
3. The date and version number of the consent will be confirmed between the person obtaining consent and the LAR.
4. The consenting process will proceed as usual with the person obtaining consent verbally going over the informed consent and answering any questions.
5. The person obtaining consent will ask for verbal informed consent to conduct screening assessments.
6. The person obtaining consent will document the conversation in the subject file or progress notes recording at a minimum:
    a. Date and time of the conversation
    b. How it occurred (e.g., telephone or video conference)
    c. Name of the witness and any other participants
    d. Confirmation that the LAR received the ICF
    e. Confirmation of verbal informed consent to conduct screening
7. The LAR will sign the ICF. This may be documented in many ways, including:
    a. The LAR may print the ICF, sign it and return a scan or picture of the form electronically. The LAR must be informed that there is a small risk of email being intercepted in route.
    b. The LAR may use an electronic signature. Some options include:
        i. Adobe Sign
        ii. Apple Pen
        iii. DocuSign
8. Documentation of the LAR signature must be received, and all other steps in the informed consent process completed, prior to any therapeutic intervention.
9. The final ICF must be filed in the designated investigator/research file location and a copy given to the LAR and participant.

### 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, the DSMB, 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 subjects 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. Investigators are subject to subsection 301(d) of the Public Health Service Act.

### 10.1.4. FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored as described in the Statistical Considerations (Section 9) and Data Handling (Section 10.1.9) sections of this protocol. 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 | Medical Monitor |
|---|---|
| W. Brooks Gentry, MD | Patrick Keenan, MD |
| InterveXion Therapeutics, LLC | Syneos Health |
| 4301 W. Markham St. #831 | 5707 Southwest Parkway Bldg 2, Suite 200 |
| Little Rock, AR 72205 | Austin, TX 78735 |
| 501 320 7601 | O: 737 484 3018, C: 512 806 4429 |
| gentrywilliamb@uams.edu | patrick.keenan@syneoshealth.com |

### 10.1.6.SAFETY OVERSIGHT

Safety oversight will be under the direction of a DSMB composed of individuals with the appropriate expertise, likely including clinical trial oversight, monoclonal antibody and methamphetamine clinical pharmacology, acute care medicine (cardiovascular and/or emergency), psychiatry or behavioral medicine, statistics, and a patient advocate or representative. Members of the DSMB will be independent from the study conduct and free of conflict of interest, or measures will be enacted to minimize real or perceived conflicts of interest. The DSMB will meet at the conclusion of ~~each~~ cohort 1 to assess safety data and intermittently as necessary. 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.

Cohort escalation review~~s~~ will be performed by the Sponsor, Medical Monitor, and DSMB between cohorts 1 and 2 and the next group will not start until after completion of this review. This~~ese~~ review~~s~~ will be scheduled to occur approximately two weeks after the last enrollee in the cohort has completed the Day 3 visit so that all Day 3 data available are considered. Safety data to be reviewed include vital signs, ECG, AEs, clinical laboratory values (serum and urine), and UDS.

### 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 or by electronic means of viewing both records, 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).

Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what

level of detail monitoring will be performed, and the distribution of monitoring reports. 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

Each 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/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 eCRF(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 adverse events (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 investigator and the IRB
- Composition of the IRB or other applicable statement
- Record of all significant communications between the investigator 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 eCRFs and of documentation of corrections for all participants
- 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 investigator 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.

### 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 sites 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 subject'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 |
| ACES | Agitation/Calmness Evaluation Scale |
| ALT | Alanine Aminotransferase |
| AST | Aspartate Aminotransferase |
| AUC | Area Under the Curve |
| AUCinf | Area Under the Curve from Time 0 Through Infinity |
| CFR | Code of Federal Regulations |
| CI | Confidence Interval |
| Cmax | Maximum Concentration |
| CMP | Clinical Monitoring Plan |
| CNS | Central Nervous System |
| COC | Certificate of Confidentiality |
| CONSORT | Consolidated Standards of Reporting Trials |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CV | Cardiovascular |
| DHHS | Department of Health and Human Services |
| DSM5 | Diagnostic and Statistical Manual of Mental Disorders 5 |
| DSM5 SUD | Diagnostic and Statistical Manual of Mental Disorders 5 for Substance Use Disorders |
| DSMB | Data and Safety Monitoring Board |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Forms |
| ED | Emergency Department |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practices |
| HACA | Human Anti-Chimeric Antibody |
| IB | Investigator's Brochure |
| ICH | International Conference on Harmonisation |
| IgG | Immunoglobulin G |
| IND | Investigational New Drug Application |
| IRB | Institutional Review Board |
| ITT | Intention-To-Treat |
| IV | Intravenous |
| IXRS | Interactive Voice/Web Response System |
| LAR | Legally Authorized Representative |
| mAb | Monoclonal Antibody |
| MedDRA | Medical Dictionary for Regulatory Activities |
| METH | Methamphetamine |
| MUD | Methamphetamine Use Disorder |
| N | Number |
| NA | Not Applicable |
| NCT | National Clinical Trial |
| NIH | National Institutes of Health |
| NIDA | National Institute on Drug Abuse |
| OHRP | Office for Human Research Protections |

