OUTLAST: A PHASE 2, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, MULTIPLE-DOSE STUDY TO EVALUATE THE SAFETY AND EFFICACY OF IXT-M200 IN TREATMENT-SEEKING INDIVIDUALS WITH METHAMPHETAMINE USE DISORDER

Protocol Number: M200C-2201

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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: _____

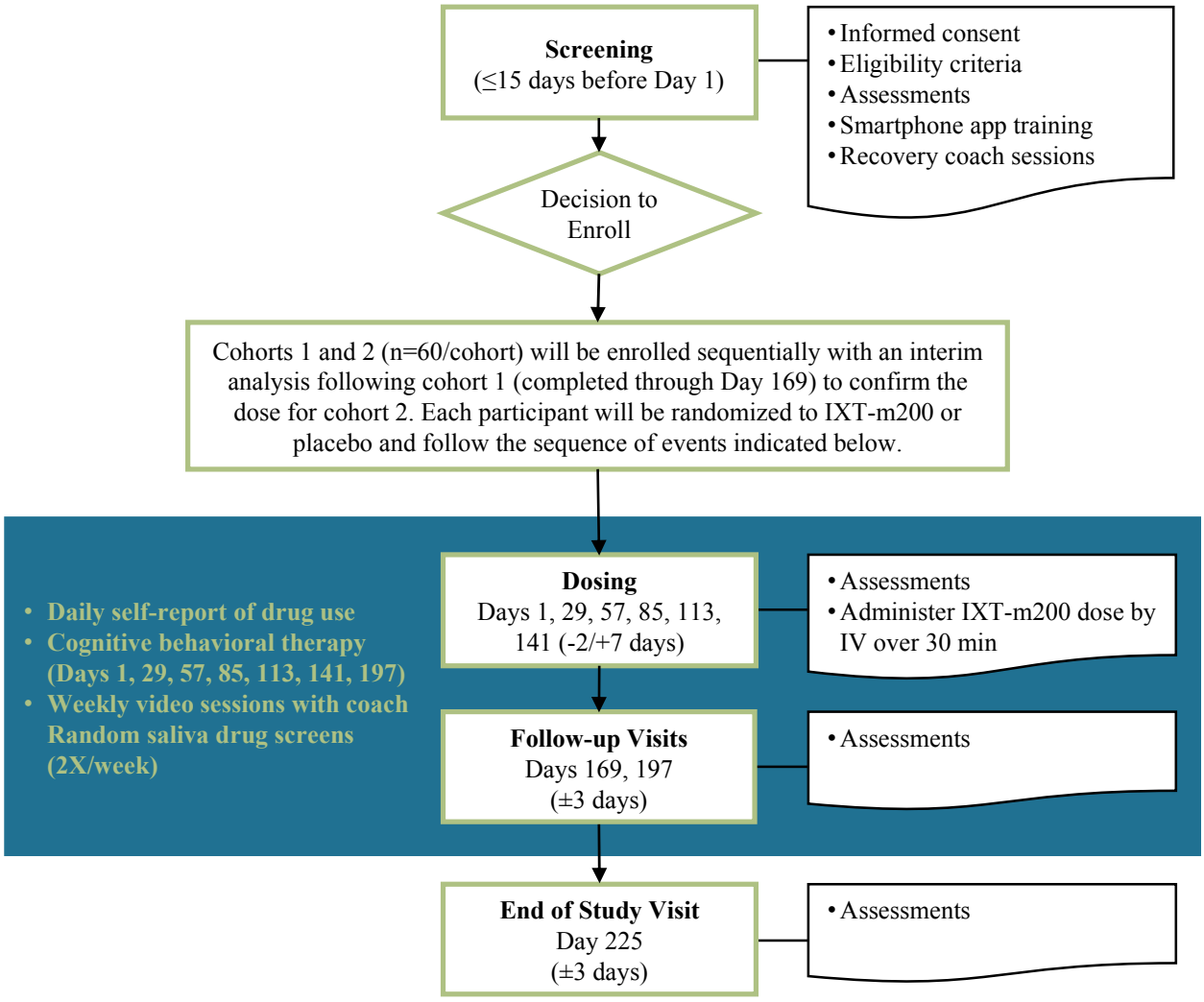
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	OUTLAST: A Phase 2, Double-Blind, Randomized, Placebo-Controlled, Multiple-Dose Study to Evaluate the Safety and Efficacy of IXT-m200 in Treatment-Seeking Individuals with Methamphetamine Use Disorder
Study Description:	This Phase 2 study will evaluate the safety and efficacy of monthly intravenous doses of IXT-m200 in treatment-seeking individuals with methamphetamine (METH) use disorder (MUD). The hypotheses are that treatment with IXT-m200 will reduce the occurrence of stimulant-positive samples compared to placebo (following an initial grace period during which relapses may occur) and improve the signs and symptoms of MUD.
Objectives:	Primary Objective: To evaluate the efficacy of IXT-m200 in preventing or reducing relapse to stimulant use. Secondary Objectives: To evaluate the efficacy of IXT-m200 in improving the signs and symptoms of MUD, increasing the number achieving early remission, improving the proportion of participants achieving stimulant abstinence, improving participant-rated quality of life, and to evaluate the safety of multiple intravenous doses of IXT-m200.
Endpoints:	Primary Endpoint: • Percent of 20 weeks abstinent from stimulants following a 4-week grace period (between Week 5 and Week 25) as measured by saliva screens and by self-report via smartphone app. Secondary Endpoints: • Proportion of responders at Week 25 as measured by DSM-5 criteria. A responder is a participant who meets the definition of early remission, i.e., ≥3 months and <12 months without meeting DSM-5 criteria while disregarding the result for craving. • Complete abstinence during the last month of study drug treatment (between Week 21 and Week 25), as measured by saliva screens and by self-report via smartphone app. • Change from screening in participant-rated quality of life as measured by the Treatment Effectiveness Assessment (TEA) at Weeks 13, 25, and 33. • Safety and tolerability of IXT-m200 assessed by physical examinations and vital sign, AE, ECG, and clinical laboratory testing. • Number of participants with anti-IXT-m200 antibody levels that are confirmed positive and have titers more than three times the minimum required dilution. Exploratory Endpoints: • Number of sequential weeks of abstinence from the end of treatment visit (Week 25), defined as four weeks after the final planned treatment visit (Week 21) as measured by saliva screens and by self-report via smartphone app. • Point-prevalence abstinence (last 7 days) as measured by saliva screens and by self-report via smartphone app at Week 25, Week 29, and Week 33.

	• Weekly abstinence from stimulants following a 4-week grace period (between Week 5 and Week 25) as measured by saliva screens. • Difference between number of adverse outcomes recorded between Week 5 and Week 33. Adverse outcomes include those queried in the Adverse Outcomes Assessment and also suicide and overall mortality. • Proportion of responders at Week 33 as measured by DSM-5 criteria. A responder is a participant who meets the definition of early remission, i.e., ≥3 months and <12 months without meeting DSM-5 criteria while disregarding the result for craving. • Difference between groups in Clinical Global Impression of Change (CGIC) at Weeks 13, 25, and 33. • Difference between groups in Patient Global Impression of Change (PGIC) at Weeks 13, 25, and 33.
Study Population:	Approximately 120 adults seeking treatment for their ongoing METH use will be randomized into the study. Approximately 36 of these will be included in the PK subset.
Phase:	2
Description of Sites:	Approximately 10 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 participants with METH use disorder. It will be administered at a dose of 1.5 g (approximately 20 mg/kg) and, depending on the results of an interim analysis, up to 3 g (approximately 40 mg/kg). IXT-m200 or placebo treatment will be given by intravenous infusion over 30 minutes. Each participant will receive 6 doses of either placebo or the same dose level of IXT-m200, spaced approximately 4 weeks apart.
Study Duration:	Approximately two years
Participant Duration:	33 weeks

1.2 SCHEMA


Screening
(≤15 days before Day 1)
• Informed consent
• Eligibility criteria
• Assessments
• Smartphone app training
• Recovery coach sessions
Decision to Enroll
Cohorts 1 and 2 (n=60/cohort) will be enrolled sequentially with an interim analysis following cohort 1 (completed through Day 169) to confirm the dose for cohort 2. Each participant will be randomized to IXT-m200 or placebo and follow the sequence of events indicated below.
• Daily self-report of drug use
• Cognitive behavioral therapy (Days 1, 29, 57, 85, 113, 141, 197)
• Weekly video sessions with coach
Random saliva drug screens (2X/week)
Dosing
Days 1, 29, 57, 85, 113, 141 (-2/+7 days)
• Assessments
• Administer IXT-m200 dose by IV over 30 min
Follow-up Visits
Days 169, 197
(±3 days)
• Assessments
End of Study Visit
Day 225
(±3 days)
• Assessments

1.3 SCHEDULE OF ACTIVITIES (SOA)

1.3.1 MAIN STUDY PARTICIPANT SCHEDULE

Assessment [a]	Screening	Dosing (-2/+7 days)						Follow-up (±3 days)			ET
Study Week	**≤-1**	**1**	**5**	**9**	**13**	**17**	**21**	**25**	**29**	**33**	**NA**
Study Day	**-15 to -1**	**1[b]**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**NA**
Informed consent	X										
Initial evaluations [p] Eligibility criteria Demographics Medical history and medications Vital signs [c] Physical exam Psychiatric exam (e.g., C-SSRS) Urine pregnancy test Saliva drug screen Drug use assessment via DSM-5 [m]	X										
Laboratory tests [d]	X	X	X	X	X	X	X	X			X
Electrocardiogram (ECG) [e]	X	X	X	X	X	X	X				
App training App download and tutorial [q] Saliva drug screens (up to 4) [k] Recovery coaching [j]	X										
Adverse Outcomes Assessment Quality of Life - TEA[f]	X				X			X		X	X
Quality of Life – PGIC and CGIC [f]					X			X		X	X
METH Use Assessments [n]	X							X		X	X
Randomization		X									
Blood for PK [g]		X	X	X	X	X	X	X	X	X	X
Blood for HACA [o]		X		X		X		X		X	X
Blood for Cytokines [l]		X	X	X	X	X	X				
Dose administration [h]		X	X	X	X	X	X				
Cognitive behavioral therapy		X	X	X	X	X	X		X		
Wellness check Update medical history Update medications Brief psychiatric evaluation Vital signs [c] Targeted physical exam Urine pregnancy test		X	X	X	X	X	X	X	X	X	X
Continuous events AE monitoring [i] Recovery coaching [j] Self-report daily drug use by app Random saliva drug screens [k]		Continuous									

Abbreviations: CGIC – Clinical Global Impression of Change; C-SSRS – Columbia Suicide Severity Rating Scale; ET – early termination; HACA – human anti-chimeric antibodies; NA – not applicable; PGIC – Patient Global Impression of Change; PK – pharmacokinetic; TEA – Treatment Effectiveness Assessment

[a] Descriptions of assessments are in Section 8.1 (efficacy) or 8.2 (safety).
[b] Study Day -1 is the day prior to the first dose. Study Day 1 is the day of the first dose.
[c] Vital sign measurements will be taken on dosing days starting with a pre-dose measurement (≤30 min prior), then 0.25, 0.5, 1, 2, and 4 hours (±5 min) after dosing starts, and as needed afterward until normalization. Measurements will be obtained once on each non-dosing day. Each test may be repeated once at each time point if the initial result is out of range.
[d] Laboratory tests require blood and urine sampling for hematology, serum chemistry, and urinalysis. Samples are to be taken 2-hr post-dose completion (±10 min) on dose days and once per visit on non-dosing days.
[e] ECGs are to be done 30-min post dose completion (±15 min) on dosing days.

