SAN FRANCISCO DEPARTMENT OF PUBLIC HEALTH

CLINICAL STUDY PROTOCOL

Study Title:	Glutide for Ending Methamphetamine (GEM)
Sponsor:	San Francisco Department of Public Health 25 Van Ness Avenue, Suite 500 San Francisco, California 94102
IND No.:	173445
Indication:	Methamphetamine Use Disorder
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TABLE OF CONTENTS

PROTOCOL SYNOPSIS

San Francisco Department of Public Health

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Study Title:	Glutide for Ending Methamphetamine (GEM)
IND Number:	173445
Study Centers Planned:	1 site in the United States
Number of Subjects Planned:	25 subjects
Target Population:	Adults with moderate to severe methamphetamine use disorder
Duration of Treatment:	Subjects will receive study treatment for 12 weeks
Objectives:	The primary objectives of this study are as follows: 1. To determine acceptability, feasibility, and preliminary efficacy of weekly injectable semaglutide for adults with methamphetamine use disorder (MeUD). 2. To evaluate safety and tolerability of semaglutide among adults with MeUD. The exploratory objectives of this study are as follows: 1. To measure the impact of semaglutide on methamphetamine cravings through the Brief Substance Use Craving Scale. 2. To measure the impact of semaglutide on inflammation related to methamphetamine use by measuring hs-CRP, IL-1β, IL-6, and TNF-α as the primary biomarkers. 3. To measure the impact of semaglutide on cognitive function through the CogState Battery.
Study Design:	Twenty-five subjects will be enrolled in this phase IIa open-label single-arm trial and will be assigned to the following treatment: Semaglutide (Wegovy) administered by clinician via subcutaneous injection once weekly for 12 weeks (N=25).

	• Semaglutide injection dose will follow the product label (0.25mg SC weekly for 4 weeks; 0.5mg SC weekly for 4 weeks; 1.0mg SC weekly for 4 weeks)
Diagnosis and Main Eligibility Criteria:	Adults aged 18 – 65 with moderate to severe MeUD and frequent methamphetamine use, BMI ≥ 25kg/m^2, with no history of diabetes, thyroid disease, significant cardiovascular disease, or moderate to severe cocaine or opioid use disorder. Reference Section 4.2 and 4.3 of the protocol for detailed Inclusion and Exclusion criteria.
Study Procedures/ Frequency:	Screening assessments will be completed across two to four visits consisting of two screening visits and up to two run-in visits. All subjects will complete the following study visits: screening 1 and 2, run-in visit 1 and 2 (as needed), enrollment (week 1), weekly study visits (weeks 2-12), with additional procedures at weeks 4, 8, and 12, and a post-study follow-up visit at week 20. Additional visits will be completed as necessary for emergent adverse events. After consent is obtained, screening assessments (split between two visits) will include: complete medical history and physical examination, mental health and substance use history by Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders IV-TR (SCID), urine testing for methamphetamine and other substances, and lab testing including comprehensive metabolic panel (CMP), hemoglobin A1c, lipase, amylase, calcitonin, and urine pregnancy test. The enrollment visit will include baseline survey, hair sample collection, urine drug testing, biomarker testing, study drug administration, medical management (MM) counseling for substance use, vital signs, and a symptom-driven physical exam. Weekly study visits (weeks 2 – 12) will include study drug administration, urine testing for methamphetamine, TLFB assessment of methamphetamine use, and adverse event assessment with a symptom-driven physical exam. Monthly visits (occurring at weeks 4, 8) will include safety lab assessment, urine testing for methamphetamine and other substances, survey, and MM counseling, in addition to all weekly study visit procedures. The week 12 visit will include all assessments for weekly and monthly visits, as well as hair sample collection, biomarker testing, and CogState Battery. Study drug will not be administered at the week 12 visit. An off-treatment follow-up visit will occur eight weeks post-study (week 20) and will include urine drug testing, vital signs, symptom-drive physical exam, survey, and AE assessment.

Test Product, Dose, and Mode of Administration:	Semaglutide (Wegovy) is manufactured for subcutaneous administration as a single-use pen that delivers 0.25, 0.5, or 1 mg per injection in the first 12 weeks of therapy (higher doses are available for later in the standard titration process). Study drug will be administered by clinician in the abdomen, thigh, or upper arm at each weekly study visit according to the following schedule: 0.25mg weekly for 4 weeks, 0.5mg weekly for 4 weeks, 1.0mg weekly for 4 weeks.
Reference Therapy, Dose, and Mode of Administration:	All participants will receive semaglutide according to the product label. Study medication will be stored in our alarm-secured pharmacy refrigerator. Medication will be administered by clinician via subcutaneous injection at each visit.
Criteria for Evaluation Safety:	To assess safety, we will closely monitor adverse events through clinician interview, vital signs (including weight), and safety labs. We will assess for AEs at every visit and complete monthly safety labs. Should a participant become pregnant or report a desire to become pregnant during the trial, the study drug will be discontinued and the event will be reported to the institutional review board (IRB) or Data and Safety Monitoring Board (DSMB).
Efficacy:	Efficacy will be evaluated using within-person changes in methamphetamine concentration in hair and self-reported methamphetamine use (co-primary) and weekly urine drug testing for methamphetamine (exploratory).

Statistical Methods:

Aim 1: To determine acceptability, feasibility, and preliminary efficacy of weekly injectable semaglutide for adults with MeUD, we will determine the ratio of eligible to enrolled participants, adherence to weekly injections, and willingness to continue therapy at study conclusion, as well as the change in methamphetamine concentration in hair samples and change in frequency of methamphetamine use by time-line followback (TLFB).

Aim 2: To evaluate safety and tolerability of semaglutide among adults with MeUD, we will closely track self-reported and laboratory adverse events and the rate of study drug discontinuation due to adverse events.

Other Exploratory Outcomes:

To explore the effect of the semaglutide on methamphetamine use, we will conduct urine drug testing for methamphetamine. We do not expect to be powered to detect a significant effect on urine positivity for methamphetamine.

To measure the impact of semaglutide on methamphetamine cravings through the Brief Substance Craving Scale.

To measure the impact of semaglutide on inflammation related to methamphetamine we will measure hs-CRP, IL-1β, IL-6, and TNF-α, with hs-CRP as the primary biomarker.

To assess the impact of semaglutide on cognitive function through the CogState Battery.

This study will be conducted in accordance with the guidelines of Good Clinical Practices (GCPs) including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
ALT	Alanine transaminase
AST	Aspartate aminotransferase (also SGOT)
BPM	Beats per minute
BMI	Body mass index
DSMB	Data safety monitoring board
DSMP	Data safety monitoring plan
CGI	Clinical Global Impression
CHR	Committee on human research
CI	Confidence interval
CRF	Case report form(s)
CMP	Comprehensive metabolic panel
C-SSRS	Columbia-Suicide Severity Rating Scale
DAIDS	Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events
FDA	(United States) Food and Drug Administration
GCP	Good Clinical Practice (Guidelines)
Hgb	Hemoglobin
hs-CRP	High-sensitivity C-reactive protein
IRB	Institutional review board
IL-1β	Interleukin-1 beta
IL-6	Interleukin-6
min	Minute
MM	Medical management
mmHg	Millimeters mercury
ng/mL	Nanograms per milliliter
NTIM	Narrow therapeutic index medication
PI	Principal investigator
SAE	Serious adverse event
SD	Standard deviation
SF-36	36 Item Short Form Survey
STI	Sexually transmitted infection
SOP	Standard operating procedure
TNF-α	Tumor necrosis factor-alpha
UCSF	University of California, San Francisco
US	United States

1. INTRODUCTION

1.1. Background

Methamphetamine is highly addictive with serious medical, societal, and economic consequences. Methamphetamine use remains more prevalent than many other drugs, including opioids, with 37 million users of amphetamines worldwide and 2.1 million past-year users in the U.S. alone in 2021. At least half of people who regularly use methamphetamine have MeUD. U.S. methamphetamine poisoning deaths have steadily risen in recent years, from 1,887 in 2011 to 32,537 in 2021. San Francisco has witnessed a marked increase in methamphetamine mortality.