| | |
|---|---|
| PANSS-EC | Positive and Negative Syndrome Scale – Excited Component |
| PI | Principal Investigator |
| PK | Pharmacokinetic |
| PP | Per-Protocol |
| QC | Quality Control |
| SA | Self-Administration |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SoA | Schedule of Activities |
| SOP | Standard Operating Procedure |
| STAMPOUT | Study of Antibody for Methamphetamine Outpatient Therapy, NCT03336866 |
| TAU | Treatment As Usual |
| TEAE | Treatment-Emergent Adverse Event |
| UBACC | UCSD Brief Assessment of Capacity to Consent |
| UDS | Urine Drug Screen |
| UPT | Urine Pregnancy Test |
| Urine AE | Cumulative Urinary Excretion |
| US | United States |
| $V_d$ | Volume of Distribution |
| WBC | White Blood Cell |

## 10.3. PROTOCOL AMENDMENT HISTORY

| Version/Date | Description of Change | Brief Rationale |
|---|---|---|
| V2 23Mar2021 | Updates throughout to allow dosing of haloperidol up to 5 mg by IM or IV | TAU may include 5 mg haloperidol. IV dosing option added to allow physicians the choice. |
| | 1.3 Clarified SOA to match section 8 for UDS. | Clarification updates only. |
| | 5.2 Updated inclusion criteria 3 with upper bound of 25 for PANSS-EC score. | To ensure that severely METH intoxicated patients are not enrolled. |
| | 6.5.1 Added dopamine (and other medications) as option for rescue medication for hypotension at specified starting dose. | To include additional rescue medications. |
| | 7.1 Added study halting rule for two Grade 3 AEs related to agitation, aggression, or anxiety. | Increased METH toxicity signs could indicate treatment failure. It is important to pause the study for review in the case of toxicity-related AEs. |
| | 8.2 Changed Day 3 clinical labs from 'repeat if needed' to 'required'. | It is likely that the Day 1 lab results would not be available in order to determine necessity of repeat lab data by Day 3. |
| | 10.1.1.2 Clarified consent process. | To note that a box will be checked if LAR consent is obtained by phone. |
| | 12.9.1 Added DSMB member names and affiliations. | To add names and affiliations. |
| V3 15Nov2021 | 1.2 Updated schema. | To remove references to time frames. |
| | 1.3 Added collection of ACES score at time 0 and broadened the window for collection of UDS, UPT, and breathalyzer. | To ensure an ACES score is captured proximate to dosing initiation and to allow UDS, UPT, and breathalyzer to occur before or after dosing. |
| | 5.2 Revised inclusion criteria 3 to increase the upper limit of the PANSS-EC assessment to 28. | To more accurately reflect moderate severity agitation, which could include a score of "4" on all 7 dimensions. |
| | 5.2 Revised inclusion criteria 5 to include a positive METH drug screen. | To allow a positive METH drug screen rather than participant or observer attribution of symptoms to METH use. |
| | 5.3 Revised exclusion criteria 1 to remove the exclusion of those requiring naloxone treatment. | Removed as unnecessary. |
| | 5.3 Revised exclusion criteria 3c to remove the | Removed as unnecessary. |

| Version/Date | Description of Change | Brief Rationale |
|---|---|---|
| | exclusion of agitation requiring restraint. | |
| | 5.3 Revised exclusion criteria 4 to include suicidality questions asked and modify the time frame of the questions asked. | To include the specific questions to be asked and the disqualification criteria in the list with other criteria. The time frames for reported suicidal ideation and suicide attempt were reduced to allow those with adolescent or >1 year ago suicide attempts to enroll. It is considered that participants who have not attempted suicide again in the past year and have also not been thinking much about it in the past month are stable enough for study enrollment. |
| | 6.2.3 Removed the frozen IP storage option. | To clarify the preferred storage condition of refrigerated. |
| | 7.2 Clarified recruitment of additional subjects. | To clarify that additional subjects may, not will, be recruited to complete the cohorts with those testing positive for METH. |
| | 8.1 Updated the rationale for the PANSS-EC range. | To clarify the change to inclusion criteria 3. |
| | 8.2 Updated the Evaluations of Drug and Alcohol Use to remove propoxyphene and change time frame for UDS and breathalyzer | To remove propoxyphene testing as unnecessary and broaden the time frame for collecting UDS and breathalyzer tests to before or after dosing. |
| | 8.2 Updated the Psychiatric Evaluation section to modify the time frame used for questions about suicide attempts and ideation. | The time frames for reported suicidal ideation and suicide attempt were reduced to allow those with adolescent or >1 year ago suicide attempts to enroll. It is considered that participants who have not attempted suicide again in the past year and have also not been thinking much about it in the past month are stable enough for study enrollment. Removed reference to IXT Suicidal Ideation Questionnaire as unnecessary. |
| | 8.2 Added bilirubin to laboratory evaluations | Test was previously omitted. |
| | 8.2 Changed time frame for UDS, urinalysis, and UPT | To broaden the time frame for collecting urine samples to before or after dosing. |
| | 8.3.2 Clarified wording to define a medically important event classified as an SAE. | To clarify the definition of a medically important event that should be considered an SAE. |
| | 8.3.6 Reduced the time frame of reporting of SAEs to Sponsor and Medical Monitor that are not life threatening to 48 hours. | To allow time for reporting to NIDA by 72 hours post-event occurrence. |
| | 9.4.3 Removed requirement for two consecutive time points following a return to | To allow subjects to be discharged faster rather than waiting on an additional time point after a return to normal. |

