Document Section Cover Sheet

Official Title: Use of a GLP-1R Agonist to Treat Opioid Use Disorder

NCT number: NCT04199728

Document: Study Protocol and Statistical Analysis Plan

Document date: 11/21/2023

PennState

HRP-592 - Protocol for Human Subject Research with Use of Test Article(s)

Protocol Title:
Use of a GLP-1R Agonist to Treat Opioid Use Disorder

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Version Date:
10 May 2023

Clinicaltrials.gov Registration #:
NCT04199728

Investigator-Sponsored Study Proposal

Universal Trial Number (UTN): U111-1236-2694

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1.0 Objectives

1.1 Study Objectives

The long-term objective of this study is to determine whether a glucagon-like peptide-1 receptor (GLP-1R) agonist, liraglutide (brand name is Saxenda®), can improve clinical outcomes in patients with opioid use disorder (OUD). We propose to study the efficacy and safety of liraglutide treatment and its effects on craving in OUD patients within a randomized, placebo controlled, double-blinded, parallel arm clinical pilot study with two objectives:

1) **To evaluate the efficacy of liraglutide (vs placebo), administered daily, in reducing craving for opioids in humans in residential treatment for an OUD.** Well-validated measures of craving, including visual cue-elicited craving, and ecological momentary assessment (daily smartphone assessments) will be used to assess craving. Based on our preclinical studies, we hypothesize that liraglutide will decrease craving among patients in treatment for OUD.

2) **To evaluate the safety of liraglutide, administered daily, in humans seeking treatment for OUD.** We will measure how liraglutide changes respiratory rate, blood pressure, and heart rate as well as blood concentrations of glucose, hemoglobin A1c (HbA1c), and fructosamine, over the course of a 18-day titration (3-dose intervention) or 30-day titration (5-dose intervention) to full treatment dosage.

1.2 Primary Study Endpoints

The primary objectives of this pilot study are 1) to determine whether liraglutide can reduce cue-elicited drug craving over 3-5 weeks while participants are in residential treatment for OUD, and 2) to study whether liraglutide can reduce ambient (daily) drug craving over approximately 21-33 days while participants are in residential treatment for OUD.

1) **Cue-elicited Drug Craving.** Change in self-reported cue-elicited drug craving from baseline (Day 1) to the end of the target drug dose (Day 19 [and additionally until Day 31 for 5-dose intervention]) will be measured on a 0-100 point visual analog scale (VAS), where 0= no craving, 100= maximum craving. Assessments are taken prior to, and immediately after, exposure to visual drug cues in the Cue Response Task.
2) **Ambient Drug Craving.** Change in ambient drug craving over time will be measured throughout the study (Days 1-21 [and additionally until Day 33 for 5-dose intervention]) using a 0-100 VAS delivered via smartphone using Ecological Momentary Assessment (EMA) 4 times per day, on each test day (Days 1 and 19 [and additionally Day 31 for the 5-dose intervention]) and on the first two days and last 2 days of each treatment dose.

1.3 Secondary Study Endpoints

The secondary objective of this pilot study is to evaluate the safety of daily administration of liraglutide in humans seeking treatment for an OUD.

1) **Cardiorespiratory Function**
    a. *Blood Pressure*. Change in blood pressure from baseline (Day 1) to: i) the beginning of each study drug dose (Days 2, 8, 14, 20, 26); ii) end of the target drug dose (Day 19 [Day 31 for 5-dose intervention]); and iii) rebound follow-up (Day 21 [Day 33 for 5-dose intervention]).
    b. *Heart Rate.* Change in heart rate from baseline (Day 1) to: i) the beginning of each study drug dose (Days 2, 8, 14, 20, 26); ii) end of the target drug dose (Day 19, [Day 31 for 5-dose intervention]); and iii) rebound follow-up (Day 21 [Day 33 for 5-dose intervention]).
    c. *Respiration.* Change in respiratory from baseline (Day 1) to: i) the beginning of each study drug dose (Days 2, 8, 14, 20, 26); ii) end of the target drug dose (Day 19 [Day 31 for 5-dose intervention]); and iii) rebound follow-up (Day 21 [Day 33 for 5-dose intervention]).

2) **Body Weight** *(kg).* Absolute and percent change in body weight from baseline through the end of rebound follow-up (Daily, from Days 1 to 21 [Days 1-33 for 5-dose intervention]).
3) **Glycemic Control.** Glycemic control will be monitored by fasting blood samples for fructosamine and A1c. Fasting blood sample measurements change slowly overtime (i.e., across weeks and months) and therefore will be evaluated only on Days 2 and 19 [and additionally Day 31 for 5-dose intervention] via venipuncture.
4) **Adverse Events.** Frequency of adverse events (AE) and serious adverse events (SAE) deemed related to treatment throughout the study period (Days 1-21 [1-33 for 5-dose intervention]), and at 30 days post-intervention (Day 49 [Day 61 for 5-dose intervention]).

1.4 Exploratory Endpoints

1) **Prefrontal Cortical Response to Drug Cues.** Change in blood oxygenation level response to visual opioid drug cues in prefrontal cortex from baseline (Day 1) to end of the target drug dose (Day 19 [additionally Day 31 for 5-dose intervention]) using Functional Near Infrared Spectroscopy (fNIRs).
2) **Rebound Ambient Drug Craving.** Change in ambient drug craving as measured by 0-100 VAS delivered via smartphone using the EMA on test days and on the first two days and last 2 days of each treatment dose from end of rebound follow up (Day 21 [Day 33 for 5-dose intervention]) to baseline (Day 1) and to end of the target drug dose (Day 19 [Day 31 for 5-dose intervention]).
3) **Rebound Blood Pressure.** Change in blood pressure from end of the target drug dose (Day 19 [Day 31 for 5-dose intervention]) to rebound follow up (Day 21 [Day 33 for 5-dose intervention]).
4) **Rebound Heart Rate.** Change in heart rate from end of the target drug dose (Day 19 [Day 31 for 5-dose intervention]) to rebound follow up (Day 21 [Day 33 for 5-dose intervention]).
5) **Rebound Respiration.** Change in respiratory from end of the target drug dose (Day 19 [Day 31 for 5-dose intervention]) to rebound follow up (Day 21 [Day 33 for 5-dose intervention]).
6) **Long-term Glycemic Control.** Change in HbA1c and fructosamine levels from Day 2 to end of the target drug dose (Day 19 [Day 31 for 5-dose intervention]).

2.0 Background

2.1 Scientific Background and Gaps

An estimated 5.6 percent of the global population used illicit drugs in 2016, with 34 million using opioids; worldwide in 2015, 450,000 people died as a result of drug use, with opioids accounting for 76 percent of deaths in those with drug use disorders [1]. In the United States, in 2017, approximately 51.8 million people aged 12 or older used an illicit drug or abused any psychotherapeutic medication. Of those, 11.4 million used an opioid such as heroin or misused prescription pain relievers [2]. According to the Centers for Disease Control and Prevention, between July 2016 and September 2017 there was a 30% increase in the number of emergency room visit for opioid overdose [3]. There were 70,237 drug overdose deaths reported in the United States in 2017, and of these, 67.8%, or 47,600, involved opioids [4], costing the nation an estimated $51.2 billion annually [5], or $504.0 billion (2.8% Gross Domestic Product) when including non-fatal impacts [6].

Glucagon-Like Peptide-1 (GLP-1) and Substance Use Disorder. A great deal of attention has focused on the reward pathway and the view that drugs of abuse hijack natural reward substrates [7, 8]. Drug-seeking animals and humans, however, are driven by a need state not unlike that of water, food, or salt [9]. GLP-1 is a hormone produced by L cells in the small intestine that reduces intake of food, in part, by increasing insulin release, decreasing glucagon release, and decreasing gastric emptying [10], producing a ‘satiety’ effect. GLP-1 is also produced by cells in the nucleus of the solitary tract (NST), and these cells project widely throughout the brain including to reward and feeding circuitry [11, 12]. Treatment with GLP-1 receptor (GLP-1R) agonists inhibits ingestion of palatable sweets, water when thirsty, and salt when sodium deficient [11, 13-19]. As such, treatment with this ‘satiety’ signal, GLP-1, was predicted to reduce drug seeking and taking in humans, as well as rats.

In preclinical studies, treatment with the GLP-1R agonist, Exendin-4 (Ex-4), has been shown to reduce a conditioned place preference for, and the accumbens dopamine response to, nicotine, cocaine, and amphetamine, and reduces cocaine self-administration in rats [15, 16, 20, 21]. Likewise, treatment with Ex-4, in a dose that does not affect responding for sucrose, decreases fixed and progressive ratio responding for cocaine [18] and, when administered centrally, cocaine-induced reinstatement [22]. Finally, the use of a GLP-1R agonist increases insulin secretion, while inhibiting glucagon, only in response to increases in glucose levels [23, 24]. As such, this treatment can potentially be used in patients with OUD without diabetes without the risk of hypoglycemia. Substantial evidence from randomized controlled trials indicate that the use of a GLP-1R agonist can produce significant, sustained weight loss in obese but non-diabetic people without causing any adverse effects on circulating glucose blood pressure, HbA1c or their lipid profile [25-27], suggesting it could be used safely in OUD patients. GLP-1R agonists, then, are promising for the treatment of substance use disorder (SUD) in humans. Further, the intervention can be readily translated for a new indication, as various formulations of GLP-1R agonists are approved for treatment of obesity and Type 2 Diabetes Mellitus (T2DM) in humans [21, 28] and already are in clinical trials for nicotine and alcohol use disorders [29-34].

2.2 Previous Data

GLP-1 and OUD. No studies to date have tested whether a GLP-1R agonist can reduce responding for opioids in humans. We have shown that administration of Ex-4 (2.4 µg/kg ip) during abstinence and prior to test (i) in rats with a history of heroin self-administration decreased cue-induced heroin-seeking (Figure 1, left) and (ii) abolished drug-induced reinstatement of heroin-seeking (Figure 1, right). In a second preliminary study, we tested the longer acting GLP-1R agonist, liraglutide [0.1 mg/kg subcutaneous, (sc)]. The half-life for liraglutide in rats is about 4 h [35]. Our results showed that daily liraglutide treatment beginning on the 11th day of heroin self-administration and continuing through abstinence: (i) reduced heroin self-administration (Figure 2, left), (ii) failed to reduce seeking during extinction (Figure 2, middle), possibly due to a slower onset of the longer acting liraglutide (liraglutide was injected 1 h before extinction testing), and (iii) significantly reduced heroin-induced reinstatement of heroin seeking behavior (liraglutide was administered 6 h prior to the reinstatement

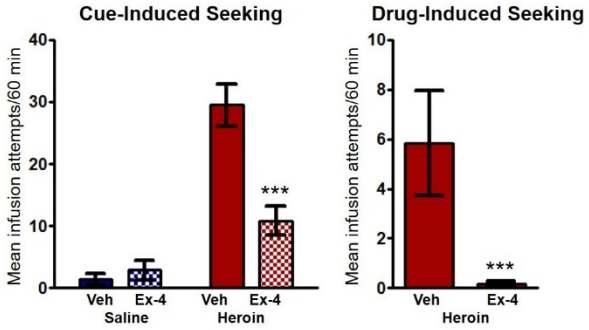

Figure 1: Mean (+/- SEM) number of infusion attempts/h during cued extinction testing (**Left**) and heroin-induced reinstatement testing (**Right**) in rats with a history saline or heroin self-administration and pretreated sc with saline (Veh) or 2.4 ug/kg Exendin-4 (Ex-4).

test, Figure 2, right). Taken together, these data provide strong support that GLP-1R agonists hold promise as a novel intervention for OUD.

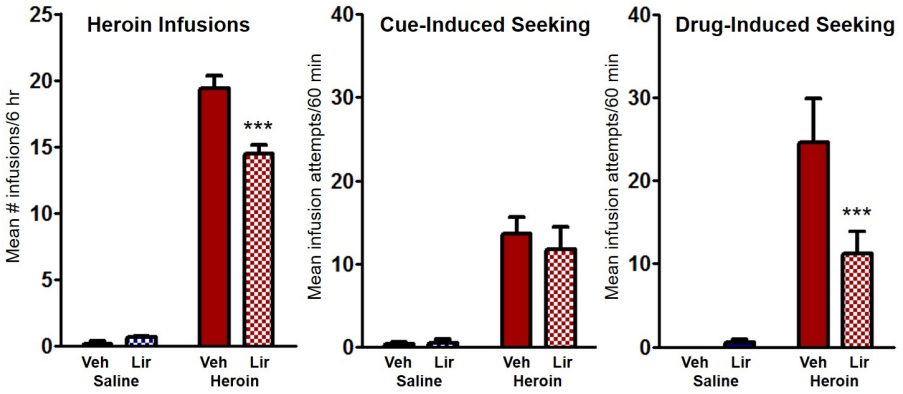

Figure 2: Mean (+/- SEM) number of infusions/6h in rats self-administering saline or 0.06 mg/inf heroin iv and treated with saline or liraglutide (0.1 mg/kg sc) (**Left**). Mean (+/- SEM) number of infusion attempts/h during cue-induced extinction (**Middle**) and heroin-induced reinstatement testing in rats with a history saline or heroin self-administration and pretreated with saline or liraglutide (1.0 mg/kg sc) (**Right**).