Methamphetamine use is also a driving force in transmission of infectious diseases, particularly HIV. Multiple studies across diverse populations (adolescents, heterosexual men and women, men who have sex with men (MSM), and people who inject drugs) have found methamphetamine use to be independently associated with a variety of high-risk behaviors, including condomless intercourse, multiple sex partners, increased duration of sex, anonymous partners, and exchanging money or drugs for sex. Longitudinal studies have also observed that methamphetamine use was independently associated with greater risk for HIV seroconversion. Because methamphetamine use is associated with high-risk sexual behavior, HIV seroconversion, STI incidence, and drug-resistant HIV, data strongly support that methamphetamine use plays an important role in perpetuating the U.S. HIV epidemic.

Notwithstanding persistent efforts to identify a pharmacotherapy for MeUD, there remain no approved medications – and mixed results with existing candidates. While some behavioral interventions report reduced methamphetamine use, behavioral interventions alone have limited effectiveness and may benefit from the addition of pharmacologic agents, similar to the management of heroin, nicotine, and alcohol use disorders, and other chronic conditions such as depression and diabetes. Studies of multiple agents, including tricyclic antidepressants, serotonin re-uptake inhibitors, and antipsychotics, as well as dextroamphetamine, modafinil, and other psychostimulants, have been disappointing. Methylphenidate has mixed results. Bupropion is commonly used in clinical practice, although trials are less promising. Our center had success twice with mirtazapine, with methamphetamine use reductions of 30-50%. However, none of these therapies is likely to be sufficient on its own and agents using novel mechanisms of action are needed.

Many investigators have come to believe that a combination pharmacotherapy that impacts multiple neurotransmitter systems will be needed to reduce methamphetamine use. There is an urgent need to identify novel classes with potential benefits that could be combined with other medications. Multiple reports suggest that glucagon-like peptide 1 (GLP-1) receptor agonists will be effective for multiple addictive disorders.

Anecdotal reports find that those treated with GLP-1 agents for diabetes have reduced interest in compulsive behaviors including drinking alcohol, smoking, skin picking, etc. There have been several trials so far addressing alcohol and tobacco use with older GLP-1 agonists, showing mixed results to-date. Among patients with alcohol use disorder, exenatide, a first-generation GLP-1 agonist, reduced cue reactivity and – among obese participants – total alcohol intake and heavy drinking days. A phase II trial of semaglutide, a second-generation agent thought to be more potent, among adults with alcohol use disorder began in 2022 (NCT05520775).

GLP-1 agonists, particularly semaglutide, hold substantial promise for treating MeUD. GLP-1 increases insulin secretion, decreases glucagon secretion, delays gastric emptying, and increases satiety, making it ideal for managing diabetes. These agents work in part by substantially diminishing food cravings – and craving for methamphetamine is a central component of MeUD, with reductions in craving often predicting success in therapeutic trials and relapse after abstinence. As the most potent agent for weight loss, with availability in weekly injections (in contrast to liraglutide which is administered daily), semaglutide holds the most promise among GLP-1 agonists for influencing MeUD, a disorder characterized by poor medication adherence (and thus benefiting from weekly administrations). Moreover, while reductions in methamphetamine use, as well as available off-label MeUD therapies like mirtazapine, are associated with unwanted weight gain that may deter some patients from remaining abstinent, semaglutide is associated with weight loss, which may help to avoid unwanted weight gain in appropriate subjects (i.e., those with preexisting elevated body mass index [BMI]). Finally, GLP-1 agonists have also been shown to be cardioprotective and neuroprotective, potentially helping to address the two main pathways of methamphetamine toxicity.

1.2. Semaglutide

Semaglutide is a polypeptide that contains a linear sequence of 31 amino acids joined together by peptide linkages. It is an agonist of glucagon-like peptide-1 receptors (GLP-1 AR). Its molecular weight is 4114 g/mol. It has the molecular formula of C187H291N45O59.

The proposed product is a clear, colorless solution of 2mg/1.5 mL semaglutide, which is meant for self-administration subcutaneously via pre-filled, disposable, single-patient use pen that delivers 0.25 mg, 0.5 mg, or 1 mg per injection. Doses of 1.7 mg and 2.4 mg are also available but will not be used in this trial. Semaglutide will be administered per product label and by a clinician.

1.3. Rationale for the Current Study

Given the prevalence and negative health outcomes associated with methamphetamine use, there is urgent need to identify effective treatments for MeUD. GLP-1 agonists, particularly semaglutide, show promise for treating MeUD by reducing cravings. Research is needed to evaluate the acceptability, feasibility, and effectiveness of semaglutide (Wegovy) for reducing methamphetamine use among adults with MeUD.

1.4. Rationale for Dose Selection of Semaglutide

We will be following the package insert guidelines for administration of semaglutide (Wegovy). We plan to use semaglutide in injection form as opposed to oral tablet form due to MeUD being characterized by poor medication adherence (and thus participants may benefit from weekly injections over daily oral administration). We will limit duration to 12 weeks in an effort to identify a signal of potential benefit, to be followed by more intensive studies if go/no-go criteria are met. Thus, this trial will achieve a maximum dose of 1mg per week. If no signs of reduced methamphetamine use are seen at this dose, a higher dose is unlikely to achieve the “response” required for medications to treat MeUD (current standard is 3 out of 4 final urines negative for methamphetamine).

1.5. Overall Risk/Benefit Assessment

Semaglutide is a US Food and Drug Administration (FDA)-approved drug with substantial promise for treating methamphetamine use disorder. Semaglutide is widely used and well-tolerated, although gastrointestinal symptoms are common and can be severe. The most common adverse events, which generally resolve with time, are nausea, vomiting, abdominal pain, constipation and diarrhea. Long-term therapy has been associated with the rare side effect of gastroparesis, as well as acute pancreatitis and hepatobiliary disease. In the setting of severe gastrointestinal symptoms, kidney dysfunction has been reported, likely due to dehydration. Worsening of diabetic retinopathy has also been reported. In animal studies, some GLP-1 agonists have been associated with thyroid tumors, although humans have a minimal concentration of GLP-1 receptors in thyroid tissue and thus may not be at risk. One notable early concern was suicidal ideation, however, in a real-world cohort of >1.5 million patients with type 2 diabetes the hazard ratio for suicidal ideation among patients on semaglutide compared to non-GLP-1 diabetes medications was 0.27 (0.20-0.60) across age, sex, and ethnicity. In this study, adverse events and safety lab results will be consistently monitored, and treatment will be discontinued as needed.

The potential risks to participants described above are reasonable given the urgent need to identify new, effective treatments for MeUD. Because millions of people use methamphetamine in the US, half of whom suffer from MeUD, the potential impacts for society are significant. Effective treatments for MeUD can potentially decrease methamphetamine toxicity deaths, reduce the spread of HIV and other STIs, and reduce healthcare utilization costs. Methamphetamine use often adversely impacts physical and psychological health, so the risks of semaglutide in comparison are low.

The study will be evaluated on an ongoing basis by a Data Safety Monitoring Board.