| Version/Date | Description of Change | Brief Rationale |
|---|---|---|
| | normal for the ACES assessment. | |
| | 9.4.3 Removed requirement to report ratio of IXT-m200 to METH. | Removed as unnecessary. |
| | 10.1.1.2 Clarified consent process by adding wording from Protocol Clarification Letter dated 07 April 2021. | Removed unnecessary wording and added section 10.1.1.2.1 describing IRB-approved consent procedures for LAR. |
| | 10.1.7 Added option for electronic SDV as needed. | To clarify that SDV could be done via electronic means if necessary and possible, and not only during an on-site visit. |
| V4 09Mar2022 | Updates throughout to change dose level for cohort 2 to 2-g doses | To update the dose level for cohort 2 to 2-g doses. Dose levels for cohorts 3 and 4 will be updated by future amendment. |
| | 1.3 Inserted UBACC in SOA | To note that the UBACC should be performed along with Informed Consent processes |
| | 2.2 Noted that the STAMPOUT study was complete and a Phase 1 study is ongoing | To provide updated background information in support of the protocol change. |
| | 4.1 Updated table of cohort dose levels | To update the dose levels for cohorts 2-4. |
| | 4.3 Updated dose levels and added supporting information | To remove unnecessary dose information for 1- and 1.5-g doses, and provide calculated dose administration rates that are supportive of the protocol change. |
| | 5.2 Added phrase to IC#6 | To allow an exception to the requirement for an LAR if the participant is capable of consenting for themselves as determined by the UBACC |
| | 5.2 Added consent or to IC#7 | To clarify that participants must consent or assent, the choice of which will depend on whether they have the capacity to consent for themselves |
| | 5.3 Adjusted EC#6 wording | To allow participants with an allergy to one of the two TAU medications to participate, so long as they are not allergic to both |
| | 5.6.1 Updated phrasing for consistency | To note that a LAR is required only if a participant is found unable to consent for themselves |
| | 6.2.4 Removed 1- and 1.5-g doses | To remove reference to doses that are now unplanned |
| | 8.2 Added description of the UBACC | To provide a description of the UBACC and clarify its use |
| | 9.4.6 Revised the purpose of the Interim Analysis | To change the purpose of the Interim Analysis slightly by determining the appropriate cohorts 3 and 4 doses rather than confirming their pre-specified levels are appropriate. |

| Version/Date | Description of Change | Brief Rationale |
|---|---|---|
| | 10.1.1 Updated Informed Consent process | Entire section updated to allow participants to consent for themselves if found to have the capacity to consent by the UBACC. If unable to consent, a LAR may be used for consent along with the written assent of the participant. All participants are to provide consent, again if they originally consented for themselves, on Day 3. |
| | 10.1.3 Added Investigator responsibility | To specify that Investigators have certain responsibilities due to the Certificate of Confidentiality. |
| V5 22Aug2022 | 1.1 Updated number of anticipated participants | Changed number from 40 to 24 in order to complete the study with equal number of participants in the low, high, and TAU groups. |
| | 4.1 Updated number of anticipated participants, number of cohorts, and timing of DSMB reviews | Changed number from 40 to 24 participants, reduced the number of cohorts required, and the timing of DSMB meetings. |
| | 4.2 Removed comment that lowest effective dose would be identified | Intermediate doses have been removed from the protocol, thus the lowest effective dose may not be identified |
| | 6.2 Clarified randomization | Required update to match cohort dose revisions |
| | 6.3 Clarified randomization | Required update to match cohort dose revisions |
| | 7.2 Updated replacement of participant | Required update to match cohort dose revisions |
| | 9 Removed reference to 4 cohorts | Required update to match cohort dose revisions |
| | 9.2 Clarified number of TAU patients needed is 8 | Required update to match cohort dose revisions |
| | 9.4.6 Removed plan for interim analysis | An interim analysis is no longer necessary following cohort 2 as the treatment for cohort 3 is TAU. |
| | 10.1.6 Updated DSMB meeting schedule | Required update to match cohort dose revisions |

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## 12 DATA AND SAFETY MONITORING PLAN

**U01 DA 053043 (PD/PI: Gentry, William B. and Stevens, Misty)**

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

**Protocol Number: M200C-2101**

**Medical Monitor: Patrick Keenan, MD**

**August 22, 2022**

This Data and Safety Monitoring Plan (DSMP) is forward looking and may not be amended in real time to reflect changes in study status, participant enrollment, etc. In the event of a conflict between the DSMP and the clinical protocol, the current clinical protocol shall be followed.

# 12.1. SUMMARY OF THE PROTOCOL

## 12.1.1. STUDY DESIGN

Refer to protocol section 4 for further details.