GLP-1R agonist treatment in humans. GLP-1R agonists have been studied for decades and are, as mentioned, an approved and effective treatment for obesity and (T2DM) in humans [27, 36, 37]. In 131 patients with T2DM, treatment with GLP-1R agonists led to significant improvement in glycated hemoglobin (HbA1c) and BMI [38]. Likewise, GLP-1R agonists in patients with T2DM led to controlled blood glucose, along with positive effects on body weight, blood pressure, and cholesterol [10]. Furthermore, neuroimaging studies have shown that GLP-1R agonists reduce brain responses to food cues in obese and T2DM participants, but not in lean participants. Specifically, Van Bloemendaal et al. [39] demonstrated that the GLP-1R agonist exenatide (relative to placebo) decreased functional magnetic resonance imaging (fMRI) measures of brain activation in the amygdala, insula, putamen, and, importantly, orbitofrontal cortex (OFC) in response to a series of food related cues (i.e., food vs non-food pictures) in subjects with obesity and T2DM. This effect was not observed in lean control subjects. The most common side effects of GLP-1R treatment are nausea and diarrhea; less common is injection-site bruising or “reactions” (i.e. erythema, pruritus, and rash) [36]. One meta-analysis found evidence of a slight increase in heart rate, a modest reduction in blood pressure, and no association with hypertension across 60 trials employing 14 different GLP-1R formulations [40]. Further work reported decreased cardiovascular risk [41] and a reduction in major adverse cardiac events including nonfatal stroke, nonfatal myocardial infarction, and cardiovascular mortality [42] in T2DM patients treated with GLP-1R agonists compared with placebo.

All GLP-1R agonists are not the same with regard to treatment of obesity or T2DM. Ex-4 (exenatide) is a short acting GLP-1R agonist with a half-life of 2.4 h in humans [43]. Liraglutide has a longer half-life of about 13 h in humans [44] and, as such, has been found useful as a once/day sc injectable formulation for the treatment of obesity [27, 45] and T2DM [46, 47]. A meta-analysis determined no cause for concern regarding neuropsychiatric safety associated with liraglutide [48].

Although liraglutide was approved for human use in 2010, there are no data testing the effectiveness in patients with an OUD. The objective of the proposed research is to test whether treatment with a GLP-1R agonist can reduce craving in humans with OUD. Here, we will conduct a pilot study to determine whether once daily treatment with liraglutide can safely and effectively reduce craving in patients in a residential treatment facility for OUD, and who are either receiving counseling (CO) or counseling plus a common medication assisted treatment (MAT), buprenorphine/ naloxone (BUP/NA). We chose liraglutide for this initial pilot study as dosing can be closely monitored due to its 13 h half-life and can be safely ramped up to an effective dose during a 4-6 week residential treatment program.

This is an innovative project that will, for the first time, test the safety and efficacy of GLP-1R agonist treatment on opioid craving. Further, because single timepoint self-report measures of craving have not been found to be strong predictors of relapse behavior [49], we will assess craving using an array of verbal, emotional, physiological, and neural indices. Emotional and physiological feedback will be

obtained using both EMA and a wearable device (i.e., a wristband). This will allow us to track not only changes in mood and craving across the day, but also changes in craving that may be elicited by the subcutaneous injection of the GLP-1R agonist or vehicle.

2.3 Study Rationale

The rationale for the proposed research is to develop an acute intervention that can improve treatment outcomes in OUD by reducing craving, a primary factor contributing to early relapse. Although liraglutide was approved for human use in 2010, there are no data testing the effectiveness in patients with an OUD. The objective of the proposed research is to test whether treatment with a GLP-1R agonist can reduce craving in humans with OUD. Understanding how a 'satiety' agent may affect craving and brain responses to drug cues in an OUD population would provide entirely novel information. If liraglutide shows a trend towards efficacy, and safety of the GLP-1R agonist is demonstrated in this population, it would provide an indication to run the second phase, multi-center clinical trial of GLP-1R agonist in OUD patients.

3.0 Inclusion and Exclusion Criteria

3.1 Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria at screening:

1. Age 18 to 75 years
2. Diagnosed with an OUD seeking treatment at Caron Treatment Centers (CaronTC) and planning on being enrolled in a residential treatment plan for a minimum of 4 weeks
3. Women of childbearing potential must consent to use a medically accepted method of birth control or to abstain from sexual intercourse while in the study
4. Able and willing to provide informed consent prior to any study-related activities
5. Must be able to read and communicate in English sufficiently to complete all study requirements, including EMA

3.2 Exclusion Criteria

Patients will be excluded from study entry if any of the following exclusion criteria exist at screening:

1. Age < 18 or > 75 years
2. Women who are pregnant, planning pregnancy, breastfeeding, or unwilling to use adequate contraceptive measures
3. History of angioedema, serious hypersensitivity reaction, or anaphylactic reaction to liraglutide or another glucagon-like peptide-1 receptor (GLP1R) agonist
4. Personal or family history of medullary thyroid carcinoma (MTC) or patients with multiple endocrine neoplasia syndrome type 2 (MEN 2) or thyroid nodule
5. Type I diabetes or history of diabetic ketoacidosis
6. Type II diabetes mellitus
7. Hypoglycemia on intake visit (blood glucose < 70 mg/dL)
8. End-stated renal failure on dialysis **or** glomerular filtration rate (GFR) <30mL/min per 1.73 square meters **or** previous renal transplant
9. Severe hepatic impairment (AST or ALT levels > 3 times upper limit of normal range) or previous liver transplant
10. Current or past diagnosis of pancreatitis, gastroparesis, or other severe gastrointestinal disease
11. Current or past diagnosis of gallbladder disease or gallstones
12. Serious cardiovascular disease within the past 6 months (e.g. uncontrolled hypertension, heart failure, significant cardiac arrhythmias, myocardial infarction, presence of angina pectoris, symptomatic coronary artery disease, deep vein thrombosis, pulmonary embolism, second- or third-degree heart block, mitral valve or aortic stenosis, hypertrophic cardiomyopathy, stroke)

13. Severe co-occurring psychiatric disorder (e.g., bipolar disorder, psychotic disorder, schizophrenia) that would, in the opinion of the Principle Investigator or study physician, interfere with participating in the study, such as if the patient needs a higher or different level of care and is going to be transferred out of Caron.
14. Suicidal ideation within the past 1 month, or history of suicide attempts within the past 1 year, unless participation is cleared by clinician assessment and/or judgement.
15. Treatment with any investigational drug in the one-month preceding the study
16. Previous randomization for participation in this trial
17. Abnormal physical exam findings, vital signs (blood pressure, heart rate, respiratory rate, body temperature), EKG measurements, and safety lab values that are deemed clinically significant by study physician

3.3 Early Withdrawal of Subjects

3.3.1 Criteria for removal from study

Blood pressure, heart rate, and respiratory rate will be measured on Days 1, 2, 8, 14, 19, and 21. On each day, each measure will be recorded 3-4 times and then averaged. Participants will be withdrawn if they experience an average daily value for any measure on Day 1, 2, 8, 14, or 19:

- Systolic blood pressure (SBP) changes >40 mmHg, or SBP <90 mmHg or >200 mmHg, or clinical symptoms of hypertension (e.g. headache, dizziness, blurred vision, nausea edema) or hypotension (e.g. dizziness, nausea, fainting) develop
- Heart rate reaches levels <40 beats/min or >120 beats/min
- Respiratory rate changes by >5 breaths/minute or reaches levels <10 breaths/minute or >24 breaths/minute

The investigators will also exercise discretion to end an individual's study participation if they should engage in behavior that could jeopardize their own health and well-being or that of others

Participants who develop any new conditions described in the exclusion criteria during the treatment phase of clinical trial will be removed from the study

3.3.2 Follow-up for withdrawn subjects

Subjects will be withdrawn from the study if the study participant withdraws consent for any reason. The primary reason for the subjects' withdrawal from the study will be recorded.

Subjects who withdraw from the study may be replaced.

Subjects withdrawn due to pregnancy, adverse events (AEs), a medical emergency, or unwillingness or inability to comply with the protocol, will undergo an End of Study telephone call (30 days after the end of study treatment) unless the withdrawal is due to death or the withdrawal of consent.

3.3.3 Discontinuation of medication

Participants who decide to discontinue study medication, but who do not withdraw their consent, will be withdrawn from the study, and will cease study tasks, although their existing data will be kept in the data set. These participants may be replaced.

4.0 Recruitment Methods

4.1 Identification of subjects

Patients who plan to remain in residential treatment for a minimum of 4 weeks at CaronTC will be identified. Patient records will be evaluated by Caron-based study staff against the study inclusion and exclusion criteria.

4.2 Recruitment process

4.2.1 How potential subjects will be recruited.

All eligible patients will be approached and recruited in the same manner following the study protocol procedures. Only IRB-approved study team members (Physicians or staff) at CaronTC will first interact with the patient in a consultation session. During the initial consultation session, the physician/staff will briefly explain the proposed study and ask the patient if they would be interested in discussing further with a research study member. If the patient is interested, a trained research study team member will discuss the full study including any risks and benefits associated with participation.

4.2.2 Where potential subjects will be recruited.

Potential subjects will be recruited on the Professionals Unit at CaronTC. Subjects may also be drawn from other units at the CaronTC if there is a planned stay of a minimum of 4 weeks.

4.2.3 When potential subjects will be recruited.

Potential subjects will be recruited prior to any study procedures taking place.

4.2.4 Describe the eligibility screening process and indicate whether the screening process will occur before or after obtaining informed consent. Screening begins when the investigator obtains information about or from a prospective participant in order to determine their eligibility. In some studies, these procedures may not take place unless HIPAA Authorization is obtained OR a waiver of HIPAA Authorization when applicable for the screening procedures is approved by the IRB.

Screening of subjects at admission is expected prior to obtaining consent to confirm that they have an established diagnosis of OUD.

Once informed consent is obtained, patients will undergo additional screening to determine if they are eligible to participate in the study based on the inclusion/exclusion criteria

5.0 Consent Process and Documentation

5.1 Consent Process:

Check all applicable boxes below:

☒ **Informed consent will be sought and documented with a written consent form *[Complete Sections 5.2 and 5.6]***

☐ **Implied or verbal consent will be obtained – subjects will not sign a consent form (waiver of written documentation of consent) *[Complete Sections 5.2, 5.3 and 5.6]***

☐ **Informed consent will be sought but some of the elements of informed consent will be omitted or altered (e.g., deception). *[Complete section 5.2, 5.4 and 5.6]***

☐ **Informed consent will not be obtained – request to completely waive the informed consent requirement.** ***[Complete Section 5.5]***

5.2 Obtaining Informed Consent

5.2.1 Timing and Location of Consent

An IRB-approved study team member will meet with the subject in a quiet private area. After careful and complete explanation of the study details, risks, and other options are provided to the subject, and a copy of the consent form will be provided to them for review. If they are interested in consenting to this study, they will be given additional time to ask questions. When all questions have be answered to their satisfaction by a study team member, the subject will be asked to sign the informed consent document.

5.2.2 Coercion or Undue Influence during Consent

During the initial consultation session, the IRB-approved physician/staff member will briefly explain the proposed study and ask the patient if they would be interested in discussing further with a research study member. If the patient is interested, a trained research study team member will discuss the full study including any risks and benefits associated with participation.

To ensure the consent process provides the patient with clear, accurate information, research staff involved in the consent process will undergo training to promote effective conversations as well as training on study-specific details.

Study team members will stress that participation is completely voluntary. Additionally, it will be carefully and clearly explained that if they should decide not to participate in this study, that decision will have no impact on the care the patient will receive.

Due to a conflict of interest by Dr. Bunce, informed consent for the study will be obtained by a non-conflicted, IRB-approved co-investigator or study coordinator, but he may be involved in the explanation of the protocol and its risks and benefits, answering patient questions, and in assuring that subjects meet the study entry criteria.

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5.3 Waiver of Written Documentation of Consent

Not applicable

5.3.1 Indicate which of the following conditions applies to this research:

☐ The research presents no more that minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

OR

☐ The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern.

OR

☐ If the subjects or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained.

Describe the alternative mechanism for documenting that informed consent was obtained:

5.3.2 Indicate what materials, if any, will be used to inform potential subjects about the research (e.g., a letter accompanying a questionnaire, verbal script, implied consent form, or summary explanation of the research)

5.4 Informed consent will be sought but some of the elements of informed consent will be omitted or altered (e.g., deception).