1.6. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

2. OBJECTIVES

The primary objectives of this study are as follows:

- To determine acceptability, feasibility, and preliminary efficacy of weekly injectable semaglutide for adults with MeUD, we will determine the ratio of eligible to enrolled participants, adherence to weekly injections, and willingness to continue therapy at study conclusion, as well as the change in hair concentrations of methamphetamine from enrollment to week 12 of treatment, and the change in self-reported methamphetamine use from the 4 weeks preceding enrollment to the final 4 weeks of treatment.

- To evaluate safety and tolerability of semaglutide among adults with MeUD, we will closely track self-reported and laboratory adverse events and the rate of study drug discontinuation due to adverse events.

The exploratory objectives of this study are as follows:

- To measure the impact of semaglutide on methamphetamine cravings through the Brief Substance Use Craving Scale.

- To measure the impact of semaglutide on inflammation related to methamphetamine use by measuring hs-CRP as the primary biomarker.

- To measure the impact of semaglutide therapy on cognitive function through the CogState Battery.

3. STUDY DESIGN

3.1. Study Treatment and Duration of Treatment

This is an open-label single-arm pilot trial to evaluate the efficacy of semaglutide in reducing methamphetamine use among adults with methamphetamine use disorder. Twenty-five subjects will be enrolled and receive semaglutide at increasing doses over a total of 12 weeks (0.25mg for 4 weeks, 0.5mg for 4 weeks, and 1.0mg for 4 weeks).

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Twenty-five (25) subjects will be enrolled in this study.

4.2. Inclusion Criteria

Subjects must meet *all* the following inclusion criteria to be eligible for participation in this study:

(1) Ability to provide informed consent before any study-related activity, willing to comply with all study procedures, and be available for the duration of the study,

(2) Age 18 – 65 years inclusive,

(3) Moderate to severe Methamphetamine Use Disorder by SCID,

(4) Self-reported methamphetamine use ≥15 days out of the past 30,

(5) Methamphetamine-positive urine during screening and run-in period,

(6) Interested in stopping or reducing meth use,

(7) BMI ≥ 25kg/m^2,

(8) Have at least 1 centimeter of scalp hair,

(9) Agree (if the participant is of child-bearing potential) to use effective contraceptive methods, unless all of the participant's male partner(s) is/are surgically sterile (underwent vasectomy). Acceptable contraceptives include oral contraceptives, contraceptive sponge, patch, double barrier (diaphragm/spermicidal or condom/spermicidal), intrauterine contraceptive system, etonogestrel implant, medroxyprogesterone acetate contraceptive injection, complete abstinence from sexual intercourse, and/or hormonal vaginal ring. Contraceptive measures sold for emergency use after unprotected sex are not acceptable methods for routine use. Women of child-bearing potential must provide negative urine pregnancy test prior to randomization.

    Note: A woman is considered fertile (of childbearing potential) following menarche and until becoming postmenopausal unless permanently sterile. Women in the following categories are not considered of childbearing potential: premenarcheal, premenopausal female with one of the following: documented hysterectomy, documented bilateral salpingectomy, documented bilateral oophorectomy. Postmenopausal female is defined as no menses for 12 months without an alternative medical cause. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the trial.

(10) Be able to provide the names of at least 2 persons who can consistently locate their whereabouts.

4.3. Exclusion Criteria

Subjects who meet *any* of the following exclusion criteria are not to be enrolled in this study:

(1) Uncontrolled hypertension or systolic BP >160 mmHg and/or diastolic BP >90 mmHg, averaged from three measurements,

(2) Resting heart rate greater than 100 bpm at baseline, on at least two measurements,

(3) Diabetes (type 1 or 2), hemoglobin A1c ≥ 6.5 at screening, or history of diabetic ketoacidosis,

(4) History or current hypoglycemia (blood glucose <70 mg/dL),

(5) History of malignant neoplasms within the past 5 years prior to screening. Basal and squamous cell skin cancer and any carcinoma in-situ are allowed.

(6) History of heart failure or severe gastrointestinal disease (including acute or chronic pancreatitis, any gastric emptying disorder, gallbladder disease; any gastric resection),

(7) Personal or family history of medullary thyroid cancer or multiple endocrine neoplasia 2A or 2B,

(8) Impaired renal function (estimated GFR <60 ml/min),

(9) Lipase, amylase, direct (conjugated) bilirubin, or alkaline phosphatase (ALP) 1.5 times the upper limit of normal, or ALT or AST more than 2.5 times the upper limit of normal,

(10) Calcitonin value equal to or above 50 ng/L,

(11) History of retinopathy,

(12) Women who are currently pregnant, or plan to become pregnant, or lactating, or of childbearing potential and are not using medically accepted forms of contraception (see inclusion criterion 9 regarding medically accepted forms of contraception).

(13) Acute or chronic illnesses likely to result in hospitalization or death during trial participation,

(14) Plan to have all hair removed or chemically treat hair during study,

Psychiatric/Substance Use Exclusions:

(1) Moderate to severe opioid, cocaine, or alcohol use disorder,

(2) Current non-drug-induced psychotic disorder by Structured Clinical Interview for DSM Disorders (SCID),

(3) History of a suicide attempt or past 30-day suicidal ideation,

(4) Have any psychiatric illness or condition which in the opinion of the PI and/or the Study Physician would preclude safe and/or successful completion of the study,

Weight-related exclusions:

(1) Uncontrolled thyroid disease,

Medication-related exclusions:

(1) Past 30 day use of sulfonylureas, insulin and insulin products, or medication used for weight management (e.g., orlistat, naltrexone-bupropion, liraglutide, semaglutide, tirzepatide, phentermine, topiramate, benzphetamine, diethylpropion, phendimetrazine).

(2) Prior use of or known hypersensitivity to any GLP-1 agonist,

(3) Any otherwise not specified concomitant medication that could compromise participant safety or treatment in the opinion of the Study Physician and/or the PIs,

General exclusions:

(1) Current, anticipated, or pending enrollment in another addiction treatment program and/or research study that could potentially affect participant safety and/or the study data/design as determined by the Principal Investigator and/or Study Physician.

(2) Planning to leave the area during the trial,

(3) Surgery scheduled during the trial, except for minor surgical procedures that, in the opinion of the PI and/or the Study Physician, will not require general anesthesia with the risk of aspiration,

(4) Unable to communicate (read, write, and speak) fluently in English,

OR

(5) Any other condition that, in the PI's judgment, interferes with safe study participation or adherence to study procedures.

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Description and Handling of Semaglutide

5.1.1. Formulation

The proposed formulations include semaglutide in a pre-filled, disposable, single-patient-use pen. Each single-use disposable pen injector delivers a discrete dose of: 0.25 mg, 0.5 mg, or 1 mg of semaglutide per pen.

Active ingredient: semaglutide

Inactive ingredients: disodium phosphate dihydrate, sodium chloride, and water for injection.

5.1.2. Packaging and Labeling

Semaglutide injection is supplied as a clear, colorless solution that contains a dose of either 0.25mg, 0.5mg, or 1mg of semaglutide in a pre-filled, disposable, single-patient-use pen injector with an integrated needle. It is supplied in cartons containing 4 pre-filled pen injectors in the following packaging configurations:

Pre-filled pen dose (cartons of 4 pens)	Dose concentration	NDC
0.25 mg	0.25 mg/0.5 mL	0169-4525-14
0.5 mg	0.5 mg/0.5 mL	0169-4505-14
1 mg	1 mg/0.5 mL	0169-4505-14

All study drug administered to study participants shall be provided in containers labeled to meet all applicable requirements of the FDA and/or other local regulations as applicable.