The hypothesis of this multisite Phase 2a study is that IXT-m200 will be well-tolerated in patients with acute mild to moderate METH toxicity. A randomized, open label design will be used in which one dose of IXT-m200 will be compared to treatment-as-usual (TAU). Approximately ~~40~~ 24 participants will be enrolled in ~~4~~ 3 cohorts. A dose escalation approach will be used so that progressively higher IXT-m200 doses will be evaluated in each of the first two cohorts. In conjunction with safety monitoring, this design assures the opportunity to observe early safety findings before any participants are exposed to the next higher dose. The randomization ratio for IXT-m200 versus TAU is defined as 4:1 for each of cohorts 1 and 2, with up to an additional 4 TAU participants in cohort 3 so that the number of participants receiving TAU equals the number receiving each dose of IXT-m200 at the end of the study.

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

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

The next page shows the Schedule of Activities.

| Assessment | Triage | Screening | Dosing and Assessments [f] | | | | | | | | | | | | | Follow-up[a] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study Day | 1 | 1 | 1 | | | | | | | | | | | | Day not specified | 3 (+2) | 28 (±7) |
| Hour | NA | <0 | <0 | 0 | 0.25 | 0.5 | 0.75 | 1 | 1.5 | 2 | 3 | 4 | 6 | 8 | >8, <Discharge from ED | Discharge from ED | NA | NA |
| Focused history and physical exam [b, c] | | X | | | | | | | | | | | | | | | X | X |
| Focused review of systems [b, c] | | X | | | | | | | | | | | | | | X | X | X |
| Medication history | | X | | | | | | | | X | | | | | | | | |
| Detailed and pertinent psychiatric history [c, d] | | X | | | | | | | | | | | | | | | | |
| Vital Signs [c] | | X | X | | | X | | X | | X | X | X | X | X | As needed | X | X | X |
| Agitation score [c] | | X | | X | | X | | X | | X | X | X | X | X | As needed | | | |
| Informed consent and UBACC | | X | | | | | | | | | | | | | | | X | |
| Eligibility criteria | | X | | | | | | | | | | | | | | | | |
| Randomization | | | X | | | | | | | | | | | | | | | |
| PK samples [d] | | | X | | | | | | | | | X | | | | X | X | X |
| Dose administration | | | | X | | | | | | | | | | | | | | |
| Observe for AEs | | | | | X | X | X | X | X | X | X | X | X | X | As needed | X | X | X |
| Assess for rescue meds | | | | | | X | | X | | | | X | | | As needed | X | | |
| Clinical labs and ECG | | | | | | Once, as soon as feasible | | | | | | | | | | | X | |
| UDS, UPT, Breathalyzer | | | Once, as soon as feasible | | | | | | | | | | | | | | | |
| Detailed and pertinent medical history [e] | | | | | | | | | | X | | | | | | | | |
| DSM5 SUD checklist | | | | | | | | | | | | | | | | | X | |
| Drug use assessment and Meth Perception Assessment | | | | | | | | | | | | | | | | | X | X |

AE – adverse event; UDS – urine drug screen; UPT – urine pregnancy test; ECG – electrocardiogram; DSM5 SUD – Diagnostic and Statistical Manual of Mental Disorders 5 for Substance Use Disorders; NA – not applicable; UBACC – UCSD Brief Assessment of Capacity to Consent

[a] If participants do not return for a follow-up visit, a phone call will be attempted to assess any AEs.

[b] Focused history, physical exam and review of systems based on main complaint, related details from other parts of the medical history and physical exam, and eligibility criteria.

[c] Assessments will be obtained as either part of triage or screening, depending on the site. PANSS-EC will be done at screening only; ACES will be done at each time point as marked.

[d] PK samples will be drawn for both IXT-m200 and METH per section 8.2.

[e] Detailed and pertinent history includes pertinent past medical, family and social histories in addition to focused history. Detailed physical exam to be completed if indicated by detailed and pertinent medical history.

[f] Subjects may be discharged at any time point after the 2-hr assessments are completed if the subject is deemed medically eligible; assessments at Day 1, Hours 3-8 may be skipped if discharged. Assessments assigned for the time of discharge from ED should be completed for all subjects.

### 12.1.2. PRIMARY AND SECONDARY OBJECTIVES AND OUTCOME MEASURES

Refer to protocol section 3.

| OBJECTIVES | ENDPOINTS | JUSTIFICATION |
|---|---|---|
| Primary | | |
| *To evaluate the safety and tolerability of IXT-m200 in patients with mild to moderate METH toxicity* | Safety and tolerability of IXT-m200 as measured by physical examinations and vital sign, AE, ECG, and clinical laboratory testing | Safety must be systematically evaluated of IXT-m200 when given to patients with ongoing METH toxicity for the first time |
| Secondary | | |
| *To determine the time course and degree of normalization of agitation and vital signs* | Agitation/sedation scores over time as measured by ACES [12] | Agitation is a significant CNS component of METH toxicity and a cause for hospital admission |
| | Vital signs including blood pressure, heart rate and temperature over time | Elevated or depressed hemodynamics are a component of CV toxicity |
| *To determine the percentage of participants requiring rescue medications for psychiatric or cardiovascular manifestations of METH toxicity* | Need for rescue medications to treat:<br>- agitation, dysphoria, or psychosis (CNS toxicity)<br>- hypertension, tachycardia, or other cardiovascular instability (CV toxicity) | An evaluation of IXT-m200 effects on requirement of rescue medications is needed |
| Tertiary/Exploratory | | |
| *To determine how long patients with METH toxicity stay in the ED* | ED length of stay as measured by disposition order time minus triage time, and as measured by disposition order time minus start of treatment time, with log transformation | Prolonged wait times are associated with a number of negative outcomes, including patient dissatisfaction, increased hospitalization rate, poor quality of care, and increased mortality [13] |

### 12.1.3. INCLUSION CRITERIA

Refer to protocol section 5.2.