[f] Quality of Life Assessments include TEA (at Screening, Days 85, 169, & 225), and PGIC and CGIC (on Days 85, 169, & 225). These assessments are to be done prior to CBT at the Week 13 visit.
[g] PK samples are to be taken pre-dose (≤30 min prior), then 4 hr (±10 min) after the start of each infusion on dosing days. Participants should be kept on site until 4 hr post infusion start to collect samples. All other PK samples are to be collected once each visit.
[h] Doses will be given over 30 min by intravenous (IV) infusion.
[i] AEs will be collected by phone call at 1 day and 1 week (±2 days) post-dose throughout the study.
[j] Recovery coaching will occur weekly via phone or video.
[k] Saliva drug screens will be done remotely and monitored by smartphone app.
[l] Cytokine samples are to be taken pre-dose (≤60 min prior) on each dosing day. If a participant has an infusion reaction, cytokine sampling at 1- and 4-hours post-dose (±10 min) should be performed.
[m] Drug use assessments at Screening include the DSM5 criteria for any drugs used regularly in the past year and questions about route and frequency of METH use.
[n] On Days 169 and 225, DSM5 criteria should be used to assess methamphetamine only and for the past 30 days, then for the past 3 months.
[o] HACA samples are to be taken pre-dose (≤60 min prior) on visit Days 1, 57, and 113, and once on Days 169 and 225.
[p] If the participant remains eligible at the end of the Screening visit, enroll them in the DynamiCare system as described in the DynamiCare Site Guide, and schedule the Day 1 visit.
[q] If a participant does not have their phone at the Screening visit, the visit should be rescheduled.

1.3.2 PK SUBSET PARTICIPANT SCHEDULE

Assessment [a]	**Screening**	**Dosing (-2/+7 days)**												**Follow-up (±3 days)**				**ET**	
Study Week	**≤-1**	**1**					**5**	**9**	**13**	**17**	**21**					**25**	**29**	**33**	**NA**
Study Day	**-15 to -1**	**1**[b]					**29**	**57**	**85**	**113**	**141**					**169**	**197**	**225**	**NA**
PK Sample Collection Day			**2 (+1)**	**8 (±2)**	**15 (±3)**	**22 (±3)**						**142 (+1)**	**148 (±2)**	**155 (±3)**	**162 (±3)**				
Informed consent	X																		
Initial evaluations [p] Eligibility criteria Demographics Medical history and medications Vital signs [c] Physical exam Psychiatric exam (e.g., C-SSRS) Urine pregnancy test Saliva drug screen Drug use assessment via DSM-5 [m]	X																		
Laboratory tests [d]	X	X					X	X	X	X	X					X			X
Electrocardiogram (ECG) [e]	X	X					X	X	X	X	X								
App training App download and tutorial [q] Saliva drug screens (up to 4) [k] Recovery coaching [j]	X																		
Adverse Outcomes Assessment Quality of Life Assessments - TEA [f]	X								X							X		X	X
Quality of Life – PGIC and CGIC [f]									X							X		X	X
METH Use Assessments [n]	X															X		X	X
Randomization		X																	
Blood for PK [g]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood for HACA [o]		X						X		X						X		X	X
Blood for Cytokines [l]		X					X	X	X	X	X								
Dose administration [h]		X					X	X	X	X	X								
Cognitive behavioral therapy		X					X	X	X	X	X						X		
Wellness check Update medical history Update medications Brief psychiatric evaluation Vital signs [c] Targeted physical exam Urine pregnancy test		X					X	X	X	X	X					X	X	X	X

Assessment [a]	Screening	Dosing (-2/+7 days)												Follow-up (±3 days)				ET	
Study Week	**≤-1**	**1**					**5**	**9**	**13**	**17**	**21**					**25**	**29**	**33**	**NA**
Study Day	**-15 to -1**	**1[b]**					**29**	**57**	**85**	**113**	**141**					**169**	**197**	**225**	**NA**
Continuous events AE monitoring [i] Recovery coaching [j] Self-report daily drug use by app Random saliva drug screens [k]		Continuous																	

Abbreviations: CGIC – Clinical Global Impression of Change; C-SSRS – Columbia Suicide Severity Rating Scale; ET – early termination; HACA – human anti-chimeric antibodies; NA – not applicable; PGIC – Patient Global Impression of Change; PK – pharmacokinetic; TEA – Treatment Effectiveness Assessment

[a] Descriptions of assessments are in Section 8.1 (efficacy) or 8.2 (safety).
[b] Study Day -1 is the day prior to the first dose. Study Day 1 is the day of the first dose.
[c] Vital sign measurements will be taken on dosing days starting with a pre-dose measurement (≤30 min prior), then 0.25, 0.5, 1, 2, and 4 hours (±5 min) after dosing starts, and as needed afterward until normalization. Measurements will be obtained once on each non-dosing day. Each test may be repeated once at each time point if the initial result is out of range.
[d] Laboratory tests require blood and urine sampling for hematology, serum chemistry, and urinalysis. Samples are to be taken 2-hr post-dose completion (±10 min) on dose days and once per visit on non-dosing days.
[e] ECGs are to be done 30-min post dose completion (±15 min) on dosing days.
[f] Quality of Life Assessments include TEA (at Screening, Days 85, 169, & 225), and PGIC and CGIC (on Days 85, 169, & 225). These assessments are to be done prior to CBT at the Week 13 visit.
[g] PK samples are to be taken pre-dose (≤30 min prior), then 4 hr (±10 min) after the start of each infusion on dosing days. Participants should be kept on site until 4 hr post infusion start to collect samples. Additional PK samples should be taken on Day 1 and 141 at 1 hr (±10 min) post-start of infusion. All other PK samples are to be collected once each visit.
[h] Doses will be given over 30 min by intravenous (IV) infusion.
[i] AEs will be collected by phone call at 1 day and 1 week (±2 days) post-dose throughout the study.
[j] Recovery coaching will occur weekly via phone or video.
[k] Saliva drug screens will be done remotely and monitored by smartphone app.
[l] Cytokine samples are to be taken pre-dose (≤60 min prior) on each dosing day. If a participant has an infusion reaction, cytokine sampling at 1- and 4-hours post-dose (±10 min) should be performed.
[m] Drug use assessments at Screening include the DSM5 criteria for any drugs used regularly in the past year and questions about route and frequency of METH use.
[n] On Days 169 and 225, DSM5 criteria should be used to assess methamphetamine only and for the past 30 days, then for the past 3 months.
[o] HACA samples are to be taken pre-dose (≤60 min prior) on visit Days 1, 57, and 113, and once on Days 169 and 225.
[p] If the participant remains eligible at the end of the Screening visit, enroll them in the DynamiCare system as described in the DynamiCare Site Guide, and schedule the Day 1 visit.
[q] If a participant does not have their phone at the Screening visit, the visit should be rescheduled.

1.3.3 DOSE DISCONTINUED PARTICIPANT SCHEDULE

This schedule will be followed only when a participant has been enrolled and dosed as normal at least once, then dosing is discontinued per section 7.2, but the participant wishes to continue in the study. Priority should be placed on those assessments in bold, blue font.

Assessment [a]	**Site Visit (-2/+7 days)**					**Follow-up (±3 days)**			**ET**
Study Week	**5**	**9**	**13**	**17**	**21**	**25**	**29**	**33**	**NA**
Study Day	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**NA**
Laboratory tests [d]	Once at first visit after dose discontinuation								X
Adverse Outcomes Assessment **Quality of Life - TEA** [f]			**X**			**X**		**X**	**X**
Quality of Life – PGIC & CGIC [f]			**X**			**X**		**X**	**X**
METH Use Assessments [n]						X		X	X
Blood for PK [g]	X	X	X	X	X	X	X	X	X
Blood for HACA [o]		X		X		X		X	X
Cognitive behavioral therapy	X	X	X	X	X		X		
Wellness check Update medical history Update medications Brief psychiatric evaluation Vital signs [c] Targeted physical exam Urine pregnancy test	X	X	X	X	X	X	X	X	X
Continuous events **AE monitoring** [i] **Recovery coaching** [j] **Self-report daily drug use by app** **Random saliva drug screens** [k]	**Continuous**								

Abbreviations: CGIC – Clinical Global Impression of Change; C-SSRS – Columbia Suicide Severity Rating Scale; ET – early termination; HACA – human anti-chimeric antibodies; NA – not applicable; PGIC – Patient Global Impression of Change; PK – pharmacokinetic; TEA – Treatment Effectiveness Assessment

[a] Descriptions of assessments are in Section 8.1 (efficacy) or 8.2 (safety).
[c] Vital sign measurements will be obtained once on each non-dosing day. Each test may be repeated once at each time point if the initial result is out of range.
[d] Laboratory tests require blood and urine sampling for hematology, serum chemistry, and urinalysis. Samples are to only be taken on the first visit following discontinuation.
[e] ECGs are to be done once per visit.
[f] Quality of Life Assessments include TEA (at Screening, Days 85, 169, & 225), and PGIC and CGIC (on Days 85, 169, & 225). These assessments are to be done prior to CBT at the Week 13 visit.
[g] One PK sample should to be taken per visit; mark this as the pre-dose sample in EDC for visits through Week 21.
[j] Recovery coaching will occur weekly via phone or video.
[k] Saliva drug screens will be done remotely and monitored by smartphone app.
[n] On Days 169 and 225, DSM5 criteria should be used to assess methamphetamine only for the past 30 days, then for the past 3 months.
[o] HACA samples are to be taken once each visit.