5.1.3. Storage and Handling

Prior to first use, study drug will be stored in our pharmacy refrigerator between 36F to 46F (2C to 8C). After first use of the pen, study drug will be stored for up to 56 days at controlled room temperature (59F to 86F; 15C to 30C) or in a refrigerator between 36F to 46F (2C to 8C). When stored at controlled room temperature, the study drug will be stored away from excessive heat, light, and moisture.

After each injection, the pen injector will be discarded in a sharps container.

All drug products will be stored in a securely locked area, accessible only to authorized site personnel. Consideration will be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions will be followed to avoid direct eye contact or exposure through inhalation when handling study drug.

5.1.4. Dosage and Administration of Semaglutide

Study drug is to be administered subcutaneously to the abdomen, thigh, or upper arm. The participant will be able to select the body area. If administering in the same body region, the administering clinician will use a different injection site.

Study drug will be administered at any time of day, with or without meals. The day of weekly administration can be changed if necessary, as long as the time between two doses is at least 2 days (>48 hours).

If a dose is missed, study drug will be administered as soon as possible at the previously used dose unless 3 or more doses have been missed. If 3 or more doses have been missed, the next dose will be administered as soon as possible according to the below table.

Management of Missed Doses

Last Dose Missed	1 or 2 missed doses	3 or 4 missed doses	5 or more missed doses
0.25 mg	0.25 mg	0.25 mg	0.25 mg
0.5 mg	0.5 mg	0.25 mg	0.25 mg
1 mg	1 mg	0.5 mg	0.25 mg

5.2. Prior and Concomitant Medications

Concomitant medications taken within 30 days prior to screening will be recorded in the source documents and case report form(s) (CRFs).

Table 1. Concomitant Medications Disallowed or to be used with Caution

Drug Class	Agents Disallowed	Use with Caution
sulfonylureas	Any	
cholecystokinetic	sincalide	
Weight control medications	Any other GLP-1 agonists	
insulin	Any insulin products	

Dipeptidyl peptidase 4 inhibitors	Any	

5.3. Study Drug Adherence

Subjects will be administered study drug by a clinician using the pre-packaged single dose pens provided by the manufacturer. Other trials of injectable medication for methamphetamine use disorder at this study site have shown high adherence rates.

5.4. Accountability for Study Drug

The investigator is responsible for ensuring adequate accountability of all used and unused study drug pens. This includes acknowledgement of receipt of each shipment of study drug (quantity and condition).

Semaglutide accountability records will:

- Record the date received, quantity, and dosage of study drug shipments received
- Record the date of administration, deidentified subject ID number, amount administered, where administered, pen lot number, and expiration date of every study drug administration

5.4.1. Investigational Medicinal Product Return or Disposal

Please refer to Section 10.1.7 for Investigational Medicinal Product Accountability.

6. STUDY PROCEDURES

The investigator will document any deviation from protocol procedures and notify appropriate regulatory authorities (e.g., IRB, DSMB, and NIH).

6.1. Subject Enrollment and Treatment Assignment

Screening will occur at screening visits 1 and 2 and up to two run-in visits. On-treatment visits will occur weekly from enrollment (week 0) through week 11.

Every effort will be made for all participants to complete all study visits, regardless of continuation of study drug.

6.2. Pretreatment Assessments

6.2.1. Screening Visits

Subjects will be screened for the determination of eligibility for participation in the study. Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic within 30 days after screening for enrollment in the study.

After consent is obtained, screening assessments (split between two visits) will include a physical exam, complete medical history (including collection of any current medications), mental health and substance use history by SCID and C-SSRS, urine testing for methamphetamine and other substances, and lab testing. Labs completed during screening include CMP, hemoglobin A1c, lipase, amylase, calcitonin, TSH (as needed) and urine pregnancy test.

Two additional "run-in visits" before enrollment will be completed as necessary in order to complete all screening assessments and, if needed, assess participant ability to adhere to the study schedule.

Participants will be compensated $25 for each screening and run-in visit.

6.2.2. Enrollment Visit (week 0)

At the enrollment visit, the participant will meet with the clinician to review and confirm eligibility criteria and suicidality screen (C-SSRS), will provide urine, hair, and blood samples (for biomarker testing), receive their first study drug injection, and receive medical management counseling for substance use, medication adherence, and side effect prevention and management. Vital signs (including weight) and a symptom-driven physical exam will be completed. Participants will also complete their baseline survey.

Baseline surveys will be completed by participants at enrollment, including assessment of reported days/episodes of other substance use (TLFB), injecting and sexual risk behaviors, substance use treatment outside the study, impulsivity, cravings, demographics, cumulative methamphetamine exposure, psychological symptoms, severity of methamphetamine dependence, and physical and psychiatric health (SF-36, CGI).

Participants will be compensated $50 for completing the enrollment visit and an additional $25 for providing hair samples.

6.3. Weekly Treatment Visits (weeks 1-3, 5-7, 9-11)

Following enrollment, participants will be seen weekly for study drug administration, urine collection for methamphetamine testing, TLFB assessment, and MM counseling. Vital signs and a symptom-driven physical exam will also be completed, and the participant will be assessed for AEs. More frequent monitoring may be performed for symptomatic participants.

We will plan to monitor participants on narrow therapeutic index medications (NTIMs). Clinicians will inquire about when participants take medications and if they are experiencing emesis, monitor problems related to gastric emptying, look for signs of sub-therapeutic effect absorption, and ensure that participants are successfully taking medications.

Counseling will involve a manualized version of the MM brief counseling platform in individual 20-minute sessions from trained study staff.

Study drug will be administered by the clinician at weekly visits according to the following schedule: 0.25mg weekly for weeks 1-4; 0.5mg weekly for weeks 5-8; 1.0mg weekly for weeks 9-12.

Participants will be compensated $25 for weekly visits.

6.4. Monthly Treatment Visits (weeks 4, 8, and 12)

Monthly visits at weeks 4 and 8 will be the same as the weekly visits with the addition of the following:

Participants will complete surveys which will assess reported days/episodes of other substance use, injecting and sexual risk behaviors, substance use treatment outside the study, impulsivity, cravings, symptoms, and severity of methamphetamine dependence.

Safety labs completed at monthly visits will include CMP, lipase, amylase, urine pregnancy test, and others as-needed for AE management.

Participants will be administered the C-SSRS.

The final treatment study visit at week 12 will be the same as the monthly visits with the following additions:

Participants will also provide hair for methamphetamine testing and blood samples for biomarker testing. The survey for week 12 will include additional sections that will assess the participant's willingness to continue therapy, participant satisfaction with the trial, perception of whether the trial helped reduce methamphetamine use, and the CogState Battery for assessment of cognitive function.

Study medication will not be administered at week 12.

Participants will be compensated $50 for week 4 and 8 visits. Participants will be compensated $75 for the final study visit and an additional $25 for providing hair samples. Participants will be compensated an additional $50 for each 4-week period in which all study visits were attended.

6.5. Post-trial Study Visit (week 20)

A post-trial visit will be conducted at week 20, 8 weeks after the final weekly study visit. At this visit, participants will undergo vital sign collection, urine drug testing, TLFB assessment, C-SSRS, and evaluation for resolution of any open AEs.

Participants will be compensated $30 for the post-trial visit.

6.6. Post Treatment Assessments

Following the completion of study drug treatment at week 12, participants will be seen on an as-needed basis to assess adverse events. This assessment may include a symptom-driven physical exam, collection of vital signs, and safety labs as-needed.

These additional visits will be compensated at $20.

6.7. Survey

Surveys will be completed by participants at enrollment and monthly (weeks 4, 8, and 12) visits, and the post-treatment visit (week 20) to assess substance use (reported days/episodes of other substance use), injection and sexual risk behaviors, substance use treatment, craving, impulsivity, and cognitive function.