Eligible participants will:

1. Be aged 18 to 45 years, inclusive;
2. Present to the ED with METH toxicity as defined in protocol;
3. Have a PANSS-EC score of 14-28, inclusive;
4. Have or agrees to have an intravenous (IV) line placed;
5. Give a history of METH use in the past 24 hours, with participant or observer attribution of symptoms to METH or have a positive METH drug screen;
6. Be accompanied or readily represented by a legally authorized representative (surrogate) who can consent to participation on behalf of the participant if participant is found not able to consent for themselves using the UCSD Brief Assessment of Capacity to Consent (UBACC); and
7. Consent or assent to participation in the study.

### 12.1.4. EXCLUSION CRITERIA

Refer to protocol section 5.3.

Eligible participants will NOT:

1. Present with concomitant opioid overdose requiring ventilatory support;
2. Be self-reported to be pregnant or lactating;
3. Be considered to have significant concomitant medical illness or trauma, or symptoms of severe METH toxicity including
    a. sepsis or febrile illness;
    b. myocardial infarction, cardiac decompensation or arrhythmias including tachycardia that is not sinus; severe hypertension (>180/110 mmHg); inadequately treated hypertension on chronic medication; history of vasculitis
    c. coma, stroke or severe head injury; new or ongoing seizure activity
    d. acute pulmonary decompensation or severe chronic obstructive pulmonary disease;
    e. any hepatic impairment and/or acute hepatitis or renal impairment due to concomitant medical illness; or
    f. current, or history of, neuroleptic malignant syndrome
4. Be considered to be at imminent risk of suicide or have disqualifying answers to the following two questions. Disqualifying answers would be 1b2 or 2b.

    1. In the past 30 days, have you considered killing yourself?
       a) No
       b) Yes - if Yes, how often?
          b1) Not often (twice or less)
          b2) Somewhat often (more than twice)

    2. In the past year, have you attempted to kill yourself?
       a) No
       b) Yes

5. Be considered to be at imminent risk of injury or danger to self, others or property;
6. Have a history of severe allergy (rash, hives, breathing difficulty, etc.), to both lorazepam and haloperidol, or known hypersensitivity or infusion reaction to any antibody medications; or
7. Be judged by the treating ED physician, investigator, or Sponsor (or designee) to be inappropriate for the study, including people whom the investigator determines cannot reasonably be consulted for assent to participation.

### 12.1.5. POWER CALCULATION AND SAMPLE SIZE

Refer to protocol section 9 and the SAP for further detail on statistical analysis.

Because Meth-OD is mainly a safety study, the sample size for this study is not based on statistical hypotheses. The number of participants within each dose group was chosen based on feasibility, as well as historical experience with initial safety and tolerability trials. From the perspective of tolerability assessment, the probability that a given adverse event would not be observed in a group of participants administered an assigned dose was analyzed for various true population incidence rates was computed (Table 1).

**Table 1. Probability of Not Observing an Adverse Event for Various True Incidence Rates**

| | Probability of Not Observing an AE in Varying Group Sizes | | | | | |
|---|---|---|---|---|---|---|
| **True incidence rate** | **4 subjects** | **6 subjects** | **8 subjects** | **9 subjects** | **12 subjects** | **18 subjects** |
| 0.10 | 0.66 | 0.53 | 0.43 | 0.387 | 0.28 | 0.150 |
| 0.20 | 0.41 | 0.26 | 0.17 | 0.134 | 0.069 | 0.018 |
| 0.30 | 0.24 | 0.12 | 0.058 | 0.040 | 0.014 | 0.002 |
| 0.40 | 0.13 | 0.047 | 0.017 | 0.010 | 0.002 | < 0.001 |
| 0.50 | 0.063 | 0.016 | 0.004 | 0.002 | < 0.001 | < 0.001 |

The probability of not observing an AE under each sample size and true incidence rate scenario was calculated using an exact test for binomial proportion assuming a two-sided Type I error (alpha) of 0.05 and near-zero null proportion of 0.000001. The values reported in the table are the Type 2 error. Analyses were conducted in SAS® 9.4.

Based on the nature of this study, the proposed sample size of 8 participants in each IXT-m200-containing treatment group adequately allows for the detection of clinically meaningful rates of adverse events with the probability of not observing an AE for true incidence rates.