Not applicable

5.4.1 Indicate the elements of informed consent to be omitted or altered
5.4.2 Indicate why the research could not practicably be carried out without the omission or alteration of consent elements
5.4.3 Describe why the research involves no more than minimal risk to subjects.
5.4.4 Describe why the alteration/omission will not adversely affect the rights and welfare of subjects.
5.4.5 If the research involves using identifiable private information or identifiable biospecimens, describe why the research could not be practicably be carried out without using such information or biospecimens in an identifiable format.
5.4.6 Debriefing

5.5 Informed consent will not be obtained – request to completely waive the informed consent requirement

Not applicable

5.5.1 Indicate why the research could not practicably be carried out without the waiver of consent
5.5.2 Describe why the research involves no more than minimal risk to subjects.
5.5.3 Describe why the alteration/omission will not adversely affect the rights and welfare of subjects.
5.5.4 If the research involves using identifiable private information or identifiable biospecimens, describe why the research could not be practicably be carried out without using such information or biospecimens in an identifiable format.
5.5.5 Additional pertinent information after participation

5.6 Consent – Other Considerations

5.6.1 Non-English-Speaking Subjects
Not applicable

5.6.2 Cognitively Impaired Adults
Not applicable

5.6.2.1 Capability of Providing Consent
5.6.2.2 Adults Unable to Consent
5.6.2.3 Assent of Adults Unable to Consent

5.6.3.1 Parental Permission
5.6.3.2 Assent of subjects who are not yet adults

6.0 HIPAA Research Authorization and/or Waiver or Alteration of Authorization

6.1 Authorization and/or Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

Check all that apply:

☐ **Not applicable, no identifiable protected health information (PHI) is accessed, used or disclosed in this study.** *[Mark all parts of sections 6.2 and 6.3 as not applicable]*

☒ **Authorization will be obtained and documented as part of the consent process.** *[If this is the only box checked, mark sections 6.2 and 6.3 as not applicable]*

☒ **Partial waiver is requested for recruitment purposes only (Check this box if patients' medical records will be accessed to determine eligibility before consent/authorization has been obtained).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Full waiver is requested for entire research study (e.g., medical record review studies).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Alteration is requested to waive requirement for written documentation of authorization (verbal authorization will be obtained).** *[Complete all parts of sections 6.2 and 6.3]*

6.2 Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

6.2.1 Access, use or disclosure of PHI representing no more than a minimal risk to the privacy of the individual

6.2.1.1 Plan to protect PHI from improper use or disclosure

Information is included in the "Confidentiality, Privacy and Data Management" section of this protocol.

6.2.1.2 Plan to destroy identifiers or a justification for retaining identifiers

Minimal screening activities prior to consent may include accessing patient charts to confirm eligibility. No identifiers will be retained for any patient who does not meet eligibility requirements to participate in the study.

6.2.2 Explanation for why the research could not practicably be conducted without access to and use of PHI

Information must be obtained from the subject's electronic medical record at Caron during recruitment to determine eligibility and, in some cases, to confirm information discussed with the subject in regard to their medical history.

6.2.3 Explanation for why the research could not practicably be conducted without the waiver or alteration of authorization

The waiver is requested only for recruitment to determine subject eligibility to ensure that no medical conditions that fall into the exclusion criteria are present and would thus preclude enrollment. This waiver will minimize the enrollment of subjects who may ultimately fail to meet the study inclusion/exclusion criteria.

6.3 Waiver or alteration of authorization statements of agreement

Protected health information obtained as part of this research will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other permitted uses and disclosures according to federal regulations.

The research team will collect only information essential to the study and in accord with the 'Minimum Necessary' standard (information reasonably necessary to accomplish the objectives of the research) per federal regulations.

Access to the information will be limited, to the greatest extent possible, within the research team. All disclosures or releases of identifiable information granted under this waiver will be accounted for and documented.

7.0 Study Design and Procedures

7.1 Study Design

Double-blinded, randomized, placebo-controlled pilot study to evaluate the effects of the GLP-1R agonist liraglutide treatment on drug craving in patients initiating residential treatment for OUD. In addition, the safety and feasibility of using GLP-1R agonist treatment in residential OUD patients will be established.

Study enrollment will not delay administration of standard of OUD therapies, such as behavioral treatments and/or buprenorphine/naloxone.

All participants, at the time of consent, will be enrolled in the 3-dose study procedure which takes 21 days to complete. As the vast majority of Caron patients remain in treatment for 28 days, the 3-dose procedure allows for the largest recruitment pool possible and provides a common procedure that all participants will complete. By Day 18 of the 3-dose procedure, participants will be asked whether they are able to, and willing to, continue the study for an additional 12 days (past Day 21) and receive 2 additional doses of the treatment medication (now considered the 5-dose study procedure). It is expected that not all participants will be willing or able to extend their study participation; additionally participants may either know their expected length of stay early (i.e., at admission to residential treatment) or not until close to completion of treatment. The decision to transition into the 5-dose procedure will be based on the participant's availability (i.e., whether the stay in treatment at Caron will be longer than the average 28 days) and on the participant's choice to extend their length of study participation.

7.2 Study Procedures

- **Physical and Psychological Screening Procedures:** The screening will include:
  - 12-lead electrocardiogram (EKG)
  - Urine pregnancy test if female with childbearing potential
  - Psychiatric assessment including: the M.I.N.I International Neuropsychiatric Interview (M.I.N.I. 7.0.2), Form 90-Drug Inventory (Form 90-DI), Hamilton Depression scale (HAM-D), State-Trait Anxiety Inventory (STAI-Y1), and Columbia Suicide Severity Rating Scale (C-SSRS)

    The C-SSRS will be administrated by appropriately trained personnel. All C-SSRS scores will be reported to the Caron Treatment Center Medical Director of Research and the Director of Research. At risk participants will be immediately reported to the Directors of Research. Any participant that reports recent suicidal ideation or behavior on the screening C-SSRS will be referred for further immediate evaluation by a clinician. Clinical judgement and additional consult with the Caron Medical Director, study PI, and/or study staff will be used to further clarify if the subject is eligible to continue in the study. Participants not at risk will be reported weekly.

    The Directors will refer the clinical decision to the psychology and medical team. If the patient is deemed to be suicidal, and is willing to get help, the psychology staff will utilize their typical protocol and resources to find placement in a local psychiatric facility (e.g., Philhaven, Lancaster Behavioral Health). The patient may be transported via ambulance or via Caron transportation (depending on how safe staff feels it is to transfer) to the facility for admission. In the case that the participant is uncooperative, Service Access and Management, Inc. (SAM) will be notified to assist with emergency planning. Any participant who develops active suicidal ideation with some intent to act with or without a specific plan will be discontinued from study treatment.

- **Body Weight:** Body weight will be measured daily throughout the study (Days 1-21 [Days 1-33 for 5-dose intervention]).

- **Blood glucose**:
    - Blood samples to assess changes in more long-term indices of glycemic control, such as hemoglobin A1c (HbA_{1c}) and fructosamine, will be collected prior to the first dose of study drug (Day 2) and at the end of the target dose (Day 19 [and additionally at Day 31 for 5-dose intervention]). Samples will be analyzed by Caron's clinical laboratory.

- **Cardiorespiratory Function:** Recordings will be collected using a portable cardiovascular autonomic cart at CaronTC. The data will be recorded via a data acquisition system (PowerLab, ADInstruments). After instrumentation, participants will rest for 10 minutes, followed by 15 minutes of continuous recordings of cardiorespiratory parameters.
    - Blood pressure, heart rate, and respiratory rate will be measured at baseline (Day 1), during study drug administration (Days 2, 8, 14, 19, 20, 26, and 31), and at the end of rebound follow-up (Day 21 [Day 33 for 5-dose intervention]). At each of these time points, participants will be placed in the supine position.
        - Blood pressure will be measured continuously using the finger volume clamp method (NOVA Finapres Medical Systems or similar) and intermittently by an oscillometric brachial artery cuff (Philips SureSigns VS3 or similar).
        - A 3-lead EKG will be used to continuously measure heart rate (Cardiocap/5 GE Healthcare or similar).
        - Respiratory rate will be measured using a pneumography belt, and oxygen saturation by pulse oximeter applied to the finger (BCI 3301 or similar).

- **Cue-elicited drug craving will be evaluated.** This will be evaluated using Visual Analog Scales (VAS) on Day 1 and Day 19 [and additionally at Day 31 for 5-dose intervention].
    - Cue-elicited craving will be measured on a 0-100 point VAS, where 0= no craving, 100 = maximum craving. Assessments will be taken prior to, and immediately after, exposure to visual drug cues in the Cue Response Task.

- **Ecological Momentary Assessment (EMA):** EMA data will be collected throughout the study (Days 1-21 [Days 1-33 for 5-dose intervention]) 4 times per day via smartphones for the first 3 days (Days 1-3) and then on a rotating "4-days on, 2-days off" schedule starting Day 6. Data to be collected include: Ambient Drug Craving; Positive and Negative Mood; Pain/Discomfort; and Sleep on 0-100 point VAS.

  The smartphones that will be used for EMA data collection will have an app (the Wear-IT app) that will be put on the study smartphone provided to the participant while they are in the study. This smartphone will have a security application installed that prevents user access to all other applications that are not associated with data collection. Smartphones will not be activated on a cellular network resulting in the disabling of voice, text, and internet functions. Research staff will use brief in-person meetings (every other day) as a means to ensure devices are being charged, build rapport, answer participant questions, monitor compliance, and to manually download data for backup storage for upload to a secure server, Virtual COLO, at University Park in State College. Participants will need to plug the phone in to charge each night.

- **Physiological Wearables:** A "wearable" wristband will be worn throughout the study (Days 1-21 [Days 1-33 for 5-dose intervention]) to monitor stress responses, including acute

changes that may be associated with the drug delivery via injection. Data collected include heart rate, actigraphy for sleep and activity measurement, and stress responses (including acute changes in these measures that may be associated with the drug delivery via injection). A body temperature compliance sensor will be used to validate that the device is being worn. So that participants do not have to charge the actigraphy wristband themselves, participants will have up to two actigraphy wristbands assigned to them, and they will be charged or, if necessary, swapped out at their check-in sessions. Participants may wear the actigraphy wristband while showering or swimming if they wish.

- **Neurophysiology Lab Day Measures:** Participants will be tested at baseline (Day 1) and at the end of the target dose (Day 19 [and additionally Day 31 for 5-dose intervention]) for cortical activity using Functional Near Infrared Spectroscopy (fNIRS) and VAS during:
    - Visual cue reactivity task to: (a) opioid cues; (b) non-opioid control cues; (c) natural reward cues (e.g., pleasant pictures of food, puppies, positive relationships, etc.) and (d) emotionally neutral stimuli (e.g., images of household objects)
    - The VAS measure of craving pre-post visual cue reactivity task
    - Balloon Analogue Risk Task (BART)

  fNIRs data files will be placed into the REDCap database, with access to these files provided to key investigators at Drexel University for signal processing and return for data analyses. These data will be de-identified and will consist only of the unique study id number, raw data, stimulus markers, and date/time stamps that have been modified so that they do not contain the actual visit date.

- **Study drug/placebo administration:** Participants will be taught self-administration by study/nursing staff.
    - All self-administrations will occur via blinded, multi-dose subcutaneous injection pens, and will be observed by nursing staff at CaronTC.
    - Participants will receive medications daily at a specified time (prior to breakfast) throughout the study, starting on Day 2.
    - Participants will be taught to inject the solutions subcutaneously in the abdomen, thigh, or upper arm, and will administer daily injections under the supervision of a study nurse or staff member.
    - Participants will be taught by study staff nurses to attach the needle, check the drug/vehicle flow, select the dose, inject the dose, remove the needle, and dispose of the needle.
    - Participants will always use a new needle for each dose administration in the study.

- **Adverse Events:** Adverse events will be monitored continuously throughout the study (Days 1-21 [Days 1-33 for 5-dose intervention]), and at 30 days post-intervention (Day 49 [Day 61 for 5-dose intervention]).

7.2.1 Enrollment and Baseline (Day 1)

Participants will be approached within 2-3 days of beginning residential treatment based on initial screening from EMR and enrolled into the study if they consent.

The following **standard of care data** will be collected from the EMR for research purposes:

- Demographic information (age, gender, race, contact information)
- Detailed medical history
- Physical examination
- Admission diagnoses

- Results from standard laboratory safety tests performed on admission (complete blood count, comprehensive metabolic panel)
- Current medication usage (concomitant medications)
- Results of urine pregnancy test at admission (if applicable)

The following **research-only activities** will be performed prior to randomization**:**

- A psychiatric assessment will be conducted:
  - M.I.N.I. 7.0.2
  - Form 90-DI
  - HAM-D
  - STAI-Y1
  - C-SSRS
- Body weight will be measured
- 12-lead EKG will be performed
- Collection of stress response, sleep, and activity measurements will be initiated via actigraphy wristband (a "wearable" wristband).

Any participant that reports recent suicidal ideation or behavior on the screening C-SSRS will be referred for further immediate evaluation by a clinician. Clinical judgement and additional consult with the Caron Medical Director, study PI, and/or study staff will be used to further clarify if the subject is eligible to continue in the study.

Participant will receive the actigraphy wristband from a study coordinator. The study coordinator will instruct the subject on use of the actigraph.

Randomization: After obtaining written consent, subjects who fulfill study criteria will be randomized to either the liraglutide or placebo treatment arm of the study using an equal allocation ratio (1:1) permuted-block randomization.