At enrollment, the survey will additionally collect demographics and assess cumulative methamphetamine exposure ("gram-year history").

At week 12, the survey will additionally assess the participant's willingness to continue therapy, participant satisfaction with the trial, and perception of whether the trial helped reduce methamphetamine use.

6.8. Assessments for Premature Discontinuation from Study

Every effort will be made to continue participants in the study, even if discontinued from or otherwise not taking study drug, or if attending visits sporadically. Participants will only be formally discontinued from the study if they elect to do so.

6.9. End of Study

Subjects are considered to have completed the study after the week 20 visit, regardless of treatment duration and early termination from study drug.

The final study visit will include a survey assessment of satisfaction with the study procedures.

6.10. Procedures and Specifications

6.10.1. Clinical Laboratory Analytes

Hematology: Hemoglobin A1c

Biomarkers: hs-CRP, IL-1β, IL-6, TNF-α

Chemistry: CMP (sodium, potassium, chloride, carbon dioxide, blood urea nitrogen creatinine, glucose, total bilirubin, total protein, albumin, calcium, ALP, AST, and eGFR), lipase, amylase, calcitonin.

Pregnancy Test: Urine b-hCG

Urine Drug Testing: qualitative urine testing for methamphetamine and 10 other substances with the iSCREEN Urine Test Drug Screen Dip Card

Hair testing. Hair collection involves taping the tips (for hair>1cm) and cutting 50-100 strands close to the scalp into aluminum foil for storage in a dark space until batch shipment for processing. Analysis of hair samples will be done by the UCSF Hair Analytical Laboratory with liquid chromatography tandem mass spectrometry (LC/MS). Hair samples are washed twice with 2 mL of water followed by washing twice with 2 mL of acetone (vortex mixed for 1 min). After removal of the solvent, samples are completely dried at ambient temperature. Samples are then cut into small pieces (approximately 1–2 mm) with scissors and weighed to ~10 mg in test tubes. Methamphetamine is extracted with 1 mL of methanol including deuterated methamphetamine (as an internal standard) in a 37˚C shaking water bath overnight (>12 hours). Extracted samples are evaporated to dryness under N_2 gas atmosphere and then reconstituted with 200 µL of 20% acetonitrile. Methamphetamine levels are determined by liquid chromatography tandem mass spectrometry (LC/MS/MS) using a Micromass Quattro Ultima and Shimadzu HPLC system equipped with a Phenomenex Synergi Polar-RP column (4.6 x 150 mm, 4 µm particle size), a mobile phase system consisting of acetonitrile:water:trifluoro acetic acid (20:80:0.05), and mass spectrometric detection with positive ionization by electrospray ionization and mass scanning by multiple reaction monitoring ($[M+H]^+$ transitions of 150/119 (Q1/Q3) *m/z* for methamphetamine and 159/125 *m/z* for deuterated methamphetamine). The standard curve range of methamphetamine by LC/MS/MS analysis is 0.00800 nanograms (ng)/mg (lower limit) to 3.20 ng/mg of hair. Because of variable inter-subject methamphetamine levels in hair (with variation based on hair melanin concentration, among other factors), we will assess the *within-person change* in cumulative methamphetamine hair levels (ng/mL) pre- vs. post-intervention. Dr. Gandhi and colleagues have demonstrated high levels of acceptability (>95%) of hair collection, as the sampling is done from the back of the head with quantity of hairs collected (<50 strands) less than the average amount of hair lost in the course of a normal day. Participants without scalp hair will not be included.

6.10.2. Medical History

A complete medical history will be taken for each participant during screening, including details of ongoing or past illnesses, health conditions, and allergies. Mental health and substance use history will be collected via SCID. The medical history will also include review of prior and concomitant medications and family history of medullary thyroid cancer or multiple endocrine neoplasia 2A or 2B.

6.10.3. Physical Examination

A full physical examination will be completed during screening and will include source documentation of general appearance, and the following body systems: Head, neck, eyes, ears, nose, throat, mouth and tongue; respiratory; cardiovascular; lymph nodes; abdomen; skin, hair, nails; musculoskeletal; neurological.

A symptom-driven physical exam will be completed at enrollment, weekly study visits, and at any required follow-up visits to assess AEs.

6.10.4. Vital Signs

Vital sign collection will include measurement of resting blood pressure, pulse, respiratory rate, temperature, and weight. Height will be collected during screening only.

Blood pressure will be measured using the following standardized process:

- Subject will sit with feet flat on the floor and measurement arm supported so that the midpoint of the manometer cuff is at heart level.
- Use a mercury sphygmomanometer or automatic blood pressure device with an appropriately sized cuff with the bladder centered over the brachial artery.
- Measure and record the blood pressure to the nearest 2 mm Hg mark on the manometer or to the nearest whole number on an automatic device.

6.10.5. Body Mass Index (BMI)

BMI will be calculated by the following equation.

$$\text{BMI} = \frac{\text{weight (pounds)} * 703}{(\text{height in inches})^2} \quad \text{or} \quad \frac{\text{weight in kilograms}}{(\text{height in meters})^2}$$

6.10.6. Liver Function

Liver function will be evaluated by AST and ALT levels, relative to laboratory range.

6.10.7. Structured Clinical Interview for DSM-IV (SCID)

The SCID will be utilized during screening to diagnose methamphetamine use disorder, cocaine or opioid use disorder and to ensure the absence of exclusionary psychiatric disorders.

7. TOXICITY MANAGEMENT

7.1. Subject Stopping Rules

Due to a clinical or laboratory event, administration of study drug may be reduced or discontinued. If study drug is stopped due to toxicity, it will not be restarted.

Subjects who meet any of the following criteria must stop study drug:

- Weight loss during treatment to a BMI < 19 kg/m^2.
- Any Grade 3 or greater rash associated with constitutional symptoms.
- Any Grade 3 or greater adverse event possibly, probably, or definitely related to the study drug will result in a pause of the study drug and prompt evaluation. If the AE is determined to be not related to the study drug and symptoms resolve, we may restart study drug with close monitoring.
- Subject reports persistent, severe vomiting or diarrhea, that may lead to severe dehydration and acute kidney injury.
- Any serious adverse event that the PI, DSMB, IRB, NIDA, or FDA advises should result in discontinuation of study drug.
- Toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest.
- Subject becomes pregnant or reports a desire to become pregnant.
- Subject requests to discontinue for any reason; it is important to determine whether the withdrawal of consent is primarily due to an AE, lack of efficacy, or other reason.
- Subject has a persistent increased heart rate >20 bpm from baseline, as measured on at least 2 consecutive visits.[1]
- Subject reports suicidal ideation or behavior on C-SSRS.

If a subject meets discontinuation criteria during treatment, every effort will be made to continue all previously planned visits with the subject, minimizing data loss.

7.2. Study Discontinuation Criteria

The study will be discontinued in the following instances:

[1] Use of methamphetamine will increase heart rate, thus a single elevated value will not result in immediate discontinuation of study drug.

- If >35% of participants discontinue study drug due to adverse events, or less if study stoppage is determined appropriate in consultation with the PI, biostatistician, DSMB, IRB, or FDA.

- Discontinuation of the study for any reason at the request of a regulatory agency, DSMB, or IRB, with appropriate justification.

The study will be paused in the following instances:

- If an SAE occurs at least possibly related to the study medication, enrollment will be paused pending DSMB review.