## 12.2. TRIAL MANAGEMENT

### 12.2.1. PARTICIPATING CLINICS

Dr. Michael Wilson
University of Arkansas for Medical Sciences
4301 W. Markham St., Little Rock, AR 72205

Dr. Thomas Robey
Providence Community Hospital
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Dr. Cameron Crandall
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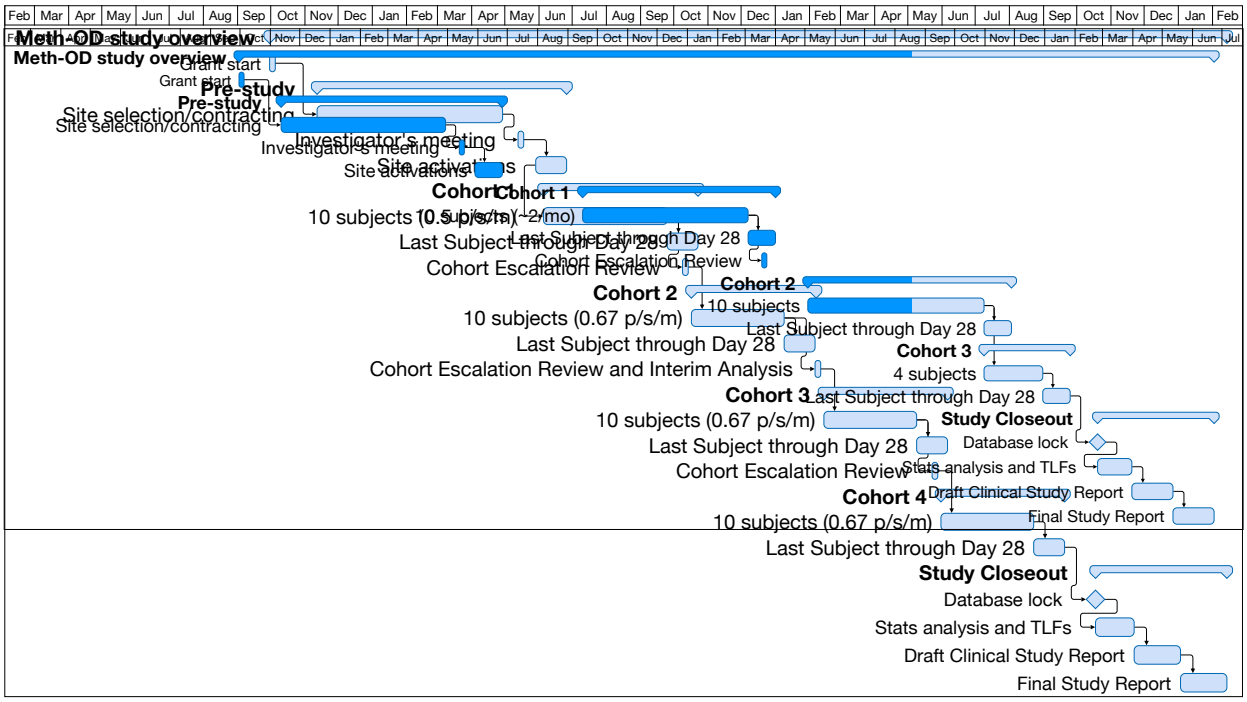
Dr. David McClellan
Sacred Heart Medical Center/Providence Medical Research Center
105 W 8th Avenue, Suite 532C, Spokane, WA 99204

## 12.2.2. PLANNED ENROLLMENT TIMETABLE




## 12.2.3. TARGET POPULATION DISTRIBUTION

| TARGETED/PLANNED ENROLLMENT: Number of Participants | | | | | |
|---|---|---|---|---|---|
| | Not Hispanic or Latino | | Hispanic or Latino | | |
| **Racial Categories** | **Female** | **Male** | **Female** | **Male** | **Total** |
| **American Indian/ Alaska Native** | 0 | 1 | 0 | 0 | 1 |
| **Asian** | 0 | ~~2~~1 | 0 | 0 | ~~2~~1 |
| **Native Hawaiian or Other Pacific Islander** | 0 | 0 | 0 | 0 | 0 |
| **Black or African American** | ~~2~~1 | ~~4~~2 | 0 | 0 | ~~6~~3 |
| **White** | ~~7~~4 | ~~12~~7 | 1 | ~~6~~3 | ~~26~~15 |
| **More than One Race** | 1 | 1 | 1 | ~~2~~1 | ~~5~~4 |
| **Total** | ~~10~~6 | ~~20~~12 | 2 | ~~8~~4 | ~~40~~24 |

## 12.3. DATA MANAGEMENT AND ANALYSIS

### 12.3.1. DATA ACQUISITION AND TRANSMISSION

Refer to protocol section 10.1.9.1.

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 eCRF(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 adverse events (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.

### 12.3.2. DATA ENTRY METHODS

All data will be collected on source documents and then entered in the eCRFs.

### 12.3.3. DATA SECURITY AND PLAN FOR PROTECTING CONFIDENTIALITY

Refer to protocol section 10.1.3.

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 subjects 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.

#### 12.3.4. DATA ANALYSIS PLAN

Refer to protocol section 9 for further details.

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.

## 12.4. QUALITY ASSURANCE AND QUALITY CONTROL

#### 12.4.1. PROCEDURES IN PLACE TO ENSURE THE VALIDITY AND INTEGRITY OF THE DATA

Refer to protocol section 10.1.8.

Each 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/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.

#### 12.4.2. PROCEDURES TO GUARANTEE THE ACCURACY AND COMPLETENESS OF THE DATA DURING DATA COLLECTION, ENTRY, TRANSMISSION, AND ANALYSIS

Refer to protocol section 10.1.7.