The following **research-only activities** will occur after randomization and will serve as baseline values to compare with values obtained after study drug dosing:

- Cue-elicited drug craving will be evaluated using VAS.
- Neurophysiology measurements using fNIRS and VAS.
- Collection of ambient drug craving, mood, and sleep data will be initiated with EMA.
- Monitoring of body weight and cardiorespiratory function.
- Aes and concomitant medications will be documented.

Collection of blood pressure, heart rate and respiratory rate data will be initiated with cardiorespiratory testing performed by study staff.

Collection of ambient drug craving, mood, and sleep data will be initiated with EMA. Participant will use the smartphone containing EMA surveys they received prior to randomization. A study coordinator will instruct the subject on use of the phone.

Cue-elicited drug craving will be evaluated by a study coordinator using VAS.

7.2.2 Study Drug Treatment, Dose 1 (Days 2-7)

During this time, the following **research-only activities** will occur:

- Blood samples will be collected on Day 2, prior to study drug administration, for monitoring of glycemic control. This will include measurements of HbA1c and fructosamine. Approximately 2 teaspoons of blood will be collected.

- During Days 2-7, liraglutide/placebo control will be administered daily at 0.6 mg before breakfast.
- Aes and concomitant medications will be documented.
- Ambient drug craving, mood, and sleep data will be collected on Days 2, 3, 6, and 7 via EMA assessment.
- Stress response, sleep, and activity measurements will be collected daily via actigraphy wristband.
- Body weight data will be collected daily.
- On Day 2, cardiorespiratory function will be measured as described in Section 7.2.

Subjects will be taught administration of liraglutide by a Caron nurse on Day 2 during the first injection of the lowest dose. Repeated instruction on liraglutide administration may be provided on subsequent drug administration days if requested by the participant until they are comfortable with the procedure.

7.2.3 Study Drug Treatment, Dose 2 (Days 8-13)

During this time, the following **research-only activities** will occur:

- During Days 8-13, 1.2 mg of liraglutide/placebo control will be administered daily at a specified time (prior to breakfast).
- Aes and concomitant medications will be documented.
- Ambient drug craving, mood, and sleep data will be collected on Days 8, 9, 12, and 13 via EMA assessment.
- Stress response, sleep, and activity measurements will be collected daily via actigraphy wristband.
- Body weight data will be collected daily.
- On Day 8, cardiorespiratory function will be measured as described in Section 7.2.

7.2.4 Study Drug Treatment, Dose 3 (Days 14-18)

During this time, the following **research-only activities** will occur:

- During Days 14-19, 1.8 mg of liraglutide/placebo control will be administered daily at a specified time (prior to breakfast).
- Aes and concomitant medications will be documented.
- Ambient drug craving, mood, and sleep data will be collected on Days 14, 15, and 18 via EMA assessment.
- Stress response, sleep, and activity measurements will be collected daily via actigraphy wristband.
- Body weight data will be collected daily.
- On Day 14, cardiorespiratory function will be measured as described in Section 7.2.

7.2.5 Study Test Day – (Day 19)

The following **research-only** measures, all completed on Day 1, will be repeated on Day 19, regardless of intervention length (i.e., 3-dose and 5-dose interventions). Day 19 will serve as the final dose (1.8 mg) day for participants in the 3-dose intervention. For participants in the 5-dose intervention, Day 19 will be the final day at the 1.8 mg dose before moving on to the 2.4 mg dose on Day 20.

- Cardiorespiratory function will be assessed via measurement of blood pressure, heart rate, and respiratory rate as described in Section 7.2.
- Blood samples will be collected for safety laboratory tests (CBC, CMP) and for monitoring of glycemic control. Approximately 4 teaspoons of blood will be collected.
- Body weight data will be collected.

- Cue-elicited drug craving will be evaluated using VAS.
- Neurophysiology measurements will be evaluated using fNIRS during: (1) Visual cue reactivity and (2) BART.
- Collection of ambient drug craving, mood, and sleep data by EMA.
- Stress response, sleep, and activity measurements will be collected via actigraphy wristband.
- C-SSRS
- Urine pregnancy test (if applicable)
- Aes and concomitant medications will be documented.

7.2.6 Days 20-21

For 3-dose intervention participants: Rebound Evaluation Period

During this time the following **research-only** measures will occur:

- Collection of ambient drug craving, mood, and sleep data by EMA through Day 21, then discontinued.
- Stress response, sleep, and activity measurements will be collected via actigraphy wristband through Day 21, then discontinued.
- Aes and concomitant medications will be documented through Day 21.
- Body weight data will be collected through Day 21.
- On Day 21, cardiorespiratory function will be measured as described in Section 7.2.

The smartphone and actigraphy wristband will be collected by a study coordinator on Day 22.

For 5-dose intervention participants: Study Drug Treatment, Dose 4

During this time, the following **research-only activities** will occur:

- During Days 20-21, 2.4 mg of liraglutide/placebo control will be administered daily at a specified time (prior to breakfast).
- Aes and concomitant medications will be documented.
- Ambient drug craving, mood, and sleep data will be collected on Days 20-21 via EMA assessment.
- Stress response, sleep, and activity measurements will be collected daily via actigraphy wristband.
- Body weight data will be collected daily.

On Day 20, cardiorespiratory function will be measured as described in Section 7.2.

7.2.7 Study Drug Treatment, Dose 4 (Days 22-25) [5-dose intervention only]

During this time, the following **research-only activities** will occur:

- During Days 22-25, 2.4 mg of liraglutide/placebo control will be administered daily at a specified time (prior to breakfast).
- Aes and concomitant medications will be documented.
- Ambient drug craving, mood, and sleep data will be collected on Days 24 and 25 via EMA assessment.
- Stress response, sleep, and activity measurements will be collected daily via actigraphy wristband.
- Body weight data will be collected daily.

7.2.8 Study Drug Treatment, Dose 5 (Days 26-30) [5-dose intervention only]

During this time, the following **research-only activities** will occur:

- During Days 26-31, 3.0 mg of liraglutide/placebo control will be administered daily at a specified time (prior to breakfast).
  - Aes and concomitant medications will be documented.

- Ambient drug craving, mood, and sleep data will be collected on Days 26, 27, and 30 via EMA assessment.
- Stress response, sleep, and activity measurements will be collected daily via actigraphy wristband.
- Body weight data will be collected daily.
- On Day 26, cardiorespiratory function will be measured as described in Section 7.2.

7.2.9 Study Test Day – (Day 31) [5-dose intervention only]

The following **research-only** measures, all completed on Day 1 and Day 19, will be repeated on Day 31.

- Cardiorespiratory function will be assessed via measurement of blood pressure, heart rate, and respiratory rate as described in Section 7.2.
- Blood samples will be collected for safety laboratory tests (CBC, CMP) and for monitoring of glycemic control. Approximately 4 teaspoons of blood will be collected.
- Body weight data will be collected.
- Cue-elicited drug craving will be evaluated using VAS.
- Neurophysiology measurements will be evaluated using fNIRS during: (1) Visual cue reactivity and (2) BART.
- Collection of ambient drug craving, mood, and sleep data by EMA.
- Stress response, sleep, and activity measurements will be collected via actigraphy wristband.
- C-SSRS
- Urine pregnancy test (if applicable)
- Aes and concomitant medications will be documented.

7.2.10 Rebound Evaluation Period, (Days 32-33) [5-dose intervention only]

During this time the following **research-only** measures will occur:

- Collection of ambient drug craving, mood, and sleep data by EMA through Day 33, then discontinued.
- Stress response, sleep, and activity measurements will be collected via actigraphy wristband through Day 33, then discontinued.
- Aes and concomitant medications will be documented through Day 33.
- Body weight data will be collected through Day 33.
- On Day 33, cardiorespiratory function will be measured as described in Section 7.2.

The smartphone and actigraphy wristband will be collected by a study coordinator on Day 34.

7.2.11 End of Study telephone call (Day 49 [Day 61 for 5-dose intervention])

All participants will have an End of Study telephone call. This will occur 30 days (+/- 5 days) from the discontinuation of medication. Patients will be asked to self-report their body weight at the time of the call.

Schedule of Study Activities: 3-Dose Study Drug Intervention

	Enrollment/ Baseline	Intervention			Test Day (Final dose)	Off Drug	Rebound Evaluation	Equipment Return	End of Study Telephone Call**
	Day 1	**Days 2-7**	**Days 8-13**	**Days 14-18**	**Day 19**	**Day 20**	**Day 21**	**Day 22**	**30 days +/- 5 days end of medication**
Study Drug/Placebo Dose		0.6 mg	1.2 mg	1.8 mg	1.8 mg	-		-	
Informed consent	X								
Data collected from Electronic Medical Record[1]	X								
M.I.N.I International Neuropsychiatric Interview (M.I.N.I. 7.0.2)	X								
Form 90-Drug Inventory (Form 90-DI)	X								
Hamilton Depression scale (HAM-D)	X								
State-Trait Anxiety Inventory (STAI-Y1)	X								
Columbia Suicide Severity Rating Scale (C-SSRS)	X				X				
Body weight	X	X	X	X	X	X	X		X
12-lead electrocardiogram (EKG)	X								
Pregnancy test[2]	X				X				
Cardiorespiratory function assessment[3]	X	X	X	X	X		X		
Blood samples for fructosamine and A1c		X[4]			X				
Cue-elicited drug craving[5]	X*				X				

	Enrollment/ Baseline	Intervention			Test Day (Final dose)	Off Drug	Rebound Evaluation	Equipment Return	End of Study Telephone Call**
	Day 1	**Days 2-7**	**Days 8-13**	**Days 14-18**	**Day 19**	**Day 20**	**Day 21**	**Day 22**	**30 days +/- 5 days end of medication**
Study Drug/Placebo Dose		0.6 mg	1.2 mg	1.8 mg	1.8 mg	-		-	
Neurophysiology measurements[6]	X*				X				
Safety labs (CBC and CMP)					X				
Ambient drug craving, mood, and sleep[7]	X*	X	X	X	X	X	X		
Actigraphy wristband ("wearable" wristband)[8]	X	X	X	X	X	X	X		
Concomitant medications	X*	X	X	X	X	X	X		
Adverse events	X*	X	X	X	X	X	X		X
Return of actigraphy wristband and smartphone								X	

*Performed AFTER randomization has occurred.
**ALL participants, unless they withdraw consent, will have an end of study telephone call.

[1]Demographics, medical history, admission diagnoses, and current medication usage.
[2]If female with childbearing potential, will collect results from test at admission as data for Day 1, with research-only pregnancy tests at Day 19.
[3]Performed on Day 1, Day 2, Day 8, Day 14, Day 19, and Day 21.
[4]Performed on Day 2 only
[5]Using Visual Analog Scales (VAS).
[6]Using fNIRS, VAS, and BART.
[7]Collection of ambient drug craving, mood, and sleep data will be initiated with Ecological Momentary Assessment (EMA). Collected on Days 1-3, 6-9, 12-15, and 18-21.
[8]Stress response, sleep, and activity measurements.

Schedule of Study Activities: 5-Dose Study Drug Intervention

	Enrollment/ Baseline	Intervention						Test Day (Final dose)	Off Drug	Rebound Evaluation	Equipment Return	End of Study Telephone Call**
	Day 1	Days 2-7	Days 8-13	Days 14-18	Day 19	Days 20-25	Days 26-30	Day 31	Day 32	Day 33	Day 34	30 days +/- 5 days end of medication
Study Drug/Placebo Dose		0.6 mg	1.2 mg	1.8 mg	1.8 mg	2.4 mg	3.0 mg	3.0 mg	-		-	
Informed consent	X											
Data collected from Electronic Medical Record[1]	X											
M.I.N.I International Neuropsychiatric Interview (M.I.N.I. 7.0.2)	X											
Form 90-Drug Inventory (Form 90-DI)	X											
Hamilton Depression scale (HAM-D)	X											
State-Trait Anxiety Inventory (STAI-Y1)	X											
Columbia Suicide Severity Rating Scale (C-SSRS)	X				X			X				
Body weight	X	X	X	X	X	X	X	X	X	X		X
12-lead electrocardiogram (EKG)	X											
Pregnancy test[2]	X				X			X				
Cardiorespiratory function assessment[3]	X	X	X	X	X	X	X	X		X		
Blood samples for fructosamine and A1c		X[4]			X			X				
Cue-elicited drug craving[5]	X*				X			X				

	Enrollment/ Baseline	Intervention						Test Day (Final dose)	Off Drug	Rebound Evaluation	Equipment Return	End of Study Telephone Call**
	Day 1	Days 2-7	Days 8-13	Days 14-18	Day 19	Days 20-25	Days 26-30	Day 31	Day 32	Day 33	Day 34	30 days +/- 5 days end of medication
Study Drug/Placebo Dose		0.6 mg	1.2 mg	1.8 mg	1.8 mg	2.4 mg	3.0 mg	3.0 mg	-		-	
Neurophysiology measurements[6]	X*				X			X				
Safety labs (CBC and CMP)					X			X				
Ambient drug craving, mood, and sleep[7]	X*	X	X	X	X	X	X	X	X	X		
Actigraphy wristband ("wearable" wristband)[8]	X	X	X	X	X	X	X	X	X	X		
Concomitant medications	X*	X	X	X	X	X	X	X	X	X		
Adverse events	X*	X	X	X	X	X	X	X	X	X		X
Return of actigraphy wristband and smartphone											X	

*Performed AFTER randomization has occurred.
**ALL participants, unless they withdraw consent, will have an end of study telephone call.