7.3. Dose Titration Rules

Study drug dose titration may be paused or reversed in the following circumstances:

- Weight loss occurs in excess of participant goals

- Study drug-related clinical or laboratory adverse events occur that study clinician and study pharmacist determine may be reduced by pausing or reducing study drug dose

8. ADVERSE EVENTS MANAGEMENT

8.1. Definition of Adverse Events, Adverse Reactions, and Serious Adverse Events

8.1.1. Adverse Event

An adverse event (AE) is any untoward medical occurrence in a clinical study subject administered a pharmaceutical medicinal product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include pre- or post-treatment complications that occur as a result of protocol specified procedures, lack of efficacy, overdose, substance use, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An expected adverse event is an AE that may be reasonably anticipated to occur as a result of the study procedures or study participation or is part of the normal disease process or progression.

An unexpected adverse event is defined as being unexpected if the event exceeds the nature, severity, or frequency described in the current University of California San Francisco (UCSF) IRB application including the protocol, consent form and investigator brochure, when applicable. An unexpected AE also includes any AE that meets the following criteria:

- Results in subject withdrawal from study participation
- Due to an overdose of study medication
- Due to a deviation from IRB-approved study protocol

An AE does not include the following:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion) performed; the condition that leads to the procedure may be an adverse event and must be reported.
- Pre-existing diseases or conditions or laboratory abnormalities present or detected during or before screening that do not worsen
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 8.5)
- Any medical condition or clinically significant laboratory abnormality with an onset date before enrollment and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history.
- Substance use or admission to substance use treatment

- Incarceration

8.1.2. Serious Adverse Events

A **serious adverse event** (SAE) is defined as an event that results in the following:

- Death
- Life-threatening event (Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect or cancer
- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.
- Event that changes the risk/benefit ratio of the study

8.1.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities (e.g., clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to investigational medical product (IMP) interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments that are associated with signs and/or symptoms will be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 8.1.1 and 8.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (e.g., anemia), not the laboratory result (i.e., decreased hemoglobin).

8.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified sub-investigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

8.2.1. Assessment of Causality for Study Drug and Procedures

The investigator or qualified sub-investigator is responsible for assessing the relationship to study procedures or medications using clinical judgment and the following considerations:

- **Unrelated**: Evidence exists that the adverse event has an etiology other than semaglutide or a study procedure. For SAEs, an alternative causality must be provided (e.g., pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).
- **Probably not**: Adverse event has improbable time relationship to intake of Wegovy or study procedure, and attribution with disease or other drugs is likely.
- **Possibly**: Adverse event has reasonable time relationship to intake of Wegovy or study procedure, and attribution with disease or other drugs is possible.
- **Probably**: Adverse event has reasonable time relationship to intake of Wegovy or study procedure, and attribution with disease or other drugs is unlikely.
- **Definitely**: There is reasonable probability that the event may have been caused by Wegovy or a study procedure.

Ineffective treatment should not be considered as causally related in the context of AE reporting.

8.3. Assessment of Severity

Severity should be recorded and graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS) Version 2.1 July 2017.[2]

8.4. Investigator Requirements for Reporting Adverse Events and Serious Adverse Events

8.4.1. Reporting to UCSF Committee on Human Research (CHR / IRB)

All AEs that are possibly, probably, or definitely related, and either serious and unexpected, or serious and more frequent or severe than anticipated, must be reported within 5-working-days of PI awareness using the Adverse Event Reporting Form on the UCSF IRB website (iRIS).

8.4.2. Reporting to Data Safety Monitoring Board (DSMB)

Reporting to Data Safety Monitoring Board (DSMB)

All SAEs and unexpected AEs meeting reportable criteria in the Data Safety Monitoring Plan (DSMP) must be reported within 10-working-days of PI awareness. A summary letter must include detailed accounts of the following:

- Summary of SAE
- Resolution
- Study Drug
- Attribution

[2] DAIDS is frequently used for the assessment of AEs for substance use disorder treatment trials, specifically those involving methamphetamine, and is the preferred AE guidance instrument of the DSMB.

- Notification

8.4.3. Reporting to NIH – National Institute of Drug Abuse (NIDA)

All SAEs meeting reportable criteria in the DSMP must be reported within 10-working-days of PI awareness to NIH. If SAE is fatal, it must be reported within 2-working-days of PI awareness.

8.5. Special Situations Reports

8.5.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, lack of effect reports and pregnancy reports regardless of an associated AE.

Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, subject, or consumer.

Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a subject.

Misuse is defined as any intentional and inappropriate use of a medicinal product that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.

8.5.2. Instructions for Reporting Special Situations

8.5.2.1. Instructions for Reporting Pregnancies

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons.

Should a participant become pregnant or report a desire to become pregnant during the trial, study drug will be discontinued and the event reported to IRB/DSMB.

Any premature termination of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) will be reported within 10 working days as an SAE. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE. Furthermore, any SAE occurring as an adverse pregnancy outcome post study will be reported to the IRB and DSMB.

8.5.2.2. Reporting Other Special Situations

All other special situations will be reported as AEs or SAEs and reported accordingly.

9. STATISTICAL CONSIDERATIONS

9.1 Analysis Objectives and Endpoints

9.1.1 Analysis Objectives

The primary objectives of this study are as follows:

- To determine acceptability and feasibility of weekly injectable semaglutide for adults with methamphetamine use disorder (MeUD).
- To evaluate safety and tolerability of semaglutide among adults with MeUD.

The exploratory objectives of this study are as follows:

- To measure the perceived effect of the semaglutide on methamphetamine use, self-reported methamphetamine use (TLFB), and urine drug testing for methamphetamine metabolites.
- To measure the impact of semaglutide on methamphetamine cravings through the Brief Substance Use Craving Scale.
- To measure the impact of semaglutide on inflammation related to methamphetamine use by measuring hs-CRP as the primary biomarker.
- To measure the impact of semaglutide therapy on cognitive function through the CogState Battery.

9.1.2 Primary Endpoints

- Eligibility to enrollment ratio
- Adherence to weekly medication injections
- Willingness to continue therapy at study conclusion
- Rate of study drug discontinuation due to adverse events
- Proportion with a pre-post reduction in concentration of methamphetamine in hair samples (enrollment vs. week 12 visit)

9.1.3 Secondary Endpoints

Secondary endpoints include the following:

- Adverse events
- Self-reported days of methamphetamine use by TLFB
- Urine drug testing (negative vs. positive for methamphetamine)
- Participant satisfaction with trial and participant perception of whether participation helped reduce methamphetamine use

- Biomarkers (hs-CRP, IL-1β, IL-6, TNF-α)
- Cognitive function (CogState Battery)
- Number of persons pre-screened, screened, and enrolled
- Scheduled visits attended, overall retention

9.1.4 Other Endpoints of Interest

- Reported days/episodes of other substance use (opioids, alcohol, cocaine, marijuana, ecstasy, etc.)
- Sexual HIV risk behaviors
- Substance use treatment (outside study)
- Impulsivity (measured via BART and the STIMP scales)
- Participant methamphetamine cravings (measured via Brief Substance Use Craving Scale (BSCS) and Visual Analog Scale Craving Scores)

9.1.5 Analysis Conventions

All individual subject data will be listed as measured. All statistical summaries and analyses will be performed using STATA software. The study drug in this study is semaglutide. Last dose of study drug refers to the last dose of semaglutide and will be used in the definition of treatment-emergent AEs and laboratory abnormalities as well as the efficacy endpoints at various post-treatment time points. An as-treated analysis will also be conducted.

9.1.6 Demographic Data and Baseline Characteristics

Demographic and baseline characteristics will be summarized using standard descriptive methods by treatment group and overall. Demographic data will include sex at birth, self-identified gender, self-identified race/ethnicity, and age.

Baseline characteristic data will include BMI and additional endpoints as necessary.