2 INTRODUCTION

2.1 STUDY RATIONALE

2.1.1 RATIONALE FOR THE COMBINED SAFETY AND EFFICACY STUDY

There are no approved medications for the treatment of METH use disorder (MUD); therefore, any progress toward development of effective medications for MUD is important. The safety of single doses of IXT-m200 has been evaluated in a Phase 1 study of healthy individuals and in a Phase 2 study in otherwise healthy non-treatment seeking participants who use METH. No significant safety events occurred (no SAEs were reported)[1]. Furthermore, Good Laboratory Practice (GLP) toxicology studies of repeated doses of IXT-m200 in rats at doses well above the proposed doses in this study have not shown significant toxicity associated with IXT-m200. However, even though the risk of severe complications associated with chimeric monoclonal antibody therapy is low, the risk of infusion reactions is not zero, and establishment of safety and tolerability of repeat doses of IXT-m200 in humans is important. Based on the clinical experience to date with IXT-m200, gathering these safety data in participants with MUD rather than in healthy volunteers is warranted. Given the safety data to date with single doses of IXT-m200 in humans, there is no reason to believe that the safety of repeated doses of IXT-m200 will be different in otherwise healthy individuals seeking treatment for MUD versus healthy non-drug users. Furthermore, the benefit-risk determination of repeat-dose testing of IXT-m200 favors testing in people seeking treatment for METH use, because healthy volunteers would not derive any benefit from such a study. Finally, the use of a serial study design which first evaluates the safety of a lower dose level before proceeding to a higher dose level further decreases any potential safety risk. Therefore, this study is a combined safety and efficacy study in otherwise healthy individuals who are seeking treatment for MUD.

This protocol is designed to evaluate safety of repeated doses of IXT-m200, to evaluate evidence of efficacy in the target population, and to evaluate trends in dose-response relationships for IXT-m200 in preventing or reducing relapse to METH use. Compared to placebo, we hypothesize that IXT-m200 will decrease relapse to stimulant use, improve the signs and symptoms of MUD, and improve participant-reported quality of life in treatment-seeking individuals with MUD.

2.1.2 RATIONALE FOR THE SELECTED POPULATION

Treatment-seeking participants with a history of ongoing METH use will be recruited. Because of the use of treatment-seeking participants in this study, comprehensive and standardized cognitive behavioral therapy (CBT) will be provided to all participants. Persons with MUD, even those who are highly motivated to stop their use and receive treatment, are at high risk for recidivism to METH use. Based on the observed safety data from our Phase 2 clinical study with IXT-m200 (STAMPOUT), which studied non-treatment-seeking participants who use METH and in which participants were given controlled doses of METH and then subsequently allowed to resume their habitual METH use, there do not appear to be significant safety risks associated with use of IXT-m200 in this population.

2.2 BACKGROUND

Study Agent
IXT-m200, also called ch-mAb7F9, binds METH with high selectivity and affinity. The product contains a murine METH-binding variable region and the constant domains of a human immunoglobulin G

(IgG) 2κ. This antibody isotype was chosen because of the lower risk of immune response compared to an IgG_1 or IgG_3. IXT-m200 targets METH, does not rely on binding to any endogenous target for its action, and has been well-tolerated in previous clinical studies (see below).

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

Nonclinical IXT-m200 Effectiveness Summary
A significant body of nonclinical work in rats indicates that IXT-m200 may be effective as a treatment for MUD by altering METH central nervous system effects. The potential human efficacy of IXT-m200 is demonstrated by multiple important *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).

Nonclinical Safety Summary of the Interaction of IXT-m200 with METH
Four key nonclinical studies were 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 consumption by a person in an effort to overcome the reduction of METH effects by the antibody.

In each of the 4 studies, rats were acclimated to high doses of METH over a 14-day period to make them tolerant to high doses of METH, similar to what occurs in 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 attempts to surmount the antibody's effects was initiated. On Day 18, rats were given 4 doses of 6 mg/kg METH spaced 2 hours apart. This binge dosing regimen was repeated on Days 21 and 24 for certain studies and groups.

The 4 studies (GLP toxicology, cardiovascular effects, METH PK, and METH distribution) collected different outcome measurements while using the same METH administration protocol. Results are summarized 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[1]. In this first clinical study, 42 participants (17 females) were dosed in 5 groups (0.2, 0.6, 2, 6, or 20 mg/kg IXT-m200), with 10 participants receiving placebo (saline). Pharmacokinetic results indicated that IXT-m200 is similar to other IgGs, with an elimination half-life of ~18 days, volume of distribution (Vd) of ~5 L and clearance of ~200 mL/d. The disposition of IXT-m200 did not appear to be affected by dose.

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

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

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

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

56 participants were included in the pharmacokinetic and safety sets, with 20 receiving the placebo, 18 receiving 6 mg/kg IXT-m200, and 18 receiving 20 mg/kg IXT-m200. IXT-m200 was well-tolerated. There were no SAEs and all AEs were grades 1 or 2; all resolved as expected. Importantly, IXT-m200 did not result in substantial hemodynamic changes when compared with METH alone. IXT-m200 met the primary study endpoint, and significantly ($p<0.001$) altered METH area under the curve (AUC) and Cmax with all METH challenges, up to 30-fold and 8-fold respectively, without altering METH renal elimination (Figure 1). IXT-m200 decreased METH Vd over 9-fold after the first METH challenge (Figure 2). There were favorable trends in DEQ data as well (Figure 3), suggesting that IXT-m200 may also have effects on the reinforcing effects of METH use.

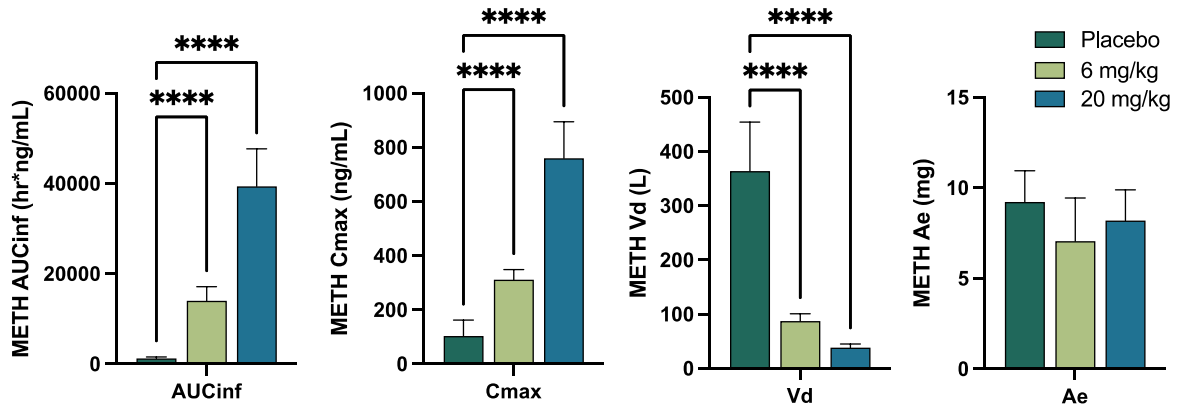


Figure 1. METH PK data from STAMPOUT demonstrate IXT-m200 alters METH distribution. Area under the curve from time 0 through infinity (AUCinf), maximum METH concentration (Cmax), volume of distribution (Vd), and cumulative urinary excretion over 36 hr (Ae) data following the day 5 challenge are plotted as mean ± SD. IXT-m200 (0, 6, or 20 mg/kg, IV) was administered one day prior to METH (30 mg, IV). ****$p < 0.0001$

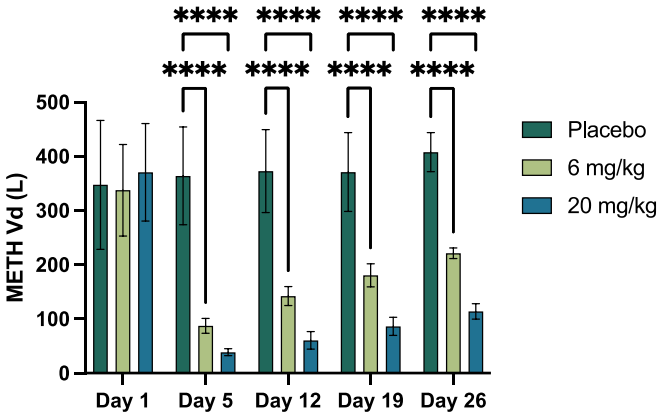


Figure 2. METH volume of distribution is significantly reduced by IXT-m200 treatment on Day 4 and the effect is still significant 3 weeks later. ****p < 0.0001

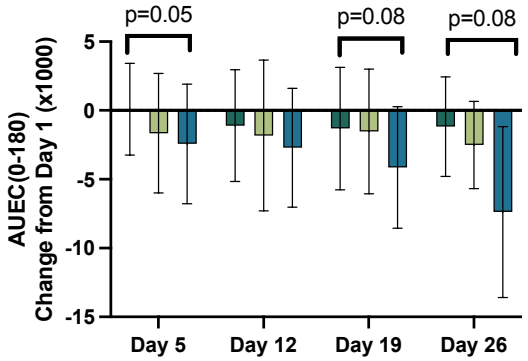


Figure 3. Subject responses on drug effects questionnaires indicate a trend toward reduction of METH effects following an IXT-m200 dose. In this example, subjects were asked "Do you LIKE any of the effects you are feeling right now?" Area under the effect curve data are plotted as the change from Day 1 (baseline).

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

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

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

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

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

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

2.3.2 KNOWN POTENTIAL BENEFITS

IXT-m200 is an investigational product and may convey no benefit to participants. Based on nonclinical studies in rodents and clinical data from the STAMPOUT study, 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 effectiveness. The risks are minimized by using a serial cohort design in which the safety of a lower IXT-m200 dose level is evaluated before moving to a higher dose level, and by combining the pharmacologic characterization of IXT-m200 with standard-of-care cognitive behavioral therapy.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
Primary	
To evaluate the efficacy of IXT-m200 in preventing or reducing relapse to stimulant use	Percent of 20 weeks abstinent from stimulants following a 4-week grace period (between Week 5 and Week 25) as measured by saliva screens and by self-report via smartphone app.
Secondary	
To evaluate the efficacy of IXT-m200 in increasing the number of participants achieving early remission	Proportion of responders at Week 25 as measured by DSM-5 criteria. A responder is a participant who meets the definition of early remission, i.e., ≥3 months and <12 months without meeting DSM-5 criteria, while disregarding the result for craving.
To evaluate the efficacy of IXT-m200 in improving the proportion of participants achieving stimulant abstinence	Complete abstinence during the last month of study drug treatment (between Week 21 and Week 25), as measured by saliva screens and by self-report via smartphone app.
To evaluate the efficacy of IXT-m200 in improving participant-rated quality of life	Change from screening in participant-rated quality of life as measured by the Treatment Effectiveness Assessment (TEA) at Week 13, 25, and Week 33.
To evaluate the safety of multiple intravenous doses of IXT-m200	Safety and tolerability of IXT-m200 assessed by physical examinations and vital sign, AE, ECG, and clinical laboratory testing.
To evaluate the immunogenicity of multiple doses of IXT-m200	Number of participants with anti-IXT-m200 antibody levels that are confirmed positive and have titers more than three times the minimum required dilution.
Exploratory	
To evaluate the efficacy of IXT-m200 in improving the length of sustained abstinence	Number of sequential weeks of abstinence from the end of treatment visit (Week 25), defined as four weeks after the final planned treatment visit (Week 21) as measured by saliva screens and by self-report via smartphone app.
To evaluate the efficacy of IXT-m200 in improving post-treatment abstinence	Point prevalence abstinence (last 7 days) as measured by saliva screens and by self-report via smartphone app at Week 25, Week 29, and Week 33.
To evaluate the efficacy of IXT-m200 in preventing or reducing relapse to stimulant use	Weekly abstinence from stimulants following a 4-week grace period (between Week 5 and Week 25) as measured by saliva screens.
To evaluate the efficacy of IXT-m200 in reducing the adverse outcomes associated with MUD	Difference between number of adverse outcomes recorded between Week 5 and Week 33. Adverse outcomes include those queried in the Adverse Outcomes Assessment and also suicide and overall mortality.
To evaluate the efficacy of IXT-m200 in increasing the number of participants achieving early remission	Proportion of responders at Week 33 as measured by DSM-5 criteria. A responder is a participant who meets the definition of early remission, i.e., ≥3 months and <12 months without meeting DSM-5 criteria while disregarding the result for craving.
To evaluate the efficacy of IXT-m200 in improving clinician-rated response to treatment	Difference between groups in Clinical Global Impression of Change (CGIC) at Week 13, 25, and Week 33.
To evaluate the efficacy of IXT-m200 in improving patient-rated response to treatment	Difference between groups in Patient Global Impression of Change (PGIC) at Week 13, 25, and Week 33.