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 or by electronic means of viewing both records, 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).

Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports. 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.

## 12.5. REGULATORY ISSUES

### 12.5.1. REPORTING OF SAES

Refer to protocol section 8.3.6.

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 Medical Monitor and Sponsor within 24 hours of site awareness.
- Other SAEs regardless of relationship, will be submitted to the Medical Monitor and Sponsor within 48 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until the investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the Medical Monitor or 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 Sponsor will be responsible for notifying the 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) and Project Scientist (PS) 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.

### 12.5.2. REPORTING OF IRB ACTIONS TO NIDA

InterveXion will be responsible for reporting IRB actions to the NIDA PO.

### 12.5.3. REPORT OF CHANGES OR AMENDMENTS TO THE PROTOCOL

InterveXion will be responsible for reports of protocol changes or amendments to the NIDA PO and PS and the FDA. Significant protocol changes will be approved by NIDA prior to implementation, unless there is an immediate safety concern for participants.

## 12.6. TRIAL SAFETY

### 12.6.1. POTENTIAL RISKS AND BENEFITS FOR PARTICIPANTS

Refer to protocol section 2.3.

**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.

**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 subjects 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 subjects [10].

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 investigator heard a single expiratory wheeze. The infusion was stopped and the subject was treated with solumedrol 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, 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 subjects were confirmed positive for HACA in the Phase 1 study. The development of HACA did not appear to be dose-related [10].

IXT-m200 is an investigational product and may convey no benefit to patients. Based on nonclinical studies in rodents [7,11], 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.

### 12.6.2. RISK MITIGATION PLAN

Refer to protocol section 6.5.2.

The following risk mitigation strategies have been designed based on other studies in people who use METH, on the problems posed specifically by enrolling participants in an emergency setting, on the clinical pharmacology of METH, and on the known pharmacology of IXT-m200:

1. Selection of a specific participant group. As stipulated in the protocol, participants who are relatively healthy with no significant medical or surgical illness will be recruited.
2. IXT-m200 dosing. IXT-m200 will be administered in escalating dose groups so that the lowest IXT-m200 dose (0.5 g) will be evaluated before the higher doses), in subsequent cohorts. This will allow determination of the effects of IXT-m200 at a low predicted effective IXT-m200 dose, before effects are assessed following a high predicted effective IXT-m200 dose.
3. Treatment in an Emergency Department. A crash cart will be available in the ED and personnel trained in CPR are always available in the ED setting. Oxygen and emergency ventilation equipment are immediately available. Normal saline will be used as the IV fluid and fluid boluses can be administered if any hypotension is seen. In the event of serious medical complications, a code may be called.
4. Frequent safety review. A formal safety review will be done between cohorts, and at any point needed based on the severity of AEs. This would include Grade 3 AE's related to worsening of METH effects in the presence of IXT-m200.

All of the study sites are EDs and therefore have all medications that might be needed to treat mAb toxicity, which may manifest as hypotension and bradycardia or tachycardia; bronchospasm with or without hypoxemia; or flushing, pruritis, and urticaria. Hospital-maintained crash carts, and oxygen and emergency ventilation equipment (Ambubags) are always available. Advanced Cardiovascular Life Support-certified providers and code teams are always available to treat life-threatening events.

### 12.6.3. TRIAL STOPPING RULES

Refer to protocol section 7.1.

Enrollment and study drug administration will be immediately paused if any 1 of the following events occurs, unless the event was clearly unrelated to study drug administration, or the event is an expected sequelae of untreated METH toxicity:

- Three (3) participants experience a Grade 3 AE.
- Two (2) participants experience a Grade 3 AE related to increased agitation, aggression, or anxiety.
- One (1) participant experiences a Grade 4 AE.
- A death occurs.

Expected sequelae of untreated METH toxicity which will not be considered grounds for a study pause include:

- Hypertension/tachycardia
- Euphoria

- Agitation
- Insomnia
- Anxiety
- Seizures
- Mania/aggression

Worsening of any of the above following administration of study drug will be considered an AE and subject to the rules for study pause above.

If any of the pause conditions are met, the Sponsor, in consultation with the investigator and Medical Monitor, will suspend enrollment until a full safety review by both the Sponsor and DSMB is performed. A decision to reinitiate enrollment will be made following relevant consultation with the appropriate authorities based on the results of the safety review.

Also refer to protocol section 10.1.2.

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, the DSMB, 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.

### 12.6.4. PROCESS OF AE/SAE COLLECTION, ASSESSMENT, AND REPORTING

Refer to protocol section 8.3.

All AEs (whether serious or nonserious) that occur after the participant has been randomized must be documented on the appropriate pages of the eCRF. 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, until a satisfactory explanation is found or the investigator 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 Sponsor, Medical Monitor and DSMB between cohorts. If an investigator decides it necessary, AEs may be reviewed at any time by consultation with the investigator, Medical Monitor, and Sponsor.

Refer to DSMP section 12.5.1 for details on SAEs.

### 12.6.5. AE/SAE FOLLOW-UP PLAN

Refer to DSMP section 12.6.4.