[1]Demographics, medical history, admission diagnoses, and current medication usage.
[2]If female with childbearing potential, will collect results from test at admission as data for Day 1, with research-only pregnancy tests at Day 19 and Day 31.
[3]Performed on Day 1, Day 2, Day 8, Day 14, Day 19, Day 20, Day 26, Day 31, and Day 33.
[4]Performed on Day 2 only
[5]Using Visual Analog Scales (VAS).
[6]Using fNIRS, VAS, and BART.
[7]Collection of ambient drug craving, mood, and sleep data will be initiated with Ecological Momentary Assessment (EMA). Collected on Days 1-3, 6-9, 12-15, 18-21, 24-27, and 30-33.
[8]Stress response, sleep, and activity measurements.

7.3 Duration of Participation

The total duration of study participation for each subject will be approximately 49 days (3-dose intervention) or 61 days (5-dose intervention).

7.4 Test Article(s) (Study Drug(s) and/or Study Device(s))

7.4.1 Description

Liraglutide (Saxenda®, Novo Nordisk) is a glucagon-like peptide-1 (GLP-1) receptor agonist approved by the FDA for the treatment of T2DM (1.8 mg/day) and obesity (3.0 mg/day) and has been deemed safe for use in populations with a history of substance use disorder (American Association of Clinical Endocrinologists, 2016; see also Saxenda package insert, Plainsboro, NJ: Novo Nordisk A/S; 2015).

Liraglutide 6 mg/ml (Novo Nordisk), will be provided as a solution in a pre-filled, multi-dose pen that delivers doses of 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg, or 3 mg of liraglutide as a subcutaneous injection.

Liraglutide and placebo will be delivered as a solution (liquid) in identical multidose pens. In order to use Saxenda® as a blinded comparator in the clinical trial, the presentation has been modified from the Marketed product. For Saxenda® (Comparator) the primary packaging materials are identical to what is approved in the Marketing authorization, except that the cartridge for the comparator is produced with an army green closure cap. The closure cap in the currently marketed Saxenda® product is a light blue cap. The cap is not in contact with the product and has no impact on the stability of the comparator. For Saxenda® (Comparator) the pen is identical to what is approved in the Marketing Authorization, except for the color of the cartridge holder and the pushbutton, where the Marketed version is purple and the clinical comparator is light brown. The pen is not in contact with the product and its color has no impact on the stability of the comparator.

New, unused liraglutide/vehicle pens will be stored according to the information stated on the trial product label. Pens will be disposed of after 30 days of initial use.

7.4.2 Treatment Regimen

The recommended maximum dosage is 3 mg/day, administered any time of day. This choice in dosage is based on the current FDA-approved dosing regimen for liraglutide to help patients manage craving in obesity. The initial dose will start at 0.6 mg/day for the first 6 days, then titrate by 0.6 mg every 6 days – to reduce the likelihood of adverse gastrointestinal symptoms – until 1.8 mg/day is reached for the 3-dose intervention and 3 mg/day is reached for the 5-dose intervention. Participants will be taught self-administration by study/nursing staff. All self-administrations will occur via blinded, multi-dose subcutaneous injection pens, and will be observed by nursing staff at CaronTC.

Participants will receive medications daily at a specified time (prior to breakfast) throughout the study. Participants will be taught to inject the solutions subcutaneously in the abdomen, thigh, or upper arm, and will administer daily injections under the supervision of a study nurse or staff member. Participants will be taught by study staff nurses to attach the needle, check the drug/vehicle flow, select the dose, inject the dose, remove the needle, and dispose of the needle. Participants will always use a new needle for each dose administration in the study. Dosages will be chosen based on current titration level in the study.

There is no provision to provide study treatment after the study.

7.4.3 Method for Assigning Subject to Treatment Groups

Participants will receive either liraglutide or placebo in a two-arm parallel group study. Interventions will be randomized in a 1:1 ratio using permuted-block randomization algorithm. The randomization will be performed using a random number generator via the PLAN procedure within SAS software, version 9.4 (SAS Institute Inc., Cary, NC). Personnel in the Department of Public Health Sciences (PHS) will use the PLAN procedure within SAS software to generate a randomization list using variable-size, random permuted blocks to ensure that the number of participants in each arm is balanced after each set of B randomized participants, where B is the block size. Personnel in PHS will choose the block sizes without revealing it to any of the investigators or study personnel who will be collecting and reviewing outcomes data. The randomization sequence will be uploaded to a secure REDCap database. Synergy Pharmacy will be given access to this REDCap database to provide the blinded, randomized labeling prior to shipping the study drugs to the CaronTC

7.4.4 Subject Compliance Monitoring

Nursing staff will chart administration of study drug into the patient's Caron EMR and study personnel will monitor and document the completion of all study procedures. Compliance is also being assessed through the wearables discussed above (Section 7.2) by a temperature sensor.

7.4.5 Blinding of the Test Article

The study drugs will be blinded to participants and investigators (double blind) through the distribution of identical injection pens. Injection pens will be ordered from Novo Nordisk and received in boxes by Synergy Pharmacy, an off-site pharmacy that works with the CaronTC. Each study drug pack will be sent to Synergy Pharmacy in a box containing a de-identified label for blinding purposes. Each box will have a specific Dispensing Unit Number (DUN). A total list of the DUNs (Total DUN list; TDL) will be supplied by Novo Nordisk indicating "liraglutide" or "placebo" for each DUNS number.

Unblinded personnel at Synergy Pharmacy will be available to handle the lists that reveal if the blinded product contains liraglutide or placebo. The laboratory staff analyzing the blood samples (as opposed to study coordinators) will be unaware of the condition and the treatment of the participants for whom they will conduct the assays as the samples will be identified only with a study number. The results of the laboratory measurements will not be shared with the treating physicians, and will not impact patient care except in an emergent situation.

7.4.6 Receiving, Storage, Dispensing and Return

7.4.6.1 Receipt of Test Article

The study drug (liraglutide or placebo) will be obtained from Synergy pharmacy after the subject is enrolled into the study. After enrollment, study team members will inform Synergy Pharmacy and will provide the information about study subjects required for dispensing the study drug.

Novo Nordisk will supply the clinical variant of Saxenda® (Comparator) and placebo in a pre-filled, multi-dose pen that delivers doses of 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg, or 3 mg of liraglutide as a subcutaneous injection. Each 1 ml of Saxenda solution contains 6 mg of liraglutide; each pre-filled pen contains a 3 ml solution of Saxenda equivalent to 18 mg of liraglutide.

Upon receipt of study shipments from Synergy, a Caron pharmacy technician will inventory/check the shipment using the shipping invoice to record lot number, expiration date, breakage, storage condition, and total quantities. The shipping invoice will be signed and dated. The shipment will

be refrigerated during shipment, and recorded on the study drug accountability log. The shipping invoice will be filed in the shipping file and the study medication will be placed into appropriate storage conditions.

7.4.6.2 Storage

The storage of the medication will be at the medical detox unit at the CaronTC. In this unit is a locked room (nurses' clinic) that contains a locked refrigerator where the medication will be stored. Therefore, the medication will be double locked. Only Caron nurses will have access to the medication. The study drugs will be refrigerated at 2°C to 8°C during storage. Caron nurses will check and record temperature daily.

7.4.6.3 Preparation and Dispensing

Synergy Pharmacy will prepare and deliver the medication after receiving a scanned signed informed consent from Caron. Synergy Pharmacy will use the randomization log to prepare the study medications for each participant. The study medications will be pre-filled injectable pens that are identically labeled for double blinding. Dispensed study medications will be labeled with the label from the Synergy Pharmacy's Computer System, conforming to state and federal law. The study's required labeling will be attached to the dispensed product in addition to the pharmacy label. No parts of the study's label will be obliterated by the pharmacy label. All study medications will be labeled with the caution, "New Drug- Limited by Federal (or United States) law to investigational use."

The study drug (liraglutide or placebo) will be ordered by the medical staff at Caron, stored in the medical unit, and dispensed using the supplied, pre-filled, multi-dose pens that deliver doses of 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg, or 3 mg of liraglutide as a subcutaneous injection. Study staff will maintain medication logs including information on time of administration, batch number, and expiration date. Study drugs will not be used after the expiration or use-by date.

Study treatment injection pens (liraglutide or placebo) will look identical.

The study drug will be obtained from the study nurse and self-administered by the participant under the observation of the study staff or study nurse.

7.4.6.4 Return or Destruction of the Test Article

Once the study drug is prepared for the subject, it can only be administered to that subject. Final reconciliation of the medication will take place at the CaronTC, if appropriate. The CaronTC performs these procedures according to DEA regulations. Non-controlled substances are stored in locked medical bins, which are then shipped to a company that will safely destroy the medication. Patients who do not complete the entire study will have their medication destroyed via Caron's established medication disposal protocols.

7.4.6.5 Prior and Concomitant Therapy

A concomitant therapy is any medication which is administered between study enrollment and the end of the study drug treatment phase. All concomitant therapies will be monitored daily and recorded at minimum

once weekly by study team members during the duration of the treatment phase with the study drug.

The subjects recruited will be current patients in a residential facility for the treatment of opioid dependence. Since the physicians at Caron will be approving patient eligibility, they will know current and past patient medication regimes. Subjects may be taking concomitant medicines/therapies for various reasons at the treatment center. The pharmacy staff at Caron will also know which medications may not be permitted to take with the medication during the study, due to potential counteracting affects.

Precautions: Saxenda is contraindicated with the use of insulin or any other GLP-1R agonist; the use of these medications are identified in the exclusion criteria.

Respiration and heart rate will be monitored at baseline and following all dosage increases.

8.0 Subject Numbers and Statistical Plan

8.1 Number of Subjects

This study will enroll 50 opioid use disordered patients in residential treatment.

8.2 Sample size determination

This is an exploratory study to accumulate pilot data. The primary endpoint of this study is cue-elicited self-reported craving VAS scores. A sample size of N=20 per group will give 80% power to detect an effect size of 0.91 based on a two-sided two-sample t-test with a significance level of alpha=0.05. Accounting for an estimated 20% attrition rate, we plan to randomize a total of 20*2/0.8=50 patients in the study. To preserve statistical power, the sample will not be balanced with regard to MAT and non-MAT participants.

8.3 Statistical methods

The primary aim is to test whether liraglutide reduces craving in patients recovering from OUD in residential treatment. Analysis of covariance (ANCOVA) will be used to compare liraglutide versus placebo treatment groups controlling for baseline values of craving. Linear mixed effects models for repeated measurements will also be used to evaluate the difference in changes in these primary outcomes between treatment groups. The baseline and post-treatment outcomes are treated as dependent variables in the mixed model. Subjects with missing values can be incorporated in the mixed model analysis when data are missing at random. The moderating effect will be assessed by adding the interaction term between moderator and treatment group in the models.

SAS (version 9.4) and R (version 3.2.5) software will be used for analyses with a significance level of 0.05. Summary statistics including means, medians, ranges, and standard deviations will be computed for each continuous variable and frequencies with percentages for categorical variables. Identified data outliers will be further examined to determine if they are data entry errors, in which case they will be modified when possible; otherwise, values will be kept for final analysis.

Primary outcomes to assess efficacy are: (1) cue-elicited drug craving rated on a 100-pt VAS; and (2) ambient drug craving, derived from EMA of daily craving throughout the study period. Data analyses for cue-elicited craving will consist of a 2 x 2 ANOVA with medication status (pre- vs post-medication) as a within-group variable and medication type (liraglutide vs placebo) as a between-group variable.

Secondary analyses of self-reported craving measures will evaluate the role of MAT, specifically BUP/NA, in these results.

EMA and Wearable Assessment: Ambient drug craving derived from the EMA will be analyzed as a multilevel model in the regression framework and will test effects of medication status within-person and medication type between-person. Secondary analyses of EMA will examine the effect of time (e.g. study day) to identify differences across condition in the rate of decline in craving across time.

Data reduction including derivation of summary features for continuously collected data (e.g., sleep data, physiological data) will be performed before formal statistical analysis. Descriptive analysis will be performed to explore distributions of data and identify potential outliers. Assumptions and goodness of fit of statistical models will be assessed. Missing data, including mobile and ambulatory attrition and drop-out will be examined to ensure the validity of statistical models used. Because ambulatory and mobile monitoring will continue during laboratory assessment days, correlation analyses will be used to confirm the agreement between corresponding measures from the two approaches; this will both speed harmonization for follow-up analyses, and provide additional validation of the measures used in the both cases.