4 STUDY DESIGN

4.1 OVERALL DESIGN

A Phase 2 double-blind, randomized, placebo-controlled, multiple-dose study will be performed to evaluate the safety and efficacy of IXT-m200 in treatment-seeking individuals who use METH. The hypotheses are that following an initial relapse, IXT-m200 will reduce the occurrence of stimulant-positive saliva samples compared to placebo and improve the signs and symptoms of MUD.

Approximately 120 participants will be randomized in two sequential cohorts. In Cohort 1, approximately 60 participants will be randomized 2:1 to IXT-m200 at 1.5 g or placebo, with approximately 40 individuals receiving treatment and approximately 20 individuals receiving placebo. An interim analysis of data collected through Week 25 will be performed between cohorts to review efficacy data and to determine the need for dose escalation. If the interim analysis supports dose escalation, then Cohort 2 will randomize approximately 60 participants 2:1 to IXT-m200 at 3 g or placebo. If the interim analysis supports dose maintenance or reduction, however, then the sample size for Cohort 2 will be recalculated. Randomization will be stratified by self-reported past month METH usage at screening (<18 days per month versus ≥18 days per month).

Approximately 18 participants of the 60 per cohort will be enrolled in the PK subset. This subset will consist of approximately 12 active and 6 placebo participants in each cohort. Additional PK samples will be taken after the first and last doses in order to determine the effect of multiple doses on antibody PK. If 18 participants have not been enrolled in the PK subset by the time a cohort is filled, the Sponsor will determine if additional enrollment is required.

Each participant will receive 6 doses given by IV infusion, with doses given every 4 weeks. Participants will also receive concurrent cognitive behavioral therapy during monthly sessions. Saliva drug tests will be conducted randomly, with each participant completing two tests each week.

The first four weeks of treatment will be considered a grace period, designed to accommodate the likelihood that participants will relapse initially and experience the effects of IXT-m200. It further allows participants time to absorb and incorporate some of the skills taught by cognitive behavior therapy. METH use endpoints will be analyzed in the weeks following the grace period.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Use of placebo is justified in this study to create a comparator control group and because there is no current established pharmacologic standard of care for MUD. Participants recruited for this study will be seeking treatment for their MUD. Because all participants will receive behavioral therapy, which is the standard of care, the use of placebo does not place participants at further risk or prevent them from receiving a benefit from the antibody medication.

OUTLAST will be the first multiple-dose study of IXT-m200. The first cohort will all be dosed with the lower IXT-m200 dose to ensure safety prior to dose escalation (or reduction) in Cohort 2.

4.3 JUSTIFICATION FOR DOSE

The IXT-m200 doses (1.5 or 3 g) were selected for this study because they are both potentially effective in reducing METH effects for several weeks. Nonclinical studies in rats suggest that when the antibody is administered several days prior to METH challenge administration, the antibody is effective at reducing METH-induced locomotor activity at a ratio of 30 METH molecules per mAb binding site[2]. (This calculation assumes that the METH dose is confined entirely to the blood volume upon administration.) Data from our Phase 2 STAMPOUT study demonstrated that IXT-m200 was effective in altering the PK of METH in humans for several weeks following a single dose when the total doses of IXT-m200 were near or less than the 1.5-g dose and the METH doses were 30 mg. Even with higher doses of METH, we predict IXT-m200 doses will reduce METH effects.

IXT-m200 will be administered via IV infusion over 30 min. This is necessary because it is a protein medication and would be metabolized to inactive components in the gastrointestinal tract if administered orally. The volume that must be given is too large to allow for intramuscular or subcutaneous administration based on the current formulation. For the 3-g dose group the dose rate will result in a rate of 40 mg/kg/hr in a 75-kg person, which is significantly lower than doses given during a multiple-dose GLP toxicology study in which the slowest rate for the high dose was 1800 mg/kg/hr.

4.4 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 1.3. The end of the study is defined as completion of the last visit or procedure in the trial globally.

Participants who have an ongoing AE at the time of study completion will be followed as described in 8.3.5. Study discontinuation and closure details are in 10.1.2.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Eligible participants will:

1. Be at least 18 years of age at the time of study consent;
2. Meet DSM-5 criteria for Substance Use Disorder associated with methamphetamine;
3. Be treatment-seeking methamphetamine users with at least 1 methamphetamine or amphetamine positive specimen during the screening period;
4. Be able and willing to read, comprehend, and give Authorization for Use/Disclosure of Health Information (HIPAA) and informed consent;
5. Be willing to comply with study instructions and dosing, agree to make all appointments, and complete the entire course of the study;
6. Agree to use protocol-specified method(s) of birth control throughout study participation;
7. Agree to adhere to Lifestyle Considerations throughout study duration (see section 5.3);
8. Have access to a smartphone or other device capable of supporting the study app;
9. Successfully complete app-based training program as evidenced by submission of at least 2 valid saliva drug screens when randomly assigned during the first two weeks after the Screening visit.

5.2 EXCLUSION CRITERIA

Eligible participants will NOT:

1. Have current dependence (past 12 months) Substance Use Disorder, defined by ≥ 2 DSM-5 criteria, for any psychoactive substance (i.e., opioids or benzodiazepines), other than methamphetamine or nicotine (any severity). Mild severity (2-3 DSM-5 criteria) Substance Use Disorder for alcohol or marijuana is allowed;
2. Be currently taking certain other drugs and medications, including: "designer drugs" (e.g., 3,4-methylenedioxyMETH (MDMA, Ecstasy, Adam, XTC) and its N-dimethyl metabolite methylenedioxyamphetamine (MDA), anti-orexigenic drugs (including over-the-counter medications for weight loss), or be chronic users of phenethylamine compounds (e.g., phenylpropanolamine, ephedrine, pseudoephedrine, amphetamine, phentermine, phenmetrazine, methylphenidate, diethylpropion, and propylhexedrine);
3. Have a known contraindication or sensitivity to IXT-m200 based on known allergies to other mAbs, any inactive ingredient of IXT-m200, or any other products required for the study procedures;
4. Have a history of severe allergy (rash, hives, breathing difficulty, etc) to any medications;
5. Have a history of allergic or environmental bronchial asthma within the past 3 years;
6. Have a current diagnosis of anorexia nervosa or bulimia disorder;
7. Have a history of unstable cardiovascular disease that is not adequately controlled at the time of eligibility determination;
8. Be mandated by the court to obtain treatment for methamphetamine dependence where such mandate required the results of methamphetamine testing to be reported to the court;
9. Have positive saliva drug screen for psychoactive substances other than amphetamines at the screening visit (positive benzodiazepine results are not exclusionary if the participant takes them chronically as prescribed and does not appear intoxicated at screening);
10. Be expected to fail to complete the study protocol due to probable incarceration or relocation from the clinic area, or any clinically significant mental or physical illness within a 1-year prior, that would impact compliance with trial requirements;
11. Have clinically significant laboratory values (outside of normal limits). The following specified ranges are allowable:
    a. Liver function tests (total, direct, and indirect bilirubin, ALT, AST, gamma-glutamyl transferase, lactate dehydrogenase and alkaline phosphatase) <3 times the upper limit of normal, and
    b. Kidney function tests (creatinine and BUN) <2 times the upper limit of normal;
12. Be considered to be at imminent risk of suicide or have a past-year history of a serious suicide attempt (defined as an attempt that results in or requires medical treatment) based on response to queries within eligibility screening about suicidal ideation and attempts;
13. Have an uncontrolled systemic disease or a medical condition that may increase the risk associated with study participation or administration of study treatment or that may interfere with the interpretation of study results;
14. Be currently participating or has participated within the last 30 days prior to the start of this study in a drug, device, or other interventional research study; unless the study is a COVID-19 study with long-term follow-ups (participant cannot have received a dose of study drug within the past 30 days);
15. Be pregnant or lactating;
16. In the Investigator's or Sponsor's (or designee) opinion, be inappropriate for the study, including those believed to be attempting to enter the study primarily for financial gain.

5.3 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.

The use of medication-assisted treatment for opioid use disorder is exclusionary, as those medications (buprenorphine, methadone, and naltrexone) are psychoactive substances.

Participants are prohibited from the following during the study period:

- Ingesting or using any other investigational drug or device.
- Donating blood, plasma, platelets, eggs or sperm.

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

Participants are required to practice an adequate method of birth control, including intrauterine device; 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 last dose of study drug.

5.4 SCREEN FAILURES

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

All participants who consent to participate but fail screening will be referred to treatment outside of the study per the recommendation of the screening physician. Individuals who do not meet the criteria for participation in this trial (screen failure) because of a short term or temporary issue may be rescreened (≥30 days later). Sponsor permission for rescreening is required for such cases.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Traditional and non-traditional advertising methods will be utilized to ensure recruitment goals are met. This will be accomplished by using advertising such as print, electronic, and/or digital newspapers, flyers, mailers, billboards, television, radio, online, social networking, study-branded materials (such as ink pens and post-it notes) and other means of communicating with the community that are IRB approved. Advertising may also encompass providing materials to potential referrers to assist with recruitment and to community agencies to assist in recruiting and retaining participants.

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

To address retention, we will incorporate procedures used in previous trials, which include frequent contact with participants throughout active study periods, incentives to motivate participants to keep study visits, and potentially providing travel vouchers for taxis and shared rides to help participants to come to clinic. In addition, this study will deliver the vast majority of encounters virtually via smartphone app. We believe that this modality will significantly reduce study burden on the participants, will dramatically increase study engagement, and will lead to improved study retention compared to studies involving primarily in-person visits.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

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

By binding METH in the bloodstream and altering METH PK, it is predicted that IXT-m200 decreases the amount of METH reaching its active sites in the brain. The presence of IXT-m200 should therefore decrease the perceived pleasurable effects of METH. Over the longer term, when combined with behavior modification therapy, IXT-m200 should reduce the frequency of METH use.