## 12.7. TRIAL EFFICACY

### 12.7.1. PLANS FOR INTERIM ANALYSIS OF EFFICACY DATA

Refer to protocol section 9.4.6.

~~Between cohorts 2 and 3, a review of the efficacy data, i.e., all secondary endpoints, will be undertaken to determine the dose levels for cohorts 3 and 4. The Medical Monitor and DSMB will provide their recommendations to the Sponsor for a final decision.~~

~~A protocol amendment will incorporate the adjustments. Further details will be provided in the DSMB Charter and the SAP.~~No interim analyses are planned.

## 12.8. DSM PLAN ADMINISTRATION

### 12.8.1. RESPONSIBILITY FOR DATA AND SAFETY MONITORING

Refer to protocol section 10.1.6.

Safety oversight will be under the direction of a DSMB composed of individuals with the appropriate expertise, likely including clinical trial oversight, monoclonal antibody and methamphetamine clinical pharmacology, acute care medicine (cardiovascular and/or emergency), psychiatry or behavioral medicine, statistics, and a patient advocate or representative. Members of the DSMB will be independent from the study conduct and free of conflict of interest, or measures will be enacted to minimize real or perceived conflicts of interest. The DSMB will meet at the conclusion of ~~each~~ cohort 1 to assess safety data and intermittently as necessary. 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.

Cohort escalation review~~s~~ will be performed by the Sponsor, Medical Monitor, and DSMB between cohorts 1 and 2 and the next group will not start until after completion of this review. Thi~~ese~~ review~~s~~ will be scheduled to occur approximately two weeks after the last enrollee in the cohort has completed the Day 3 visit so that all Day 3 data available are considered. Safety data to be reviewed include vital signs, ECG, AEs, clinical laboratory values (serum and urine), and UDS.

### 12.8.2. PERSONS RESPONSIBLE FOR MONITORING THE TRIAL

Safety monitoring will be the responsibility of the investigators, Medical Monitor and the DSMB. Each investigator and the Medical Monitor will provide recommendations to the Sponsor based on their

perspectives. The Sponsor, by the actions of its Chief Medical Officer, W. Brooks Gentry, will then determine whether cohort enrollment should continue or if changes should be made.

### 12.8.3. DISCLOSURE OF ANY CONFLICT OF INTEREST IN THE DSM

Employees at the selected trial sites have no financial interests in InterveXion, and therefore the monitoring done at the study sites and by the clinical monitor will not be conflicted. As described above, the DSMB will be recruited to have no serious conflicts of interest and any unavoidable conflicts will be properly disclosed.

Dr. Gentry maintains an active conflict management plan with UAMS. A component of this plan is that human studies related to InterveXion are to be performed by a contract research organization (CRO) in which safety can be assessed by the CRO. Dr. Gentry is not involved in any way with subject recruitment or with the day-to-day management of the trial. All safety decisions will be made with the input of the investigator, Medical Monitor, and DSMB.

InterveXion also maintains records on conflicts for its investigators.

### 12.8.4. FREQUENCY OF DSM

Refer to DSMP section 12.4.2 for clinical monitoring frequency and section 12.8.1 for DSMB meeting frequency.

### 12.8.5. CONTENT OF DSM REPORT

Content of DSM report *(to be submitted to NIDA PO and PS annually at the same time as the RPPR is due)*

- Brief description of the trial and progress
- Enrollment update and baseline sociodemographic characteristics
- Retention and disposition of study participants (active, completed, and terminated/withdrawn)
- Regulatory Issues (amendment, deviations, IRB report, QA issues)
- AEs and SAEs listings

## 12.9. DSM BOARD PLAN

### 12.9.1. MEMBERS AND AFFILIATION

- ~~Pedro Delgado, MD (Chair) – Saint Maarten Campus, American University of the Caribbean School of Medicine~~
- Keith Coffee, MD (Chair) – Medical and Scientific Operations, Peachtree Bioresearch Solutions
- Lauren Whiteside, MD – Dept of Emergency Medicine, University of Washington
- Travis Rieder, PhD – Berman Institute of Bioethics, Johns Hopkins University
- Lukas Makris, PhD – Statistical Consultant, Stathmi, Inc.
- Theodore Treese, MD, MBA – Psychiatrist and Principal Investigator, Adaptive Clinical Research, Inc.

### 12.9.2. CONFLICT OF INTEREST

Refer to DSMP section 12.8.1.

### 12.9.3. FREQUENCY OF MEETINGS

Refer to DSMP section 12.8.1.

### 12.9.4. PROTECTION OF CONFIDENTIALITY

The DSMB members will be required to sign confidentiality agreements prior to participation.

### 12.9.5. MONITORING ACTIVITIES (INITIAL AND ONGOING STUDY REVIEW)

The Board will meet to review the protocol, monitor recruitment, adverse events, data quality, and overall study performance. Details of the monitoring activities will be outlined in the DSMB Charter.

### 12.9.6. COMMUNICATION PLAN TO IRB, NIDA, AND FDA

The DSMB's recommendations following interim reviews will be reported to InterveXion as Sponsor. If the recommendation is other than that the study should continue as designed, and if study changes are made as a result, InterveXion will promptly report to the IRB, NIDA, and FDA if necessary, according to applicable regulations and ICH Guidance.