The primary endpoints of the EMA assessment will be the rate of reduction of craving across the approximately 21 day study period in the treatment condition compared to the control condition while controlling for the traditional craving triggers of sleep, stress, hunger, affect, and pain and discomfort. Sleep and activity will be measured using a multimodal approach with self-report via the morning EMA survey and wearable actigraphy to measure and account for subjective biases in sleep timing. Craving reduction will be primarily measured using EMA assessment, and will be modeled using linear mixed models in the multilevel modeling (MLM) framework. In MLM, subject-specific random effects are combined with population-level fixed effects to account for variability both within each individual and between individuals in a manner that allows participants with incomplete data to be included in the model. Craving reduction will be modeled as an effect of time in treatment, and differences in rate of craving reduction will be tested as an interaction between treatment state and time. Drs. Brick, Cleveland, and Kong each have extensive experience analyzing similar data in the multilevel modeling framework.

For secondary safety outcomes, intensive longitudinal methods such as time-varying effect models will be used to assess for changes in continuously measured outcomes (e.g. blood pressure, heart rate, respiratory rate, body weight) to account for repeated measures. The proportion of participants experiencing AE and SAE will be compared between treatments using chi-square analysis.

For exploratory outcomes, analysis of fNIRs-based neuroimaging will utilize a 2 (Medication Status) x 2 (Medication Type) ANOVA to evaluate the change in oxygenation in prefrontal cortex in response to opioid drug cues vs neutral cues, with a region of interest in left middle frontal gyrus. Analysis of safety outcomes from baseline to the end of target dose and to end of rebound follow-up will be analyzed using intensive longitudinal methods similar to the analysis of secondary outcomes. Changes in indices of glycemic control measured at baseline and at end of the target dose (e.g. HgA1c, fructosamine) will be calculated as deltas, with comparisons made between treatments using unpaired t-tests or Mann Whitney U tests as appropriate.

Interim Power Analysis: one or more interim power analyses may be conducted during the study to assess the effect size needed to observe a significant drug effect for primary, secondary, and/or exploratory endpoints based on the data collected at that time. These analyses would not bias type 1 error rates and the study team will use this information to determine whether and when to perform an interim data analysis to justify advancement to the second phase of the funding award (UH phase). In particular, the confidence intervals around the parameters representing the primary endpoint will be used as an approximation of the power available for our primary endpoints using the current data. This

will be weighed against the original proposed power and the PI's estimates of likely power after completion of the grant period to determine whether an interim analysis is warranted.

9.0 Data and Safety Monitoring Plan

9.1 Periodic evaluation of data

To monitor safety throughout the course of the study, every effort will be made to remain alert to possible Aes/SAEs. If an AE/SAE occurs, the first concern should be for the safety of the subject; CaronTC's medical staff is available 24/7 and will be immediately alerted in the event of a SAE. If necessary, appropriate medical intervention will be provided. At the signing of the written consent form, each subject will have been given the names and telephone numbers of study site staff for reporting Aes/SAEs and medical emergencies.

In this study, any AE/SAE experienced by the subject between the time of first dose of study treatment and 24 hours after the last dose will be recorded on the case report form, regardless of the severity of the event or its relationship to study treatment. During study treatment, the research team will assess the subject for Aes and will record any new Aes/SAEs or updates to previously reported Aes on the electronic case report form.

9.2 Data that are reviewed

Data collected as primary outcomes, secondary outcomes, exploratory outcomes, and safety profile for the study will be reviewed. Primary outcomes include cue-elicited drug craving and ambient drug craving. Secondary outcomes include blood pressure, heart rate, respiration, body weight, and AE. Exploratory outcomes include prefrontal cortical response to drug cues, markers of long-term glycemic control and rebound in ambient drug craving, blood pressure, heart rate, and respiration.

9.3 Method of collection of safety information

Safety information will be collected in the REDCap research database throughout the study. The safety of the study drug will be evaluated by clinical assessments and laboratory tests.

9.4 Frequency of data collection

Primary outcome data for cue-elicited drug craving will be collected on the day before drug treatment (Day 1) and Day 19 (additionally Day 31for the 5-dose intervention). Ambient drug craving data will be collected on test days and on the first two days and last 2 days of each treatment dose (Days 1-21 [Days 1-33 for 5-dose intervention]). Secondary outcome data for the physical/psychological screening will be collected on Day 1. Cardiorespiratory function data will be collected periodically throughout the study (Days 1, 2, 8, 14, 19, 21 [5-dose intervention: 1, 2, 8, 14, 20, 26, 31, 33]). HbA1c and fructosamine monitoring (blood draw) data will be collected on Days 2 and 19 [additionally Day 31 for 5-dose intervention]. See also table of study events, section 7.2.

9.5 Individuals reviewing the data

The DSMB will be responsible for safeguarding the interests of participants in this trial. This responsibility will be exercised by providing recommendations for continuation or early termination of the trial, based on assessment of safety. The DSMB may also formulate recommendations related to the selection, recruitment or retention of participants, their management and adherence to protocol-specified interventions, and the procedures for data management and quality control. The DSMB will be advisory to the PI, to the medical monitor (Dr. Jessica Fournier), and to their co-investigators. The PI will be responsible for promptly reviewing and implementing DSMB recommendations.

The DSMB will consist of at least 3 independent experts who have no conflicts of interest. Members of the DSMB will include Dr. Urs Leuenberger, a cardiologist and clinician scientist with expertise in mechanisms of neurocirculatory control, broad clinical experience and a track record of clinical research, translational research, human studies and clinical trials at Penn State University; Dr. Ayesha Siddiqui, a board-certified physician in internal medicine and endocrinology, currently practicing at the Penn State Health Cocoa Outpatient Center; and Dr. Tonya King, a professor in biostatistics in the Public Health Sciences department at the Penn State College of Medicine that has served on many DSMBs for the NIH- or industry-sponsored clinical trials. Representation from the Office of Patient Oriented Research (OPOR) also will participate. The approval of the DSMB will be required for any significant changes in protocol recommended by the clinical Project PI, on consultation with Study Physicians, during the course of the study.

The DSMB membership will be restricted to individuals who have no apparent financial, scientific or regulatory conflicts of interest. DSMB members are expected to declare any other potential conflicts of interest so that other members can judge whether any such conflicts might affect objectivity. Members who develop significant conflicts of interest during the course of the trial are expected to resign from the DSMB. DSMB members are otherwise expected to continue their participation until the trial is closed. If necessary, the PI will appoint replacements for any DSMB members who resign, subject to concurrence of the remaining DSMB members.

9.6 Frequency of review of cumulative data

Safety is constantly monitored during the study and any concerns are brought to the attention of the PI immediately. Summary data will be provided at least once per month to the medical monitor to review recruitment and enrollment, protocol adherence, data quality, and Aes. The Aes will be documented and reported appropriately according to the Human Subjects Protection Office (HSPO) policies and procedures.

The DSMB will meet every 6 months with the PI, or more often if needed. In preparation for these meetings, the PI will provide information by email regarding enrollment, protocol adherence, and data quality. The DSMB will also assess safety data including common and serious AE. In the case of an unanticipated or serious AE, the DSMB will be notified within 24 hours of the PI's notification of the event. The PI will provide the DSMB with a list of non-serious AE during regularly scheduled meetings.

9.7 Statistical tests

For details, see the statistical section under 8.3.

9.8 Suspension of research

After periodic evaluation of study result and safety profile, the PI can terminate the research anytime based on outcomes of periodic safety monitoring and benefit/risk outcomes and would be assessed with the IRB and DSMB.

10.0 Risks

The following risks are associated with the GLP-1R agonist liraglutide during study treatment

Potential risks associated with the study drug: There is a potential risk of experiencing side effects from the investigational drug. Common side effects of liraglutide include: nausea, diarrhea, vomiting, and decreased appetite. These side effects dissipate over time and are minimized with appropriate dose titration. Other potential side effects, though expected to be rare, include: hypoglycemia, constipation, headache, dyspepsia, fatigue, dizziness, abdominal pain, increased lipase, and vaso-vagal response if there is a history of vaso-vagal response. Serious side effects include: risk of thyroid c-cell tumors, acute pancreatitis, acute gallbladder disease, risk of hypoglycemia with concomitant use of anti-diabetic therapy, heart rate increase, renal impairment, and

suicidal behavior and thoughts. There is also potential risk of irritation at the injection site, and increased drug craving in response to needle use.

An allergic reaction to liraglutide can include hives; fast heartbeat, dizziness, trouble breathing or swallowing, and swelling of face, lips, tongue, or throat. There is also potential risk of irritation at the injection site, and increased drug craving in response to needle use. The side effects of acute withdrawal from liraglutide include nausea and vomiting. With a half-life of 13 hours, liraglutide should be completely eliminated in 65 hours, within the 4-day rebound follow-up observation period. Since liraglutide has not been previously used in patients with OUD, it is considered an investigational drug. Since this drug has not been previously given in OUD, there may be risks that are not known at this time.

Overdose of the study drug, according to the literature, is limited to severe nausea and vomiting and occasional abdominal pain and diarrhea. None of the reported cases resulted in hypoglycemia.

Hypoglycemia signs and symptoms

- Feeling shaky
- Being nervous or anxious
- Sweating, chills and clamminess
- Irritability or impatience
- Confusion
- Fast heartbeat
- Feeling lightheaded or dizzy
- Hunger
- Nausea
- Color draining from the skin (pallor)
- Feeling Sleepy
- Feeling weak or having no energy
- Blurred/impaired vision
- Tingling or numbness in the lips, tongue, or cheeks
- Headaches
- Coordination problems, clumsiness
- Difficulty concentrating
- Slurred speech
- Nightmares or crying out during sleep
- Seizures
- Loss of consciousness

Blood Pressure and Heart Rate: Frequent blood pressure measurements with the cuff around the arm or finger may be inconvenient and may produce some discomfort and occasional bruising of the upper arm. There is a minimal risk of skin irritation from the EKG patches.

Blood Sampling: There are minor risks and discomforts associated with blood sampling. We will draw blood from the antecubital veins which may cause a brief period of pain and possibly a small bruise at the site. Occasionally, a person feels faint when their blood is drawn. There is a small risk of bleeding after removal of the needle, which can be prevented by tight compression. Rarely, an infection develops which can be treated. Rarely, a clot could form. It is possible that exposure to needles during blood sampling may serve as a trigger for opioid use for some participants.

Pregnancy: This treatment may hurt an unborn child. Subjects will be advised to use approved birth control such as birth control pills, birth control shots, IUD, diaphragm, or condoms while in this study. Subjects will be instructed to inform us if they become pregnant or father a child while in this study. Women able to become pregnant will have a urine test to make sure they are not pregnant before receiving treatment in this study and

at Day 19 [an additional pregnancy test will be given at Day 31 for the 5-dose intervention]. They will be encouraged to use birth control or refrain from intercourse throughout the study. Study drug will be discontinued in case of pregnancy.

Potential risks associated with exposure to drug-related cues: There is a risk of relapse to those in recovery when they are exposed to drug cues in the cue reactivity task. Participants may experience an increase in craving in response to opioid-related images.

Risks related to exposure to fNIRs: There are no known discomforts or risks associated with the brain imaging study. Risks of fNIRs were previously found to be minimal. FDA approval has been granted for research purposes for the technology that is used in this specific device (FDA 510(K) Numbers K011320; K042501). In this fNIRs Devices system: 1) No voltage in excess of 12.2 volts is available; 2) The sensor pads can be washed, disinfected and autoclaved; 3) The safety of fNIRs for use on brain tissue can be demonstrated by comparing the risks associated with experimental exposure to everyday risks. The instrument used in the current research employs light emitting diodes (LEDs) to generate the near infrared light for measuring changes in hemoglobin. LEDs are electronic devices that are illuminated when electricity is passed through them. LEDs use a semiconductor diode that emits light when charged. There currently exists no specific safety regulations applied to LEDs, although they fall within the Class I standards for safety. In other words, the risks associated with spending 20-30 minutes in a protocol utilizing fNIRs are less than the risks associated with spending an equivalent amount of time in the sunlight in the US without a hat. In summary, exposing the brain to the infrared light generated by these LEDs poses no greater risk than spending an equivalent amount of time (about 1 hour) exposed to sunlight. There is minimal risk of headache from the use of sensors.

Actigraphy/Wearables: There is no known risk to wearing the wrist actigraphs. A minor skin rash may develop from the wristband, but this risk is very slight.

Questionnaires: The interviews and forms are routine, standardized forms for psychology research. They pose no known risks, although certain questions may be mildly upsetting because they may probe sensitive psychological areas and others inquire about family history of medical and psychological illness or alcohol and substance use. Appropriate referrals are offered if areas of concern arise in the course of collecting this information. Research participants are free to skip any questions that make them uncomfortable.

Other risks
There is a risk that blood tests will reveal that patients are positive for hepatitis or HIV. These infections are required by law to be reported to the Pennsylvania Department of Health.

There is a risk of loss of confidentiality if a patient's information or identity is obtained by someone other than the investigators, but precautions will be taken to prevent this from happening. The confidentiality of the patients' electronic data will be maintained as required by applicable law and to the degree permitted by the technology used. Absolute confidentiality cannot be guaranteed.

There is a risk from randomization as patients will be assigned to a treatment program by chance. The treatment a patient receives may prove to be less effective or to have more side effects than the other research treatment or other available treatments.