Cognitive Behavioral Therapy
All participants in this trial will attend regular cognitive behavioral therapy (CBT) sessions. These individual sessions will be conducted by a trained therapist at the study site. CBT generally focuses on the following topics: recognizing and changing patterns of use, coping with cravings, changing negative thoughts, improving decision making, learning to say no, and improving problem-solving. The content of these sessions is prearranged and sequenced using a manualized format.

Other Participant Support
A smartphone app will be used to engage participants frequently, provide study payments, deliver access to a recovery coach, collect daily drug use reports, and conduct video-monitored saliva drug testing. The app will provide payment for completion of study-required activities such as clinic visits, saliva testing, and self-reports of drug use. The app also connects each participant with a recovery coach who will be available for a phone/video call once per week throughout the study. In addition to the scheduled calls, the coach will be available by text during working hours. The app will also collect data for two efficacy assessments, the saliva drug screens (8.1.2) and self-reported past day drug use (8.1.3).

6.1.2 DOSING AND ADMINISTRATION

Participants will only be randomized and dosed with study drug if they have passed all screening requirements before or on Day 1. Participants will be randomized on Day 1. In Cohort 1, participants will get 1.5 g IXT-m200 or placebo (2:1). If the interim analysis supports dose escalation, participants will receive 3 g IXT-m200 or placebo (2:1) in Cohort 2. If the interim analysis does not support dose escalation, participants in the treatment arm will receive 1.5 g IXT-m200 or a lower dose and the sample

size will be recalculated. Each participant will receive 6 doses of assigned study drug, spaced 4 weeks apart.

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

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

Further doses will not be given to any participant that experiences an SAE that is attributed to the study drug (by a causality grading of possibly, probably, or definitely; see section 8.3.3.2), but the participant will be followed to completion. No dose adjustments will be made.

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

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

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

Placebo: An unblinded pharmacist will be responsible for acquiring commercially available normal saline for use as placebo for IXT-m200.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Study Intervention: IXT-m200 is formulated as a solution containing approximately 20 mg/mL IXT-m200 in 10 mM sodium phosphate, pH 6.5, 150 mM sodium chloride, and 0.05% w/v polysorbate 80. The product is a clear solution packaged in glass vials with stoppers and flip-off seals. Catalent Pharma Solutions manufactures the formulated active pharmaceutical ingredient.

Labels will be similar to the following:

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

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

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

6.2.3 PRODUCT STORAGE AND STABILITY

IXT-m200 vials are single-use and should be stored refrigerated at 2 to 8°C (preferred) or frozen at -20°C. The stability of the product is still under investigation and stability protocols will run concurrent to the study. A previous lot of IXT-m200 remained stable after 48 months of refrigerated storage when the stability protocol was terminated.

6.2.4 PREPARATION

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

Placebo: Normal saline requires no preparation prior to administration.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

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

Participants who qualify will be randomized in two sequential cohorts. The dose groups of IXT-m200 or placebo will be at a 2:1 ratio in Cohort 1 and, if the interim analysis supports dose escalation, 2:1 in Cohort 2. If the interim analysis supports dose maintenance or reduction, then the sample size will be recalculated. Placebo participants will be combined for analysis at the end of study. Randomization will be stratified by self-reported past-month METH usage at screening (<18 days versus ≥18 days).

Unblinding of treatment assignment during the study is discouraged and should occur only if it is absolutely necessary for the investigator, Medical Monitor, Sponsor, or participant to know what he or she received for safety reasons. If the Sponsor, the investigator, or Medical Monitor deems identification of the study drug to the participant as necessary for the purpose of providing urgent care, the pharmacy will inform the investigator of the assignment, who will notify the Medical Monitor, Sponsor, and participant. The process of unblinding will be appropriately documented in the investigator file. The date and reason for the unblinding must be recorded. When possible, the Medical Monitor and Sponsor should be notified prior to unblinding; otherwise, they must be notified within 24 hours after unblinding.

6.4 STUDY INTERVENTION COMPLIANCE

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

CBT session attendance will be documented by the site.

6.5 CONCOMITANT THERAPY

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

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

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. The Sponsor, in consultation with the investigator and Medical Monitor, will suspend enrollment until a full safety review by the Sponsor and Data and Safety Monitoring Board (DSMB) is performed if any 1 of the following events occurs, unless the event was unrelated to study drug administration i.e., causality was graded as unrelated or unlikely:

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

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

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

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

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

Participants that will no longer be dosed with study drug but agree to continue participation in other study procedures and assessments will be considered ‘discontinued’. Participants are free to discontinue at any time upon request. Participants will be encouraged to complete study visits, assessments, and therapy sessions, even if they elect to discontinue study drug administration. In this case, all study activities will be completed per protocol with the exception of dose administrations.

An investigator may discontinue a participant from study drug administration for the following reasons:

- the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation, such as pregnancy,

- any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant,
- significant non-compliance by the participant,
- if, in the investigator's opinion, continuation with study drug administration would be detrimental to the participant's well-being,
- at the specific request of Sponsor or the investigator.

Participants who miss dosing days and return to the study at a later point are not automatically disqualified from resumption of dosing. Please discuss with Sponsor if two or more consecutive dosing visits are missed and the participant later wishes to resume treatment.

In all cases, the reason for withdrawal or discontinuation must be recorded in the 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 withdraw from further participation in the study, the research staff will cease to try to make further contact.

There will be no replacement of participants who withdraw or are discontinued following the first dose of study drug.

7.3 LOST TO FOLLOW-UP

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

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

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

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

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

8.1.1 QUALITY OF LIFE

- The Treatment Effectiveness Assessment (TEA)[5] will be performed at screening and at selected subsequent visits per the Schedule of Activities.
- The Patient Global Impression of Change (PGIC) and Clinical Global Impression of Change (CGIC) scales will be used at selected time points after the first dose.

8.1.2 SALIVA DRUG SCREENS

- Qualitative saliva drug screens will be used during screening and twice weekly throughout the study (Weeks 1-32) to screen for substances of abuse including amphetamine, cocaine, methamphetamine, and opiates. Saliva testing will be strictly monitored by performance of a specific series of steps recorded by video and reviewed by a trained professional to ensure validity of the test results.

8.1.3 SELF-REPORT OF DRUG USE VIA APP

- Participants will be required to install an app on their smartphone, tablet, or similar device which records daily self-reported drug use from Day 1 through Week 32 or the Early Termination visit. The app will query participants daily on their past-day use, upload responses to a database at regular intervals, and notify investigators when participants are non-responsive.

8.1.4 METHAMPHETAMINE USE ASSESSMENTS

- DSM-5 criteria checklist should be used to assess participants for Methamphetamine Use Disorder and the number of criteria met. At screening the checklist should be completed for past year history. At each subsequent assessment time point (Week 25 and Week 33), the checklist should be completed for the past 30 days AND for the past 3 months, separately.
- Also at Screening, participants should be asked, "What is the main way you take methamphetamine?" Potential answers would be Smoked, Snorted, Intravenous, or Oral.
- Participants should also be asked, "How many days in the past month did you use METH?" Answers should be categorized as <18 days or ≥18 days.

8.1.5 ADVERSE OUTCOMES ASSESSMENT

- To assess the frequency of adverse outcomes, the following questions should be asked at Screening and Weeks 13, 25, and 33. All responses should be counted over the past 3 months.
- Questions:
    - How many unintended encounters with the criminal justice system have occurred? This does not include scheduled appointments with parole officers, court dates, or similar follow-ups to previous events. However, this does include interactions due to domestic disturbance, petty theft, DUI, etc.
    - Have you required emergency medical intervention due to methamphetamine use? This might be from a methamphetamine overdose or injury due to use. If yes, how many times?
    - Have you tested positive for HIV or Hepatitis where you had not been positive before?

8.2 SAFETY AND OTHER ASSESSMENTS

Assessments are to be performed at the time points described in the Schedule of Activities (1.3). The procedures for the collection, handling, and shipping of laboratory samples will be specified in the laboratory manual(s) provided to the study site.

8.2.1 ELIGIBILITY CRITERIA

- DSM-5 criteria checklist should be used to assess participants for Substance Use Disorders (including METH, opioids, alcohol, nicotine, marijuana, etc.)

8.2.2 MEDICAL AND MEDICATION HISTORY

- A complete medical history will be obtained by interview and any available medical records at screening. Interim medical history will be obtained at all subsequent time points; any new events starting after randomization will be recorded as AEs.
- A past-30-days medication history will be obtained by interview and any available medical records at screening. Concomitant medications will be updated at all subsequent visits.

8.2.3 VITAL SIGNS

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

8.2.4 PHYSICAL EXAM

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

8.2.5 PSYCHIATRIC EVALUATION

- A complete psychiatric history will be obtained at screening evaluating for (but not limited to) the following: major current depression, psychosis, bipolar illness, organic brain disorder, anorexia nervosa or bulimia disorder or dementia, which require ongoing medication or which would make study compliance difficult in the opinion of the investigator.
- The psychiatric history will be updated at selected subsequent visits. When updating psychiatric history, participants should be asked, “Since your last visit, have you had a serious plan or attempt to kill yourself?”
- Suicide-related thoughts and behaviors will be assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS) at screening (past year version). The C-SSRS captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period. The scale includes suggested questions to solicit the type of information needed to determine if a suicide-related thought or behavior occurred. The C-SSRS will be administered by appropriately trained site personnel. For participants determined to be at imminent risk of suicide, a referral to a clinician should be made.
- The C-SSRS may be administered at any time to a participant who indicates, or is suspected to have, new suicidal intentions during the study.

8.2.6 PREGNANCY TEST

- Urine pregnancy tests will be performed on all females at all visits, unless hysterectomy is reported in the medical history. Results from this test should be reviewed prior to dosing. Pregnant participants should not receive any further doses, but all other assessments should be completed.

8.2.7 LABORATORY TESTS

The below laboratory tests will be centrally assessed:

- Hematology
  - Erythrocytes: red blood cell (RBC) count, hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, red cell distribution width, and reticulocyte count as an absolute value.
  - Leukocytes: WBC and differential (basophils, eosinophils, lymphocytes, monocytes, and neutrophils) reported as absolute values.
  - Coagulation: platelet count, prothrombin time measured as international normalized ratio, activated partial thromboplastin time.
- Serum Chemistry
  - Liver: alkaline phosphatase, ALT, AST (serum glutamic-oxaloacetic transaminase), bilirubin (total, direct, and indirect), gamma-glutamyl transferase, and lactate dehydrogenase.
  - Renal: blood urea nitrogen, creatinine, and uric acid.
  - Electrolytes, sodium, potassium, chloride, and carbon dioxide.
  - General: creatine phosphokinase (CPK), albumin, calcium, magnesium, glucose (fasting), phosphate, protein (total), amylase, lipase and prostate specific antigen.
- Urinalysis
  - Samples will be assessed macroscopically first and only if needed, microscopic examination will follow.
  - Microscopic: pH, specific gravity, glucose, ketones, leukocyte esterase, nitrites, occult blood, and protein, RBCs/hpf, WBCs/hpf, bacteria, casts, epithelial cells, mucous threads, and crystals.