9.2 Data Analysis

9.2.1 Primary Analysis

Specific Aim 1: To determine the feasibility and acceptability of treating adults with MeUD with semaglutide, we will determine the ratio of eligible to enrolled participants, adherence to weekly injections, and willingness to continue therapy at study conclusion. To evaluate preliminary effect on methamphetamine use based on hair testing and TLFB, we will conduct within-person comparisons of the four weeks prior to enrollment to the final four weeks of medication treatment. Hair samples in people who use methamphetamine daily are reported to be 80-360ng/mg of hair, although results vary by study. In a study matching hair sampling to self-reported use, 0.25-4 grams/day (mean 1.2, median 0.9; SD 1.2) corresponded to 0.38-53.15ng/mg of hair (mean 6.10, median 2.12; SD 9.56). We will have 80% power to detect that 75% have lower levels at week 12 than their baseline sample as opposed to the 50% which would be expected with no change in use.

We will also calculate a Pearson's coefficient correlating changes in methamphetamine concentration in hair with changes in TLFB.

Go/No-go criteria: We will proceed with the next phase of the trial if (1) enrollment of 25 individuals is achieved with at least 20 completing treatment, (2) adherence to weekly study medication injection is ≥70% of available injections, and (3) no medication-related SAEs are reported.

Specific Aim 2: To evaluate safety and tolerability of semaglutide among adults with MeUD. We will focus primarily on the rate of discontinuation of study drug due to AEs. The rate of discontinuation of semaglutide in trials varies, based both on the length of the trial and comorbidities. For patients with comorbidities, discontinuation rate ranges from 15% at 26 weeks to 20% at 100 weeks. When converted to a rate, discontinuation due to AEs in obesity trials ranged from 7.2258 to 10.3259 per 100 person-years, although discontinuation tends to occur mostly in the early months of trials due to AEs that often resolve during treatment. We will also classify AEs as any AE that results in stopping study medication (either by study stopping rules [i.e., excessive weight loss, grade 3 rash, grade 3 or greater event associated with study drug, or any event PI/IRB/DSMB/FDA/NIH advise should result in stoppage] or participant decision), specific common AEs (reported by more than 2% of study participants in both groups), AEs for general organ system categories, and AEs potentially related to study drug use. For laboratory values (including creatinine, lipase, and amylase) and other continuous variable safety outcomes, means and standard deviations (or median and inter-quartile range, for right-skewed distributions) will be presented, in combination with the proportions with values outside the normal range. Binary AE measures will be analyzed using exact methods, since they are expected to be uncommon, while continuous safety outcome variables will be analyzed using regression models. Expected adverse event outcomes are primarily gastrointestinal (~75-85%; including abdominal pain [6- 20%], constipation [3-24%], diarrhea [9-30%], nausea [16-44%], vomiting [5-24%], fatigue [11%], headache [15%]; with less common events including increased ALT [3%], and acute pancreatitis or gastroparesis [<1%]).

Minimum Detectable Effects (MDE): We expect a discontinuation rate due to adverse events of 7-10 per 100 person-years, most of which occur in the early months, thus representing at least 3% of participants discontinuing the medication during the 12-week trial. Based on our small sample size, we will have 80% power to rule out a 12-week discontinuation rate of 9% overall and 11% on the semaglutide arm.

9.2.2 Exploratory Analyses

*As-treated analyses***.** In the primary intent-to-treat (ITT) analyses, outcomes will be included in the analysis without regard to adherence to treatment. We will also conduct an as-treated analysis, using cumulative adherence, calculated as the number of dosing events. Restricted cubic spline terms for adherence in this model will account for non-linearity

Impact on craving and other outcomes. As the impact of GLP-1 agonists may be through reduced craving, we will specifically assess craving through the Brief Substance Use Craving Scale (3 items). We will calculate the composite score (0-27 points) and anticipate a median score of 12+/-4 at baseline. Assuming a moderate correlation (rho=0.70) over time, we will have 80% power to detect a difference of 0.34 standard deviations (SD). We will conduct similar analyses for impulsivity.

Evaluation of biomarkers. We will assess hs-CRP, IL-1β, IL-6, and TNF-α, with hs-CRP of primary interest because it is readily available for clinical use. Among people with MeUD, mean CRP is 3.50mg/L (SD 2.50). For this, assuming moderate correlation, we have 80% power to difference of 0.34 SD.

Cognition. The CogState Battery has 5 tasks, scored separately, assessing verbal learning and memory, working memory, spatial working memory, problem solving, and social cognition. As an example of the analytic approach, the International Shopping List (ISL) task is used to reflect verbal learning and memory. In a study of a MeUD treatment intervention, ISL scores rose in the treatment arm from 19 to 26 out of 40, SD 2.5. We will have 80% power to detect a difference of 1.1 points on a two-sided 0.05 level test.

9.2.3 Additional Outcomes

Additional analyses. We will also conduct as-treated analyses, analyze for effects of study participation and treatment effects in participants who decline substance use counseling, and analyze data by consecutive weeks of meth-abstinence.

9.3 Sample Size

Sample size justification:

To determine the feasibility and acceptability of treating adults with MeUD with semaglutide, we will determine the ratio of eligible to enrolled participants, adherence to weekly injections, and willingness to continue therapy at study conclusion. To evaluate preliminary effect on methamphetamine use based on hair testing and TLFB, we will conduct within-person comparisons of the four weeks prior to enrollment to the final four weeks of medication treatment.

The pilot will be considered a success, and plans for a Phase IIb trial will commence, if the following criteria are met:
(1) the ratio of enrolled:eligible, adherence to weekly injections, and willingness to continue therapy exceed 70%; and
(2) hair testing or TLFB show reduced methamphetamine use in the final 4 weeks of the trial compared to 4 weeks preceding enrollment.

Hair samples in people who use methamphetamine daily are reported to be 80-360ng/mg of hair, although results vary by study. In a study matching hair sampling to self-reported use, 0.25-4 grams/day (mean 1.2, median 0.9; SD 1.2) corresponded to 0.38-53.15ng/mg of hair (mean 6.10, median 2.12; SD 9.56). We will have 80% power to detect that 75% have lower levels at week 12 than their baseline sample as opposed to the 50% which would be expected with no change in use. of methamphetamine use. We will also calculate a Pearson's coefficient correlating changes in methamphetamine concentration in hair with changes in TLFB.

10 RESPONSIBILITIES

10.1 Investigator Responsibilities

10.1.1 Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonization (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject.

10.1.2 Institutional Review Board (IRB) Approval

The investigator will submit this protocol, informed consent form, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IRB. The investigator will not begin any study subject activities until approval from the IRB has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB any modifications made to the protocol or any accompanying material to be provided to the subject after initial IRB approval, with the exception of those necessary to reduce immediate risk to study subjects.

10.1.3 Informed Consent

Study staff are responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential risks of the study and before undertaking any study-related procedures. The investigator will use the most current IRB-approved consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness as required by IRB or by local requirements.

10.1.4 Confidentiality

The investigator will assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Laboratory specimens will be labeled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions. Subject data will be processed in accordance with all applicable regulations.

10.1.5 Study Files and Retention of Records

The investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, CRF and query forms, IRB and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each subject:

- Subject identification (name, date of birth, gender);
- Documentation that subject meets eligibility criteria, ie, history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- Documentation of the reason(s) a consented subject is not enrolled
- Participation in study (including study number);
- Study discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of study drug, including dates of dispensing;
- Record of all adverse events and other safety parameters (start and end date, and including causality and severity);
- Concomitant medication (including start and end date, dose if relevant; dose changes);
- Date of study completion and reason for early discontinuation, if it occurs.