11.0 Potential Benefits to Subjects and Others

11.1 Potential Benefits to Subjects

It is unclear whether liraglutide treatment will lead to any benefits in study subjects as no data are currently available. However, possible benefits the subject may experience from this research study include the possible reduction of opioid craving, which might improve their day-to-day function, and/or reduce near-term relapse to opioid abuse.

11.2 Potential Benefits to Others

The potential benefit to society and others includes increasing knowledge regarding the effects of liraglutide on clinical outcomes and its effect on the stress-immune response in acute hyperglycemic patients. New knowledge gained from this study could give way to novel treatments to help OUD recovery for a high-risk population.

12.0 Sharing Results with Subjects

Any clinically relevant study results (including, but not limited to, EKG and blood tests) will be shared with subjects and their treating physicians. No other study results of an individual subject's result will be shared with subjects or any treating physician.

13.0 Subject Payment and/or Travel Reimbursements

Participants will be reimbursement for their time in the amount of $25 for the initial evaluation, $50 for the first test day (Day 1, when fNIRs tasks and Cued response assessments are performed), $50 for the 3-5 weeks (approximately 21-33 days) of EMA and physiological measures, $75 for the second test day (Day 19) and $50 for the third test day (Day 31) [5-dose intervention only]; when fNIRs tasks and Cued response assessments are performed), $20 for the rebound follow-up, and $30 for the follow-up phone call, for a total of $250 ($300 for 5-dose intervention). Payments will be titrated relative to the tasks accomplished. Reimbursements will be paid using Target gift cards because neither alcohol nor tobacco products can be purchased at Target.

14.0 Economic Burden to Subjects

14.1 Costs

There will be no added costs to the participants enrolled in this study. Any research-only laboratory tests and data collection procedures completed will be paid for by the research study.

14.2 Compensation for research-related injury

It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to subjects or their insurance carriers.

15.0 Resources Available

15.1 Facilities and locations

All recruitment and study procedures will be performed at the CaronTC, a treatment facility in Wernersville, PA.

15.2 Feasibility of recruiting the required number of subjects

We have previously conducted three successful studies (two involving prescription opioids) at the CaronTC [50-55]. The professionals unit has 12 beds, and has typically had 30%-40% of those beds filled with patients with OUD. In addition, a recent census at CaronTC indicates a total of about 30 patients with OUD per month could be available for recruitment into the study from other units, which should be more than adequate to recruit the required sample size.

15.3 PI Time devoted to conducting the research

The PI has allocated sufficient time to work closely with the study team members. There will be regular meetings with study co-investigators to allow ongoing discussions, interim analyses and to address any operational issues.

15.4 Availability of medical or psychological resources

The CaronTC's Medical staff is available on a 24/7 basis.

15.5 Process for informing Study Team

The research team will be given specific duties to conduct the research study. The study coordinators will be provided with training to conduct the screening process, and instruct participants on how to use the equipment required for the study (actigraphs, smartphones). Staff members and nurses at Caron will be instructed on medication distribution and administration procedures. The PI and/or study coordinator will communicate updates to all team members as they become aware of any changes or updates.

16.0 Other Approvals

16.1 Other Approvals from External Entities

National Institute of Health (completed and approved)

16.2 Internal PSU Committee Approvals

Check all that apply:

☐ Anatomic Pathology – **Penn State** Health **only** – Research involves the collection of tissues or use of pathologic specimens. Upload a copy of "HRP-902 – Human Tissue For Research Form" in CATS IRB.

☐ Animal Care and Use – **All campuses** – Human research involves animals and humans or the use of human tissues in animals

☐ Biosafety – **All campuses** – Research involves biohazardous materials (human biological specimens in a PSU research lab, biological toxins, carcinogens, infectious agents, recombinant viruses or DNA or gene therapy).

☐ Clinical Laboratories – **Penn State Health only** – Collection, processing and/or storage of extra tubes of body fluid specimens for research purposes by the Clinical Laboratories; and/or use of body fluids that had been collected for clinical purposes but are no longer needed for clinical use. Upload a copy of "HRP-901 – Human Body Fluids for Research Form" in CATS IRB.

☐ Clinical Research Center (CRC) Advisory Committee – **All campuses** – Research involves the use of CRC services in any way.

☒ Conflict of Interest Review – **All campuses** – Research has one or more of study team members indicated as having a financial interest.

☐ Radiation Safety – **Penn State Health only** – Research involves research-related radiation procedures. All research involving radiation procedures (standard of care and/or research-related) must upload a copy of "HRP-903 – Radiation Review Form" in CATS IRB.

☐ IND/IDE Audit – **All campuses** – Research in which the PSU researcher holds the IND or IDE or intends to hold the IND or IDE.

☒ Scientific Review – **Penn State Health only** – All investigator-written research studies requiring review by the convened IRB must provide documentation of scientific review with the IRB submission. The scientific review requirement may be fulfilled by one of the following: (1) external peer-review process; (2) department/institute scientific review committee; or (3) scientific review by

the Clinical Research Center Advisory committee. NOTE: Review by the Penn State Health Cancer Institute (PSCI) Protocol Review Committee or the PSCI Disease Team is required if the study involves cancer prevention studies or cancer patients, records and/or tissues. For more information about this requirement see the IRB website.

17.0 Multi-Site Study

17.1 Other sites

Not applicable

17.2 Communication Plans

17.3 Data Submission and Security Plan

17.4 Subject Enrollment

17.5 Reporting of Adverse Events and New Information

17.6 Audit and Monitoring Plans

18.0 Adverse Event Reporting

18.1 Adverse Event Definitions

Adverse event	Any untoward medical occurrence associated with the use of the drug in humans, whether or not considered drug related
Adverse reaction	An Adverse Reaction is an adverse event for which the causal relationship between the drug and the adverse event is suspected.
Suspected adverse reaction	Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than "adverse reaction". • *Reasonable possibility.* For the purpose of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.
Serious adverse event or Serious suspected adverse reaction	Serious adverse event or Serious suspected adverse reaction: An adverse event or suspected adverse reaction that, in the view of either the investigator or sponsor, results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Suspicion of transmission of infectious agents must always be considered a serious adverse event.
Life-threatening adverse event or life-threatening suspected adverse reaction	An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator (i.e., the study site principal investigator) or sponsor, its occurrence places the patient or research subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that had it occurred in a more severe form, might have caused death.
Unexpected adverse event or Unexpected	An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure, not listed as per the reference safety information (Prescribing information), or elsewhere in the current IND application; or is not listed at the specificity or severity that has been

suspected adverse reaction.	previously observed and/or specified. For the assessment of expectedness, a current version of the Prescribing information, or any updates thereof, would be used.

Unanticipated adverse device effect	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or IDE application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

18.2 Recording of Adverse Events

All Aes (serious or non-serious) and abnormal test findings observed or reported to study team which are believed to be associated with the study drug will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.

Pregnancy: Pregnancy complications will be recorded as AE. Outcome of the pregnancy will be followed up. If the infant has a congenital anomaly/birth defect this must be reported and followed up as an SAE. Any pregnancy occurring during the trial period will be reported to the IRB, NIDA, and Novo Nordisk within the same timelines described for reporting of AE.

18.3 Causality and Severity Assessments

The investigator will promptly review documented adverse events and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse event; 2) if there is a reasonable possibility that the adverse event was caused by the study drug(s) or device(s); and 3) if the adverse event meets the criteria for a serious adverse event.

If the investigator's final determination of causality is "unknown and of questionable relationship to the study drug(s) or device(s)", the adverse event will be classified as associated with the use of the study drug(s) or device(s) for reporting purposes. If the investigator's final determination of causality is "unknown but not related to the study drug(s) or device(s)", this determination and the rationale for the determination will be documented in the respective subject's case history.

18.4 Reporting of Adverse Reactions and Unanticipated Problems to the FDA

18.4.1 Written IND/IDE Safety Reports

Not applicable

18.4.2 Telephoned IND Safety Reports – Fatal or Life-threatening Suspected Adverse Reactions

Not applicable

18.5 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) possibly or probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

In the event of an SAE or life-threatening adverse reaction, Caron medical staff will be immediately informed and address the situation. Dr. Bunce and the medical monitor will be contacted within 12

hours. SAEs will be reported to the DSMB within 24 hours, and to the IRB within 10 days, of the PI's notification of the event. The need to suspend or modify the study procedures will be assessed with the IRB and DSMB. All non-serious Aes will be summarized and included in regular reports to the IRB and DSMB.

Reporting Adverse Reactions and Unanticipated Problems to NIDA
SAEs will be systematically evaluated at each clinic visit. Any SAE, whether or not related to study medication, will be reported to NIDA. SAEs that are "unexpected" and "possibly or probably related" to the research procedures will be reported to the IRB. The clinical PI, Dr. Bunce, will report any SAEs to NIDA within 72 hours of first becoming aware of the event. The initial SAE report will be followed by submission of a completed SAE report to NIDA. All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable.

Reporting of IRB actions to NIDA
Any actions recommended by the IRB will be reported to NIDA within 5 calendar days of the PI's notification.

Report of Changes or Amendments to the Protocol
Planned changes to the study will be reported and must receive approval from the Penn State IRB and NIDA prior to implementing these changes, except where necessary to eliminate apparent immediate hazards to the participants. In the case of changes implemented to eliminate immediate hazards to the participants, the emergency protocol changes will be reported to the IRB using a Reportable New Information submission. Electronic copies of all documents submitted to the IRB and NIDA will be maintained in the records. All research will continue to be conducted without inclusion of the modification until IRB and NIDA approval have been received.

Novo Nordisk safety reporting
The safety reporting requirement from Novo Nordisk states that, at minimum, all serious adverse reactions (SARs) and pregnancies occurring during the use of a Novo Nordisk product must be reported to Novo Nordisk. In addition to SARs, any other events that have been submitted to the health authorities according to local regulatory requirement must also be reported to Novo Nordisk at the time of submission to health authorities at the latest.

18.6 Unblinding Procedures

In case of a medical emergency, when the knowledge of the subject's treatment assignment may influence the subject's clinical care, the treating physician may contact Synergy Pharmacy to access the subject's treatment assignment. The research team members will document the reasons for unblinding in the subject's source documentation. Study team members will not share the information with personnel involved with the analysis and conduct of the study.

18.7 Stopping Rules

Blood pressure, heart rate, and respiratory rate will be measured on Days 1, 2, 8, 14, 19, and 21. On each day, each measure will be recorded 3-4 times and then averaged. Participants will be withdrawn if they experience an average daily value for any measure on Day 1, 2, 8, 14, or 19:

- Systolic blood pressure (SBP) changes >40 mmHg, or <90 mmHg or >200 mmHg, or clinical symptoms of hypertension (e.g. headache, dizziness, blurred vision, nausea edema) or hypotension (e.g. dizziness, nausea, fainting) develop
- Heart rate reaches levels <40 beats/min or >120 beats/min
- Respiratory rate changes by >5 breaths/minute or reaches levels <10 breaths/minute or >24 breaths/minute

The medical monitor will be alerted and immediate medical assistance will be sought from the medical staff at Caron if participants experience any of these events, or more serious AEs. The investigators will also exercise discretion to end an individual's study participation if they should engage in behavior that could jeopardize their own health and well-being or that of others.

Participants who develop any new conditions described in the exclusion criteria during the treatment phase of clinical trial will be removed from the study.

19.0 Study Monitoring, Auditing and Inspecting

19.1 Study Monitoring Plan

19.1.1 Quality Assurance and Quality Control

The study will be monitored by Clinical Trial Monitoring Team from the Department of Public Health Sciences at Penn State Hershey College of Medicine.

Staff within the Department of Public Health Sciences will be monitoring the study for protocol compliance, data quality, and regulatory compliance. This will include reviewing the informed consent process and completed forms, verifying the presence of essential documents in the study regulatory binder, completing source document verification for data entered into REDCap, ensuring the study is implemented as planned, reviewing adverse events and the reporting of serious adverse events, and ensuring that all data quality rules have been executed and resolved and all data queries are resolved and closed.

The monitor will create a detailed report following each scheduled monitoring session to forward to the PI and will verify that proposed action items are addressed and completed. The monitoring will occur at regular intervals as specified in the monitoring plan developed by Public Health Sciences and PSU Sponsor Investigator.

19.1.2 Safety Monitoring

The PI will confirm that all AE are correctly entered into the AE case report forms by the coordinator; be available to answer any questions that the coordinators may have concerning AEs; and will notify the IRB and/or DSMB of all applicable AEs as appropriate. All AE assessments will be made by the PI AND one of the following: Dr A Scioli (physician and study team member), the medical monitor, or Dr N Raja-Khan (physician and study team member).

The Research Coordinator will complete the appropriate report form and logs; assist the PI to prepare reports and notify the IRB and/or DSMB of all Unanticipated Problems/SAE's.

The Monitor will confirm that the AEs are correctly entered into the case report forms. The Monitor will also confirm that the adverse events are consistent with the source documents and are reported to the appropriate regulatory bodies as required.