8.2.8 ELECTROCARDIOGRAMS

- Electrocardiograms (ECG; 12-lead) will be recorded after the participants have been supine for 5 minutes. Standard ECG parameters including heart rate, QRS, PR, QT, and QTc intervals will be measured. The ECGs will be read by a study physician to assess for any abnormalities. Abnormal ECG parameters include, but are not limited to ventricular hypertrophy, left axis deviation, atrial or ventricular arrhythmias other than sinus, and prolonged QTc (greater than 500 ms). ECGs may be repeated if data quality is compromised due to poor lead placement or machine error.
- Confirmed ECG anomalies will be referred for appropriate medical follow-up.

8.2.9 BLOOD FOR PK, HACA, AND CYTOKINES

- PK of IXT-m200: A validated enzyme linked immunosorbent assay procedure will be used to quantitate IXT-m200 in serum samples. Approximately 1 mL per sample is required.
- HACA: A validated electrochemiluminescent procedure will be used to analyze HACA in serum samples. Approximately 1 mL per sample is required.

- Cytokine panel to include at a minimum IL-6, IL-8, and TNFα levels will be determined only if any study drug infusion reaction occurs.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

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

The AE may be:

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

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

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

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

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An SAE is an AE that at any dose:

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

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

Medical and scientific judgment will be exercised in deciding whether other AEs, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but 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 in the British Journal of Clinical Pharmacology[6] will be used to categorize the severity of all AEs. The stopping rules outlined in Section 7.1 will apply.

The following criteria will be used:

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

For example, if hypotension is not immediately responsive to medications, this will constitute a Grade 3 reaction and it will be documented as such. Similarly, if bronchospasm (SaO2 < 93% on oxygen) occurs and requires medications, this will constitute a Grade 3 reaction, and will be documented as such.

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

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

DEFINITELY – The AE:

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

PROBABLY – The AE:

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

POSSIBLY – The AE:

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

UNLIKELY – The AE:

- does not follow a reasonable temporal sequence from study drug administration;

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

UNRELATED – The AE:

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

8.3.3.3 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.

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, during engagement of the participant with the smartphone app, or upon review by a Study Monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate 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 after randomization, it will be recorded as an AE. If changes occur before randomization, these should be reported as medical history.

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 7 (for nonserious AEs) or 30 days (for SAEs) after the last day of study participation for participants who withdraw. For all events occurring prior to randomization to treatment, these events should be recorded on the medical history case report form page. For all events after randomization to treatment, these should be recorded on the AE/SAE case report form pages. For all other participants, reportable events will be recorded 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 into a treatment group 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 to a maximum of 15 days following the end of study visit. Should the AE result in death, a full pathologist's report should be supplied, if possible.

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 site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the 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 study Sponsor will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the Sponsor's initial receipt of the information. In addition, the Sponsor must notify FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the Sponsor determines that the information qualifies for reporting.

The NIDA Project Officer (PO) and Science 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 (SAETRS).

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

Not applicable.

8.3.9 REPORTING OF PREGNANCY

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

pregnancy if the participant is willing. Generally, follow-up will be no longer than 6 to 8 weeks after the estimated delivery date. While pregnancy itself is not considered an AE or SAE, any pregnancy complications will be recorded as an AE or SAE.

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

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

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

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

8.4.2 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 participant 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

9.1 STATISTICAL HYPOTHESES

The primary objective of the study is to evaluate the efficacy of IXT-m200 in preventing or reducing relapse to stimulant use. The primary efficacy endpoint is percent of 20 weeks abstinent from stimulants following a 4-week grace period between Week 5 and Week 25 based on saliva screens and by self-report via smartphone app. Each dose group of IXT-m200 will be compared to the placebo group.

For each IXT-m200 dose group, the hypotheses are as follows:

> Null Hypothesis (H_0): There is no difference between the IXT-m200 group and the placebo group in percent weeks abstinent between Week 5 and Week 25.
>
> Alternative Hypothesis (H_1): There is a difference between the IXT-m200 group and the placebo group percent weeks abstinent between Week 5 and Week 25.

The secondary efficacy objectives are to evaluate the efficacy of IXT-m200 over placebo in the proportion of participants achieving early remission, achieving stimulant abstinence, or improving participant-rated quality of life as measured by the following endpoints:

- Proportion of responders at Week 25 as measured by DSM-5 criteria for early remission. For each IXT-m200 dose group, the hypotheses are as follows:

  > Null Hypothesis (H_0): There is no difference between the IXT-m200 group and the placebo group in proportion of responders.
  >
  > Alternative Hypothesis (H_1): There is a difference between the IXT-m200 group and the placebo group in proportion of responders.

- Complete abstinence during the last month of study drug treatment (between Week 21 and Week 25), as measured by saliva screens and by self-report via smartphone app. For each IXT-m200 dose group, the hypotheses are as follows:

  > Null Hypothesis (H_0): There is no difference between the IXT-m200 group and the placebo group in the proportion of participants achieving stimulant abstinence (responders) between Week 21 and Week 25.
  >
  > Alternative Hypothesis (H_1): There is a difference between the IXT-m200 group and the placebo group the proportion of participants achieving stimulant abstinence (responders) between Week 21 and Week 25.

- Change from screening in the Treatment Effectiveness Assessment (TEA) at Week 13, 25, and 33. For each IXT-m200 dose group and at each timepoint of interest, the hypotheses are as follows:

  > Null Hypothesis (H_0): There is no difference between the IXT-m200 group and the placebo group in the change from screening Treatment Effectiveness Assessment.

Alternative Hypothesis (H_1): There is a difference between the IXT-m200 group and the placebo group in the change from screening Treatment Effectiveness Assessment.

The SAP will describe any hypotheses for the exploratory endpoints. The study will use a two-sided Type 1 error rate (alpha) of 5% for comparing each IXT-m200 arm versus placebo; there will be no multiplicity adjustments for multiple comparisons for multiple endpoints and between multiple dose groups. All p-values reported will be nominal.

9.2 SAMPLE SIZE DETERMINATION

A total of approximately 300 participants are expected to be screened, with a goal of randomizing approximately 120 participants (60% screen failure rate).

Approximately 120 participants will be randomized into this study in two sequential cohorts. The first cohort will randomize approximately 60 participants 2:1 to IXT-m200 1.5 g or placebo and, if the interim analysis supports dose escalation, the second cohort will randomize approximately 60 participants 2:1 to IXT-m200 3.0 g or placebo. If the interim analysis supports dose maintenance or reduction, then the sample size may be recalculated. Randomization will be stratified by self-reported past-month METH usage at screening (<18 days versus ≥ 18 days). Final analyses will compare each IXT-m200 dose group to the placebo group pooled over both cohorts.

A sample size of 40 participants in each dose group would provide 90% power to detect a difference in % weeks abstinent between Week 5 and Week 25 that is 0.73 times the pooled standard deviation, assuming a two-sided 5% alpha. Table 1 presents potential scenarios for the power analyses. For example, if the standard deviation is 20%, then the study has 90% power to detect a difference of 14.6% or larger between the IXT-m200 group and placebo (approximately 2.92 weeks).

Table 1. Minimum detectable difference between each IXT-m200 group (n=40) versus the placebo group (n=40)

Power	Detectable difference	Examples of detectable differences with varying pooled SD		
		20%	25%	30%
0.80	0.63 × pooled SD	12.6%	15.8%	18.9%
0.85	0.68 × pooled SD	13.6%	17.0%	20.4%
0.90	0.73 × pooled SD	14.6%	18.3%	21.9%

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

The literature suggests that dropout rates in the study population may be up to 50% [7]; the analyses of the primary endpoint will account for missing data using imputation.

9.3 POPULATIONS FOR ANALYSES

The study analysis populations will consist of:

Population	Description
Enrolled	All participants who sign the ICF.
Intent-to-Treat (ITT)	All randomized participants. Participants will be categorized by their randomized treatment assignment.

Population	Description
Modified Intent-to-Treat (mITT)	All randomized participants who received at least one dose of study drug. Participants will be analyzed according to their randomized treatment assignment.
Per-Protocol (PP)	All randomized participants who receive at least one dose of study treatment excluding participants with major protocol deviations with the potential to impact efficacy assessments. Participants will be analyzed according to the treatment which they received (i.e., a participant randomized to placebo who received only active study drug in error will be analyzed with active participants, and a participant randomized to active who received only placebo will be analyzed with the placebo participants). The PP population will exclude participants who received some active drug and some placebo. InterveXion will conduct a blinded review of the protocol deviations prior to database lock to determine if any participant should be excluded from the PP population.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

A statistical analysis plan (SAP) will document the complete details of the planned statistical analyses and will be completed prior to unblinding of the study data. The SAP will include more detail of analysis populations, summary strategies, and any amendments to the proposed analyses listed here, if necessary, and will supersede the summary statistical descriptions below.

The results of this study will be reported using summary tables, figures, and data listings. Figures, similar to heat maps, will be used to depict the testing result at each time point of interest. Cumulative distribution functions of percentage of abstinence will also be presented for relevant outcome data.

Unless otherwise indicated, the pre-specified efficacy analyses will be conducted using the ITT population. The study will use an overall two-sided Type I error rate of 5%; results will be reported with a two-sided 95% confidence interval (CI) and p-value. The SAP will detail the approach to control for multiplicity.

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

All summaries will be by treatment group.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary efficacy endpoint is percent of 20 weeks abstinent from stimulants based on saliva screens and by self-report via smartphone app during a 20-week period between Week 5 and Week 25, after a four-week grace period during which relapses may occur. A combination of self-report and saliva screens data and concordance will be used to score each day of the study within these time frames. The primary efficacy endpoint analysis will use the ITT population.

Participants self-report stimulant use on a daily basis; a saliva screen is taken twice a week at two random timepoints. Data that contribute to the primary endpoint will be collected from the day after a participant's Week 5 visit through the next 20 weeks. The SAP will detail the visit windows.