10.1.6 Case Report Forms (CRFs)

For each subject consented, a CRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. CRF should be completed on the day of the subject visit to enable the sponsor to perform central monitoring of safety data. Prior to database lock (or any interim time points as described in the clinical data management plan), study staff will confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. The CRF will capture the data required per the protocol schedule of events and procedures.

10.1.7 Investigational Medicinal Product Accountability and Return

Used (empty or partially empty) and unused study drug supplies will be destroyed on site according to appropriate standard operating procedure (SOP).

If study drug is destroyed on site, the investigator must maintain accurate records for all study drug destroyed. Records must show the identification and quantity of each unit destroyed, the method of

destruction, and the person who disposed of the study drug. Upon study completion, copies of the study drug accountability records must be filed at the site.

10.1.8 Inspections

The investigator will make available all source documents and other records for this trial to IRBs or to regulatory authority or health authority inspectors.

10.1.9 Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

10.1.10 Protocol Modifications

Protocol modifications may be made by the investigator. The investigator must submit all protocol modifications to the IRB in accordance with local requirements and receive documented IRB approval before modifications can be implemented.

10.1.11 Access to Information for Auditing or Inspections

Representatives of regulatory authorities may conduct inspections or audits of the clinical study. The investigator agrees to provide to representatives of a regulatory agency access to records, facilities, and personnel for the effective conduct of any inspection or audit.

10.1.12 Study Discontinuation

The investigator reserves the right to terminate the study at any time. Should this be necessary, the investigator will arrange discontinuation procedures and notify the appropriate regulatory authority(ies) and IRB. In terminating the study, the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

11 APPENDICES

Appendix 1. Study Procedures Table

Appendix 2. Suicidality SOP

Appendix 3: Description and Dates of Amendments

Appendix 1. Study Procedures Table

Table 3: Study Procedures Summary								
	Screening (2 visits)	**Run-in (≤2 visits)**	**Enrollment (week 0)**	**Weekly (weeks 1-3, 5-7, 9-11)**	**Weeks 4, 8**	**Week 12**	**FU-week 20**	**PRN Visits**
Informed consent	**X**							
Urine drug test	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Medical history	**X**							
Physical exam	**X**							
Vital signs (incl. weight)	**X**		**X**	**X**	**X**	**X**	**X**	**X**
Suicidality screen (C-SSRS)	**X**		**X**		**X**	**X**	**X**	
Study drug administration			**X**	**X**	**X**			
Interview/survey			**X**		**X**	**X**	**X**	
Symptom-driven physical exam			**X**	**X**	**X**	**X**	**X**	**X**
Med. Mgmt. Counseling			**X**	**X**	**X**	**X**		
AE Assessment			**X**	**X**	**X**	**X**	**X**	**X**
Hair sampling			**X**			**X**		
Safety labs	**X***				**X****	**X****		**X**
Biomarker testing			**X**			**X**		

*Baseline safety labs include: comprehensive metabolic panel (CMP), hemoglobin A1c, lipase, amylase, calcitonin, and urine pregnancy test. TSH will be conducted as needed.
**Follow-up safety labs limited to CMP, lipase, amylase, urine pregnancy test, and as-needed labs for clinical adverse event assessment.

Appendix 2. Suicidality SOP

Version:	Review:	Pages:
2.0	Annually	2
Author:	**Approved By:**	**Effective Date:**
John Walker, Finn Black	Phillip Coffin	07/23/24

Location:	Subject:
25 Van Ness Avenue, Suite 500 San Francisco, CA 94102	Urgent/Emergency Care Procedures
Function:	**Distribution:**
Provides guidelines for managing medical and psychiatric emergencies during visits with research participants.	S:\Prevention\Research\ Clinician\SOPs and S:\Prevention\Research\Psychiatric Emergency

When to use this protocol: This protocol applies to all study visits (in office or remote) with a research participant when there is a suspected psychiatric emergency.

General safety protocols for participant study visits:

1. **Have emergency resources available:** During each study visit, study staff should have contact information available for the study clinicians (John Walker and Finn Black) and medical director (Phillip Coffin) including office and cell phone numbers, and crisis services numbers in case of a psychiatric or medical emergency.
2. **Have participant emergency contacts available:** The participant's physical address, phone number, and emergency contacts for the participant should be confirmed and updated as described in the study protocol.

Psychiatric emergencies:

When to use this protocol: This protocol applies to all visits with a research participant when there is a suspected psychiatric emergency. Psychiatric emergencies include situations where a person is in immediate danger of harming themselves or other people, or situations where a person is unable to meet their basic survival needs due to their mental health.

1. **Initial assessment:** Research associates (RAs) are not required to assess participants beyond asking the mental health questions included as part of study procedures. RAs should notify a research clinician in any of the following situations:
    a. Participant discloses current suicidal or homicidal thoughts and has a plan to act on these thoughts.

b. Participant is acutely psychotic and there is concern the participant may come to harm or harm others if allowed to leave the premises.
c. RA is concerned that participant is unable to meet their basic survival needs due to mental illness (e.g., participant is unable to seek shelter or eat).

2. **Call for assistance:** The participant should be thanked for sharing this information and told that this situation will best be addressed by a licensed study clinician who will meet with the participant or join the Zoom call if the visit is remote.
    a. The research associate will stay on Zoom with video on and call the study clinician. If the study clinician is available, the zoom link will be shared via email with the clinician so the clinician can join the call.
    b. If a study clinician is not available within 10 minutes, the medical director, Phillip Coffin [cell (917) 882-7344] should be called.
    c. If licensed study staff are unavailable, the RA should call the SFDPH Mobile Crisis Team at (415) 970-4000.
3. **Clinician assessment:** A licensed study clinician will assess the situation in conjunction with the medical director, if available, and determine course of action:
    a. Participant is at serious, imminent risk of harm to self or others:
        i. Clinician can call to consult with the SFDPH Mobile Crisis team at (415) 970-4000 OR arrange for transportation to Psychiatric Emergency Services (PES) at ZSFGH [(628) 206-8125] or DORE Urgent Care Clinic [(415) 553-3100]. Transportation to PES or DORE should be by EMS (by calling 911 and explaining the situation) or the Mobile Crisis Team.
        ii. If transfer to PES or DORE Urgent Care Clinic is needed, clinician should stay with the participant until a warm hand off of the participant to EMS or Mobile Crisis takes place.
    b. Participant is **not** at serious, imminent risk of harm to self or others but does require urgent mental health services:
        i. Participant has established mental health care:
            1. The participant will be encouraged to contact their mental health provider. A staff member will help to facilitate contacting the provider if the participant requires assistance.
            2. The clinician will obtain a consent for release of information if the participant would like the clinician to contact or confer with their mental health provider directly.
            3. Provide participant with crisis resources wallet card.
        ii. Participant requires linkage to mental health care:
            1. Give participant the 24 hour S.F. Behavioral Health Mental Health Access Line [(415) 255-3737 or (888) 246-3333] and the Suicide Prevention Lifeline (1-800-273-8255). Participants who prefer text can use the Crisis Text Line (text HOME to 741741).
            2. Refer participant to same-day care through Westside Crisis (415-355-0311 X1220 at 245 11th Street, drop-in hours M–F 7:30am-3pm, participants need to arrive at 7am to be seen the same day for Medi-Cal/Medicare/uninsured patients).
            3. Provide participant with crisis resources wallet card.

Appendix 3. Description and Dates of Amendments

Amendment 1:

In this amendment we made revisions to the inclusion and exclusion criteria based on feedback from NIDA during their review process.

Addition of measures in the survey assessment (CGI, SF-36), and TSH to safety labs.