20.0 Future Undetermined Research: Data and Specimen Banking

Not applicable

20.1 Data and/or specimens being stored
20.2 Location of storage
20.3 Duration of storage
20.4 Access to data and/or specimens
20.5 Procedures to release data or specimens
20.6 Process for returning results

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22.0 Confidentiality, Privacy and Data Management

See the Research Data Plan Review Form.

23.0 Optional Sub-study: Polysomnography Assessment

In addition to the main part of the research study as explained above, there is a supplemental part to the research study. Participants can be in the main part of the research without agreeing to be in this supplemental part of the study.

Study Objectives
Preliminary data suggest that the study medication, liraglutide, may help to improve sleep. Liraglutide decreases orexin transmission, which, in turn, reduces arousal, leading to improved total sleep time and increases percentage of slow wave (Stage III) sleep. The supplemental part of the study will evaluate the effect of liraglutide on objective measures of sleep, assessed with overnight polysomnography (PSG).

1. **To evaluate the efficacy of liraglutide (vs placebo), administered daily, in improving objective total sleep time (TST) as measured by PSG in opioid use disorder patients in residential treatment.** Specifically, we hypothesize that**: l**iraglutide will be more effective than placebo in increasing objective TST in OUD patients undergoing residential treatment for OUD.

2. **To evaluate the efficacy of liraglutide (vs placebo), administered daily, on the objective measures of %slow wave sleep (%SWS), as measured by PSG, in opioid use disordered patients in residential treatment.** Specifically, we hypothesize that liraglutide, relative to placebo, will increase the %SWS, which will contribute to overall sleep quality.

Primary end point
The primary objectives of the supplemental study is to determine whether liraglutide can improve objective TST measured by PSG over 3-5 weeks while participants are in residential treatment for OUD. For the 3-dose intervention, change in TST will be measured by performing PSG at baseline, prior to receiving the first dose of liraglutide (Night 1) and the night after receiving the final target drug dose (Night 19). For the 5-dose intervention, change in TST will be measured by performing PSG at baseline (prior to receiving the first dose of liraglutide, Night 1), the night after receiving the final 1.8 mg (third) drug dose (Night 19), and the night after receiving the final 3.0 mg (fifth) drug dose (Night 31).

Secondary end point
The secondary end point of the study is to determine whether liraglutide improves %SWS measured by PSG over a 3-5 week period while participants are in residential treatment for OUD. For the 3-dose intervention, change in %SWS will be measured by performing PSG at baseline, i.e., prior to receiving the first dose of liraglutide (Night 1) and the night after receiving the final target drug dose (Night 19). For the 5-dose intervention, change in %SWS will be measured by performing PSG at baseline, i.e., prior to receiving the first dose of liraglutide (Night 1), the night after receiving the final 1.8 mg (third) drug dose (Night 19), and the night after receiving the final 3.0 mg (fifth) drug dose (Night 31).

Exploratory end point
The exploratory end point is to determine if the improvement in TST and %SWS is accompanied by decreased craving, insomnia severity, and prefrontal cortical brain response to visual drug cues following 18-30 days of treatment with liraglutide in OUD patients in residential treatment. We will examine the correlation between improvements in TST, %SWS, and craving and insomnia severity as measured by self-report and prefrontal response to drug cues.

Background
Scientific Background and Gaps
Sleep problems are common – and undertreated – symptoms in most substance use disorder syndromes, including OUD [56-62]. Sleep problems are 8-9 times more prevalent among patients in early treatment for opioid use disorders (OUD) than the general population [63-67]. Aside from misuse, or abuse, even regular, chronic use of opioids is known to interfere with sleep via several mechanisms, leading to increased Stage I [68-70] and Stage II sleep [70], reduced levels of sleep efficiency, rapid eye movement (REM) sleep [57, 58, 69-74], and percentage of non-rapid eye movement (NREM) slow wave sleep (%SWS) [57, 58, 71-74]. Peles et al. [75] also found that the %SWS was correlated with of the severity of OUD. Thus, the persistence of insomnia,

especially when associated with decreased SWS, is a predictor of relapse following discharge from residential treatment with an OUD. Sleep problems may persist for months following withdrawal, contributing to high rates of relapse [76-78]. To date, there are no approved medications for insomnia in patients with OUD. The standard hypnotic medications used to treat sleep disorders cannot be used in OUD patients because of their addictive properties. The two most commonly used FDA-approved medications for OUD treatment, methadone and buprenorphine, do not improve sleep for the majority of patients [67], and indeed, may make is worse due to their agonism or partial agonism on the opioid receptors. Trazodone and other antidepressants like doxepin/mirtazepine, are commonly prescribed off-label for the treatment of insomnia in the general population [79, 80], and are the standard of care for the treatment of insomnia in SUDs [80, 81]. However, previous studies with trazodone and other antidepressants in post-withdrawal SUD participants have shown mixed efficacy, with little to no relief for a large percentage of the population [82, 83]. *Collectively, these findings suggest that there is a significant need to develop more efficacious treatments for insomnia in patients with SUDs in general, and OUD in particular.*

Glucagon-Like Peptide-1 (GLP-1), Orexins and Sleep

In addition to its potential to reduce craving in OUD patients, there is evidence that the study drug, a GLP-1r agonist, may also improve sleep. In a mouse model, the GLP- 1R agonist Exendin-4 was shown to increase NREM sleep time (Stage III %SWS sleep) by 93% over the first 6 hours of the dark cycle in mice [84]. We are unaware of any study of the effects of a GLP-1r agonist on sleep architecture in humans. We believe its effect on sleep may due to the effect of GLP- 1R agonism on orexin transmission.

Orexin is one of the wake neurotransmitters that play a role in the wake-sleep cycle. It is believed that orexin is involved with sending wake signals to other parts of the brain. Inhibiting the action of orexin by blocking transmission is expected to result in decreased arousal and increased sleep. The orexin type-2 receptor, in particular, has been shown to be associate with arousal, whereas the orexin type-1 receptor has been associated with positive mood. In a preclinical study by our group, the administration of the GLP1 agonist, Ex-4 has been shown to increase both orexin 1 [85] and orexin 2 (unpublished) receptor mRNA expression in the nucleus accumbens shell. This effect suggests that GLP1 agonism decreases orexin transmission, leading to a compensatory increase in orexin receptors in the nucleus accumbens. The orexin receptor antagonist, suvorexant, decreases arousal and improves sleep in humans (marketed as Belsomra) and is FDA approved for the treatment of primary Insomnia. Given that a GLP1 agonist can decrease orexin neurotransmission, and thereby dampen arousal, treatment with a GLP-1r agonist may improve sleep - in addition to decreasing craving. *As such, we hypothesize that the GLP-1r agonist, liraglutide, is a novel and promising therapeutic to improve sleep in patients with OUD, as it may not only decrease craving, but also improve sleep by acting on the orexin-mediated arousal and reward pathways.*

Study Rationale

The rationale for the proposed research is to develop an intervention that can improve sleep outcomes in addition to reducing craving in OUD patients, a combination of factors which contribute to early relapse. Although liraglutide was approved for human use in 2010, there are no data testing the effectiveness in craving and sleep in patients with an OUD. Because of its importance to health and well-being, and its role in relapse, both objective (wrist actigraphy) and intensive subjective (Ecological Momentary Assessment, EMA) measures of sleep were included in the parent UG3 grant study, in addition to well-validated self-reported sleep inventories. However, the existing animal research model shows that GLP-1r agonism improved the percentage of slow wave sleep (%SWS), an important aspect of sleep architecture that cannot be measured with self-report or wrist actigraphy.

The objective of the proposed supplemental research is to use the gold-standard, polysomnography, to evaluate the hypothesis that treatment with a GLP-1R agonist can improve sleep in humans with OUD. If liraglutide shows a trend towards efficacy in improving sleep, and safety of the GLP-1R agonist is demonstrated in this population, it would provide an indication to run a multi-center clinical trial of GLP-1R agonist in OUD patients.

The inclusion, exclusion criteria, recruitment methods and consent process for the polysomnography studies are the same as those described above for the primary study.

Study Design and Procedure

Study Design

The polysomnography portions will be inserted into the study design (described above) on Nights 1, 19, and 31, as described below.

Study procedures

Following randomization and full screening, the first PSG recording will be collected on baseline night (Night 1) before starting liraglutide/placebo. A second PSG study will be conducted 6 days after reaching the 1.8 mg dose of liraglutide, on Night 19. For the 5-dose intervention only, a third PSG study will be conducted 6 days after reaching the 3.0 mg dose of liraglutide, on Night 31. PSG studies will be performed at Caron treatment center in the patients' own rooms. An appropriately trained study team member (Project Coordinator or Research Support team member) will set-up the sleep recording. Training for the Sleep Project Coordinator will be provided by registered polysomnography technicians from the Sleep Research & Treatment Center involved in research and/or clinical care and supervised by the sleep co-investigators (Krishnamurthy, Fernandez-Mendoza) in this study. Training will include all aspects necessary for a gold-standard, ambulatory PSG recording, including 1) application and removal of electrodes, 2) set-up of PSG equipment, 3) calibration of signals, 4) software and hardware management, 5) disposal and/or clean-up of supplies for research purposes, and 6) secure transfer of the sleep data files to the PSHealth network using Kiteworks. Data transferred via Kiteworks will be scored by an independent technician (sleep scorer) not involved in data acquisition.

The polysomnography (PSG) assessments will only be set up and taken down (patient unhooked from equipment and electrodes) by appropriately trained Penn State study team members (Project Coordinators). The use of portable PSG units (not in-lab PSG) requires a trained technician to get good signal, but does not require a Registered Polysomnographic Technologist (RPSGT) to successfully gather good-quality data. RPSGTs are required for accreditation of clinical sleep centers, but not for research studies as long as the investigator team includes sleep specialists with demonstrated experience who assure appropriate training and skills with adequate expertise and resources. The study team includes two board-certified sleep specialists and sleep researchers who have demonstrated experience in PSG and in training research technicians for successful outcomes. The Penn State Project coordinator will be trained by the two board-certified sleep specialists, including hands-on training with other human research technicians trained in PSG and/or RPSGTs currently working in the clinical sleep center and within the sleep research division

The appropriately trained study team member will be using a Natus Trex HD ambulatory PSG system, and standard PSG methodology. The PSGs will include two central, frontal, and occipital electroencephalogram channels, two electrooculograms, chin and limb electromyograms, and an electrocardiogram during the baseline and follow up. Additional sensors to detect sleep disordered breathing events, including chest and abdominal bands, a thermocouple, a nasal cannula, and a pulse oximeter, all of which are standard in PSG studies, will be included. Application of the PSG sensors will begin around 9:15, and participants will be instructed to go to bed at the time closest to their habitual bedtime, within a time range of 10pm to 11pm, and to get up at 6am (which is within their Caron-scheduled wake time. (All morning patient medication at Caron is provide at the Neag Medical Center from 6:15am to 6:50am, so this time is consistent with their typical schedules.)

Data from the PSG study will be collected on a study-dedicated laptop. The data will be securely transferred to the Sleep Research and Treatment Center (SRTC), Penn State Health and Penn State College of Medicine via https://kiteworks.pennstatehealth.net for further storage, scoring, interpretation and analysis using Cerner's environment within Penn State Health secure network. Data sent to the SRTC from the study team will be identified by the participant's random ID number only. This will allow investigators to pair the polysomnographic sleep study data with the clinical data collected in the primary study, described above.

Sleep records will be manually scored by a trained technologist following the current version of American Academy of Sleep Medicine (AASM) Manual. Standard PSG sleep parameters, including total sleep time, wake after sleep onset, and the percentage and duration of each sleep stage will be calculated using Sleepworks (Natus) software.

Participants will be allowed to request a sleep physician report of their sleep stages, breathing patterns (e.g., sleep apnea) or other physiologic measures that they may share with their primary care provider, if desired, for further clinical care outside of the study.

All other aspects of the study (e.g., drug and placebo administration, adverse event monitoring, enollment and randomization, duration of the study procedure, etc), including self-reported craving (0-100 VAS) will be conducted as described in the primary study above. Subjects will also complete the 7-item self-reported Insomnia Severity Index (ISI), the gold-standard subjective measure of insomnia severity in clinical trials (PMID: 21532953; PMID: 33164741). The ISI is already embedded into REDCap from our previous studies and will be added to this optional sleep study to measure the potential improvement in subjective insomnia severity from baseline (initial evaluation, Night 1) to post intervention (Nights 19 and 31), as mentioned in the exploratory endpoints above.

Risks
There are no known risks associated with the polysomnographic recordings of sleep. On rare occasions, some individuals can have mild allergic reactions to the tape applied over the electrodes, or allergies to latex. We will minimize this risk by using hypoallergenic tapes. There can be some mild discomfort in applying the skin electrodes as the skin is cleaned, or while wearing the electrodes at night.

Subject payment and travel information
In addition to the reimbursement for participating in the main parts of the study, participants will receive an additional reimbursement of $90 for the first PSG, $90 for the second PSG, and $90 for the third PSG [5-dose intervention only] for a total of $180 [$270 for three nights] for participating in the supplemental polysomnographic sleep recordings. Reimbursements will be paid using Target gift cards as neither alcohol nor tobacco products can be purchased at Target.