A modified combined self-report and pharmacokinetic-1 (SRPHK1) algorithm[8] will be used to derive if a day is a "use day" or an "abstinent day". Briefly the rules of the algorithm (as listed in Somoza et al., 2008 with minor modifications) are:

1. Always label self-reported use days as use days.
2. Label any day covered by a positive saliva screen as a use day. However, if that day is a self-reported no-use day and one of the one or two previous days was self-reported as a use day, assign the saliva-based use to the self-reported use day. If self-report is missing for the day prior to the positive saliva sample, the day will be considered a use day.
3. Label as missing any self-reported no-use days not followed by a saliva sample within 7 days. Also label as missing any day having a missing self-report and no saliva-based indication of use or no use.
4. Treat all other self-reported no-use days (temporarily) as "unknown".
5. Treat "unknown" days as described below:
    a. Calculate the "concordance rate" as follows:
    (1) determine the number of instances in which a day has been assigned a saliva screen status of use but the participant reports no use;
    (2) divide this number by the total number of saliva samples;
    (3) subtract the resulting fraction from 1.
    b. If the concordance rate is ≥0.7 (i.e., if we can trust that the participant tells the truth in his or her self-report), label all remaining "unknown" days as no-use days; otherwise label all remaining "unknown" days as missing.
6. Weeks with missing values for every day will be imputed as a non-abstinent week.

A visit week with no use days is an abstinent week and a visit week with any use day is a non-abstinent week. For each participant, the percent weeks abstinent is the number of weeks (observed or imputed) divided by the weeks in the period of interest (i.e., 20 weeks for the primary endpoint).

The primary efficacy analysis is based on a test of the difference between each IXT-m200 dose group and the placebo group in percent weeks abstinent, as estimated using an analysis of covariance (ANCOVA). The dependent variable in the model is percent weeks abstinent; the independent variables in the model will be treatment group assignment and stratification level of past-month METH use at screening.

Adjusted means and standard errors for each treatment group and the estimated difference between the groups and associated 95% confidence intervals and two-sided p-values will be reported.

Sensitivity analyses will be described in the SAP and may explore the impact of missing data and standard-based imputation with control-based MI.

Details of the primary and sensitivity analyses, including imputation models, will be described in the SAP.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The secondary endpoints will be tested using a two-sided alpha of 0.05; no multiplicity adjustment is planned, and p-values will be nominal. Secondary endpoint analyses will use the ITT population.

9.4.3.1 PROPORTION OF EARLY REMISSION RESPONDERS AFTER TREATMENT

The first secondary efficacy endpoint is proportion of responders after treatment (measured over the 3 months prior to the Week 25 visit). A participant will be considered a responder if they meet the definition of achieving early remission, which is to report no DSM-5 criteria, while disregarding the result for craving, over the past 3 months.

The proportion of participants achieving a response will be compared in each IXT-m200 dose group versus the placebo group using a risk difference. The risk difference will be computed using a binomial model with an identity link. The independent variables in the model will include treatment group and stratification level of past-month METH use at screening. For each comparison and outcome, the 95% confidence interval and two-sided p-value will be reported. A sensitivity analysis will be based on a logistic regression model testing the null hypothesis that the odds ratio is 1.

If the logistic or binomial regression models fail to converge, the models will be re-run without the stratification level variable. If they still fail to converge, a Cochran-Mantel-Haenszel test with an exact method will be used to compare the proportion of participants who respond in each group.

Standard errors will be reported for the proportion of responders in each treatment group and the estimated difference between the proportion of responders in each group. The estimated difference for the proportion of responders in each treatment group, associated 95% confidence intervals, and two-sided p-values will also be reported.

9.4.3.2 COMPLETE ABSTINENCE DURING LAST MONTH OF TREATMENT

The second secondary efficacy endpoint is the complete abstinence during the last month of study drug treatment (between Week 21 and Week 25), as measured by saliva screens and by self-report via smartphone app. A modified SRPHK1 algorithm [8] will be used to derive if a day is a “use day” or an “abstinent day” (see Section 9.4.2). A participant will be categorized as fully abstinent if the imputation algorithm resolves to zero days of use; otherwise, a participant will be categorized as not abstinent (failure).

The proportion of participants achieving complete abstinence will be compared in each IXT-m200 dose group versus the placebo group using both an odds ratio and a risk difference. The analysis approach is identical to that for the first secondary endpoint as both are binary outcomes.

9.4.3.3 TREATMENT EFFECTIVENESS ASSESSMENT

The third secondary efficacy endpoint is the difference between groups in the change from screening in participant-rated quality of life as measured by the Treatment Effectiveness Assessment (TEA) at Weeks 13, 25, and 33.

The Treatment Effectiveness Assessment includes four items with 10 ordinal response options ranging from “not well at all” to “extremely well” (Likert scale), where higher values indicate better quality of

life [5]. The Treatment Effectiveness Assessment score is the sum of the four responses (minimum = 4, maximum = 40); the Treatment Effectiveness Assessment score will not be computed if the participant did not respond to all four items.

Change from screening in Treatment Effectiveness Assessment scores at each post-screening timepoint will be compared in each IXT-m200 group versus the placebo group using a mixed model for repeated measures (MMRM), which assumes unobserved values are missing at random. The dependent variable is change from screening in Treatment Effectiveness Assessment score. The independent variables in each model will include treatment group, stratification level of past-month METH use at screening, screening Treatment Effectiveness Assessment score; visit, and treatment group by visit interaction term. In the event that the model does not converge, then an ANCOVA model will be fit with the change from baseline at the final timepoint as the outcome, baseline outcome value, treatment group, and stratification factor as covariates in the model. For each comparison and timepoint, the adjusted means and standard errors for each treatment group and the estimated difference between the groups and associated 95% confidence intervals and two-sided p-values will be reported.

9.4.4 SAFETY ANALYSES

All safety analyses will be performed on the ITT Population. Descriptive statistics will be used to summarize AEs, serious AEs, AEs causing withdrawal from study, AEs judged by the investigator as potentially related to study drug, changes in laboratory and vital signs. AEs will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term.

Anti-IXT-m200 antibody results will be summarized by treatment group overall and at each timepoint. The number and percentage of participants with samples that screened positive or negative for anti-IXT-m200 antibodies will be presented; for participants with positive screen results whose samples were confirmed positive, the number and percentage of participants with each titer category will be presented.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Demographic and baseline characteristics (age, sex, race, ethnicity, body weight, height, BMI, and days per month of METH use) will be summarized by treatment group using descriptive statistics for the ITT population.

9.4.6 PLANNED INTERIM ANALYSES

The DSMB will review an interim analysis report after the last participant in Cohort 1 has available Week 25 data (or has previously discontinued) at which time the DSMB will review efficacy in addition to the typical safety report content. On the basis of the Week 25 interim analysis, the DSMB may recommend whether to proceed to Cohort 2 and which dose to use for the IXT-m200 group (e.g., escalate to 3.0 g, continue at 1.5 g, or reduce). If the DSMB recommends continuing dosing at 1.5 g in Cohort 2, the sample size will be recalculated. The DSMB may also recommend that the study be stopped early if there is sufficient evidence that any of the circumstances in section 10.1.2 apply.

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

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

9.4.7 SUB-GROUP ANALYSES

Selected safety and efficacy analyses may be performed in the following subgroups:

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

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

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

9.4.9 EXPLORATORY ANALYSES

Exploratory analyses will be performed on the ITT population. See Table 2 for planned exploratory endpoints and associated analyses; the SAP will describe the methods for summarizing these outcomes. Additional exploratory analyses may be described in the SAP.

Table 2. Planned exploratory analyses

Endpoint	Analysis
Number of sequential weeks of abstinence from the end of treatment visit (Week 25), defined as four weeks after the final planned treatment visit (Week 21), as measured by saliva screens and by self-report via smartphone app.	"Use day" or "abstinent day" will be derived as described for the primary endpoint (see Section 9.4.2). For each participant, sequential weeks abstinent counting backwards from the Week 25 visit will be calculated based on use/abstinent days, for a minimum of 0 weeks and maximum of 24 weeks of abstinence.
Point prevalence abstinence (last 7 days) as measured by saliva screens and self-report via smartphone app at Week 25, Week 29, and Week 33.	For each visit of interest, abstinence or use will be based on the self-reported use in the previous 7 days and saliva screens. A "Use day" or "abstinent day" will be derived as described for the primary endpoint (see Section 9.4.2). A participant will be categorized as fully abstinent if they report no stimulant use on all 7 previous days and their saliva sample is negative (responder); a participant will be categorized as not abstinent if they report any stimulant use in the previous 7 days or their saliva sample is positive (failure).

Endpoint	Analysis
Weekly abstinence from stimulants following a 4-week grace period (between Week 5 and Week 25) as measured by saliva screens.	For each week, participants will be categorized as abstinent or not abstinent based on twice weekly saliva samples.
Difference between number of adverse outcomes recorded between Week 5 and Week 33. Adverse outcomes include those queried in the Adverse Outcomes Assessment and also suicide and overall mortality.	The number of participants reporting each measured Adverse Outcome and the total will be reported.
Proportion of responders at Week 33 as measured by DSM-5 criteria. A responder is a participant who meets the definition of early remission, i.e., ≥3 months and <12 months without meeting DSM-5 criteria while disregarding the result for craving.	The number of participants reporting no DSM-5 criteria, while disregarding the result for craving, over the past 3 months will be reported.
Difference between groups in Clinical Global Impression of Change (CGIC) at Week 13, 25, and Week 33.	The comparison between groups will be based on an ANCOVA model with CGIC as the outcome and treatment group and stratification factor as covariates.
Difference between groups in Patient Global Impression of Change (PGIC) at Week 13, 25, and Week 33.	The comparison between groups will be based on an ANCOVA model with PGIC as the outcome and treatment group and stratification factor as covariates.

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

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator or designee will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks

of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with advisors or think about it prior to agreeing to participate. The participant will sign the ICF prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the ICF will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated at the sole discretion of the Sponsor. Written notification, documenting the reason(s) 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. Participants will be contacted, as applicable, and informed of changes to the study visit schedule.

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

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

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

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality is held strictly in trust by the participating investigators, their staff, and the Sponsor and their agents. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. All personal details of participants will be treated as confidential by the investigator and staff, and handling of personal data will be in compliance with the Health Insurance Portability and Accountability Act of 1996 and any applicable state laws governing the individual study sites. The study participants' contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, institutional policies, or Sponsor requirements.

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

Certificate of Confidentiality (COC): To further protect the privacy of study participants, a COC is granted by the National Institutes of Health (NIH) to all awardees conducting research that collects or uses identifiable, sensitive information. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants. 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 above. After the study is completed, the de-identified, archived data will be maintained as long as regulations require, and will be made available by the Sponsor for use by other researchers including those outside of the study via a data sharing agreement.

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

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

No genetic analysis will be performed.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Sponsor Contact	**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

There will be a Data and Safety Monitoring Board (DSMB) for this trial, which will regularly review unblinded safety data by treatment group from the study.

The DSMB will be composed of individuals with the appropriate expertise, likely including monoclonal antibody and methamphetamine clinical pharmacology, psychiatry or behavioral medicine, statistics, and a patient advocate or representative. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet approximately quarterly to review unblinded data and assess safety data on each arm of the study. 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 and the Sponsor, by the actions of its Medical Expert, will determine whether cohort enrollment should continue or if changes should be made.

The DSMB will participate in the Interim Analysis as described in section 9.4.6.

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

10.1.9.2 STUDY RECORDS RETENTION

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

The following records must be retained by the investigator:

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

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

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol; or any noncompliance with the clinical trial protocol, GCP, or study manual 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 participant's rights, safety, or well-being. Deviations will be categorized by type and will be reviewed on an ongoing basis.

10.1.11 PUBLICATION AND DATA SHARING POLICY

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

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

10.1.12 CONFLICT OF INTEREST POLICY

Any conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The Sponsor has established policies and procedures to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CGIC	Clinical Global Impression of Change
CBT	Cognitive Behavioral Therapy
CFR	Code of Federal Regulations
CI	Confidence Interval
Cmax	Maximum Concentration
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine Phosphokinase
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CV%	Coefficient of Variation
DEQ	Drug Effects Questionnaire
DHHS	Department of Health and Human Services
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ET	Early termination visit
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
HACA	Human Anti-Chimeric Antibodies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICF	Informed Consent Form
IgG	Immunoglobulin G
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
METH	Methamphetamine
MDA	Methylenedioxyamphetamine
MDMA	MethylenedioxyMETH
MI	Multiple Imputation
mITT	Modified Intent-to-Treat
MMRM	Mixed Model for Repeated Measures

MUD	Methamphetamine Use Disorder
NIH	National Institutes of Health
NIDA	National Institute on Drug Abuse
OHRP	Office for Human Research Protections
OUTLAST	A Phase 2, Double-Blind, Randomized, Placebo-Controlled, Multiple-Dose Study to Evaluate the Safety and Efficacy of IXT-m200 in Treatment-Seeking Individuals with Methamphetamine Use Disorder
PGIC	Patient Global Impression of Change
PK	Pharmacokinetics
PO	Program Officer
PP	Per-Protocol
QC	Quality Control
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAETRS	Serious Adverse Event Tracking and Reporting System
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
SRPHK1	Self-Report and Pharmacokinetic-1 Algorithm
STAMPOUT	Study of Antibody for Methamphetamine Outpatient Therapy
TEA	Treatment Effectiveness Assessment
US	United States
Vd	Volume of Distribution
WBC	White Blood Cell

10.3 PROTOCOL AMENDMENT HISTORY

Version - Date	Description of Important Changes	Brief Rationale
1 – 03 Sept 2021	New document	New protocol
2 – 29 Nov 2021	1.1 Updated hypotheses, objectives, and list of endpoints	To improve the trial and align with FDA feedback
	1.3 Increased the window size for dosing visits, added footnote 'f' to specify Quality of Life Assessments, added Methamphetamine Use Assessments, added windows for PK subset samples	To improve dosing compliance, to add clarity and specify visit dates for new assessments of methamphetamine use
	3 Updated list of objectives and endpoints	To improve the trial and align with FDA feedback
	4.1 Updated hypotheses	To improve the trial hypotheses
	5.1 Added inclusion criteria 9	To include a criteria describing the minimum criteria for acceptably using the study app and successfully completing training on both the app and saliva test kits
	5.2 Updated exclusion criteria 9 to specify a saliva drug screen and what drugs are not disqualifying at the screening visit	To clarify the requirement
	5.2 Updated exclusion criteria 11 to include additional liver function tests	To specify which liver function tests are included in the expanded limits for eligibility
	5.2 Updated exclusion criteria 12 to note past-year history of a serious suicide attempt	To match the time frame of C-SSRS (past year version) assessment planned
	7.1 Inserted statements clarifying that missed doses do not disqualify a participant from resuming dosing.	To clarify that missed doses do not preclude further dosing.
	8.1 Inserted clarifying introductory comments, updated the saliva drug screen panel, and added new sub-section with methamphetamine use assessments	To add clarity and describe added assessments of methamphetamine use
	8.2 Updated medication history to past year, clarified when psychiatric evaluation by C-SSRS would lead to a referral, removed requirement for quantitative urinalysis	To refine the study requirements and better match the eligibility criteria
	8.3.2 Updated description of an SAE that is an important medical event	To add clarity
	8.3.4 Updated the time frame for recording reportable AEs	Limited recording of events to a reasonable time frame after last doses of IP are given. If a participant completes the study, that will be 3 months after the last dose

Version - Date	Description of Important Changes	Brief Rationale
	8.3.5 Reduced the length of time an AE would be followed following the end of study visit	Limited following AEs to a reasonable time frame after last doses of IP are given.
	8.3.6 Reduced the time frame of reporting non-expedited SAEs by investigators to the medical monitor and Sponsor to 48 hours	To allow Sponsor sufficient time to report to NIDA by 72 hours
	9.1 Updated hypotheses to match updated endpoints	Required to match updated endpoints
	9.4.1 Added description of specific figures and cumulative distribution functions to be included in the report.	To provide a data presentation requested by FDA
	9.4.2 Added clarifying words and sentences	To clarify that only intermittent missing data will be imputed using multiple imputation, and to clarify that when all data are missing from a week the result will be imputed as non-abstinent.
	9.4.3 Added section to describe analysis of new key endpoint	To add new required section
	9.4.4 Updated throughout to match the updated secondary endpoints	Required to match updated endpoints
	9.4.5 Separated immunogenicity analysis and added detail	To match the separation of immunogenicity as its own endpoint
	9.4.7 Updated potential recommendations by DSMB to include stopping the study early if any circumstances from section 10.1.2 apply.	To add clarity
	9.4.8 Added sub-groups for BMI and CBT attendance	To add detail
	9.4.10 – Noted that additional analyses will be described in the SAP and include added endpoints	To add clarity
3 – 20 July 2022	1.1 Updated study objectives, endpoints, and study population description	To improve the trial and better align with FDA feedback
	1.3.1 Added a title to note that the schedule applied to all main study participants; clarified psychiatric exam includes C-SSRS; added line for drug use assessment by DSM-5 at Screening; inserted Adverse Outcomes Assessment; separated Quality of Life assessments; separated cytokine sampling by creating a new line; provided specific dates for assessments in footnotes where multiple assessments were on the same line of the table; removed reference to the PK subset	For clarity and to add the new Adverse Outcomes Assessment

Version - Date	Description of Important Changes	Brief Rationale
	1.3.2 Added new schedule of activities table for PK subset participants	For clarity
	3 Deleted previous key secondary endpoint and reordered secondary and exploratory endpoints; added new exploratory endpoint analyzing adverse outcomes associated with MUD	To better align with FDA feedback
	4.1 Added paragraph describing the PK subset	To describe the number of participants to be included in the PK subset and its purpose, and include this description in the overall study description
	5.3 Added statement that medication-assisted treatment (MAT) for opioid use disorder is not allowed	To clarify that participants would not be eligible if using MAT
	5.4 Added need for Sponsor permission to rescreen a potential participant	To allow the Sponsor to review a request for rescreening
	6.1.1 Corrected some details about the smartphone app including that it does not send participant reminders and that recovery coaching will continue throughout the trial without tapering and stopping	To correct these details that were missed in a previous amendment
	6.1.2 Added causality grades that would result in dose discontinuation in a specific participant	To clarify that only SAEs that are likely caused by the study drug will result in dose discontinuation
	7.1 Added causality grades for AEs that would count toward the criteria for suspension of enrollment	To provide clarity that AEs that are graded as unrelated or unlikely would not count toward the criteria for suspending enrollment
	8.1.4 Added questions to be asked at Screening related to a participant's methamphetamine use history	To collect these data for background and stratification purposes
	8.1.5 Added the Adverse Outcomes Assessment to be administered	Added questionnaire to allow for comparison of the number of adverse outcomes in treated and placebo groups
	8.2.2 Added phrasing to instruct that new events after randomization should be recorded as AEs; corrected 'past-year' to 'past-30-days' for collection of medical history	To correct the protocol to intended language
	8.2.5 Added a question to be asked when updating psychiatric history	To monitor for suicidal ideation and attempts in this population
	8.2.6 Added instructions to review pregnancy test results prior to dosing and that tests are not required after report of hysterectomy	To ensure that pregnant participants do not receive further doses of study drug

Version - Date	Description of Important Changes	Brief Rationale
	8.2.7 Updated urinalysis description to state that macroscopic analysis would be done first, followed by microscopic analysis only if indicated	To align with planned analysis
	8.3.4 Added statements indicating that AEs prior to randomization should be recorded as medical history and any after randomization should be recorded as AE or SAE as appropriate	To clarify reporting guidelines since the screening period may be several weeks
	9.1 Removed descriptions of previous key secondary endpoint analysis (related to a reduction in DSM-5 criteria), and descriptions of analyses of CGIC and PGIC endpoints	To match updated endpoints
	9.4.3 Previous section describing the analysis of the prior key secondary endpoint was removed and subsequent sections renumbered	To match updated endpoints
	9.4.3.3 (previously numbered 9.4.4.3) Removed reference to analysis of CGIC and PGIC endpoints	To match updated endpoints
	9.4.9 Updated Table 2 to match new order of endpoints and to include the new endpoint related to adverse outcomes	To match updated endpoints
4 – 07 Oct 2022	1.2 Updated schema to include recovery coach sessions during screening and to shorten the screening period to 15 days prior to Day 1	To match changes throughout the protocol
	1.3 Changed the Screening window to Study Days -15 to -1; added footnote p; clarified only 4 saliva drug screens assigned during Screening window; and added recovery coaching to the Screening window	To facilitate site operations and patient adherence to the early testing regimen
	5.1 Changed Inclusion criteria #9 to require only 2 valid saliva tests within 2 weeks for eligibility.	To increase site and patient flexibility in assessing eligibility
	5.2 Appended the parenthetical phrase to exclusion criteria #9	To allow those participants on stable benzodiazepine therapy to qualify
	5.2 Appended the statement concerning COVID-19 clinical studies	To allow those patients who are participating in the long-term follow-up portion of a COVID-19 study to enroll
	5.4 Removed the term ‘medical’ in the second paragraph describing temporary issues	To allow the Sponsor to consider giving permission to rescreen a participant that did not meet criteria other than because of medical issues.

Version - Date	Description of Important Changes	Brief Rationale
5 – 03 Feb 2023	1.3.1 and 1.3.2 added footnote q and last sentence to footnote f	To clarify that participants must bring a smartphone to the Screening visit, or else it should be rescheduled, as described in protocol clarification letter dated 03 Jan 2023. To clarify that certain assessments are to be done prior to CBT at Week 13.
	1.3.3 Added new section	To describe the assessments to be done for participants that are dosed at least once and then discontinue dosing.
	5.2 Update exclusion criteria 1	To clarify that Substance Use Disorders are determined over the past year as described in the protocol clarification letter dated 22 Nov 2022.

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