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Title of Grant: Laboratories for Early Clinical Evaluation of Pharmacotherapies for Substance Use Disorders

Study Title: Phase Ib/2a drug-drug interaction study of lemborexant as an adjunctive treatment for buprenorphine/naloxone for opioid use disorder

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List of Abbreviations

AE	adverse event
ALT	alanine aminotransferase
ASI-lite	Addiction Severity Index
OREXIN 1 AND 2 RECEPTOR	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid glutamate receptor
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BP	blood pressure
BUN	blood urea nitrogen
C24	concentration at 24 hours post-dose
CFR	Code of Federal Regulations
C-SSRS	Columbia Suicide Severity Rating Scale
CGI-I	Clinical Global Impression Improvement
CGI-S	Clinical Global Impression Severity
CL/F	Apparent total clearance of the drug from plasma after oral administration
CMAX	Maximum (peak) plasma drug concentration
CNS	Central Nervous System
COWS	Clinical Opiate Withdrawal Scale
CRF	Case Report Form
CRU	Clinical Research Unit
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HIPAA	Health Insurance Portability and Accountability Act of 1996
HR	Heart rate
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	intravenous
LDH	lactate dehydrogenase
OCS	Opioid Craving Scale

MAT	Medication Assisted Treatment
MINI	Mini-International Neuropsychiatric Interview for DSM-5
NIDA	National Institute on Drug Abuse
OUD	Opioid Use Disorder
PhAB	Phenotypic Assessment Battery
PI	Principal Investigator
PK	Pharmacokinetic
PD	Pharmacodynamic
PO	Program Officer
SAE	serious adverse experience
t ½	half-life of elimination
Tmax	time to reach maximum plasma concentration
SOWS	Subjective Opiate Withdrawal Scale
VAS	Visual Analog Scale

PROTOCOL SYNOPSIS

TITLE	Phase Ib/2a drug-drug interaction study of lemborexant as an adjunctive treatment with buprenorphine/naloxone for opioid use disorder
SPONSOR	F. Gerard Moeller, M.D.
FUNDING ORGANIZATION	National Institute on Drug Abuse
NUMBER OF SITES	1
RATIONALE	The overall goal of this project is to develop initial human data on effects of novel compounds on safety (interactions with opioid drug, e.g., buprenorphine-naloxone) and efficacy (subjective effects on craving, anxiety, and opioid withdrawal) in opioid use disorder subjects currently in treatment with buprenorphine-naloxone. The compound to be studied will be the orexin 1 and 2 receptor receptor antagonist lemborexant. Orexin 1 and 2 receptor antagonists have been shown to reduce heroin self-administration in rodents and also have shown potential to reduce the use of other drugs including cocaine and alcohol (described in detail in Background section below).
STUDY DESIGN	This is a randomized, double-blind, placebo-controlled phase 1b/2a study.
PRIMARY OBJECTIVE	1. We propose to examine safety-tolerability and drug-drug interactions between lemborexant and buprenorphine-naloxone in participants with opioid use disorder who are in MAT with buprenorphine-naloxone.
SECONDARY OBJECTIVES	2. Simultaneuously with the safety study, we propose a to examine lemborexant early signal of efficacy (anticraving, anxiolysis, and reduced subjective withdrawal symptoms) in subjects with opioid use disorder who are in MAT with buprenorphine-naloxone.
NUMBER OF SUBJECTS	18 completers

SUBJECT SELECTION CRITERIA	N=18 (nine men and nine women) with opioid use disorder (OUD) who are currently in treatment at the Motivate clinic or other outpatient treatment setting with buprenorphine naloxone are targeted for completing at least one drug-drug interaction treatment session with primary endpoint data (at least 12 lemborexant treated participants and 6 placebo treated subjects). Participants must meet all of the following; **INCLUSION CRITERIA:** 1) Males and females between 18 - 65 years-of-age; 2) Understand the study procedures and provide written informed consent in English language; 3) Meet current DSM-5 criteria for opioid use disorder, of at least moderate severity, currently engaged in medication assisted treatment at a buprenorphine-naloxone sublingual film daily dose ranging from 8mg/2mg to 24mg/6mg or buprenorphine sublingual tablet 5.7mg/1.4mg to 17.1/4.3 once daily; 4) Have a positive urine drug screen for buprenorphine during screening and on admission to the clinical research unit to document buprenorphine use; 5) Have a Pittsburgh Sleep Quality Index (PSQI) Total Score of 6 or higher. **EXCLUSION CRITERIA**: 1) Contraindications for participation as determined by medical history and physical exam performed by study NP or study physician; 2) Pregnant or nursing women; 3) Baseline ECG with clinically significant abnormal conduction; 4) Uncontrolled serious psychiatric or major medical disorder, including COPD. Narcolepsy is also considered exclusionary; 5) Taking prescription or over-the counter drugs or dietary supplements known to significantly inhibit CYP3A4 (such as Clarithromycin, telithromycin, nefazodone, itraconazole, ketoconazole, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir); or CYP3A4 inducers (such as phenobarbital, phenytoin, rifampicin, St. John's Wort, and glucocorticoids. 6) Prescribed medications for insomnia or unable to discontinue over-the-counter drugs or dietary supplements used to treat insomnia on study days. 7) Current severe alcohol use disorder or current benzodiazepine use disorder 8) Current DSM-5 diagnosis of any psychoactive substance use disorder other than opioids, cocaine, marijuana, or nicotine, or mild or moderate alcohol use disorder. Diagnosis of mild to moderate use disorder for alcohol will not be considered exclusionary.

	9) Any previous medically adverse reaction to opioids or lemborexant: 10) Significant current suicidal or homicidal ideation (C-SSRS “yes” answers on questions 4 or 5) or a history of suicide attempt within the past 6 months. 11) Subjects with Suicidal Behaviors Questionnaire-Revised score ≥8 at the screening visit. 12) Any other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	Lemborexant 5 mg, 10 mg Product will be administered orally once on each laboratory day in the cliniocal research unit (CRU) only.
CONTROL PRODUCT, DOSE AND ROUTE OF ADMINISTRATION	Placebo Subjects who are randomized to placebo will receive identical capsules to the test product at the same time administered orally.
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Subjects will be on study for up to approximately 60 days (including intervening weekends) Screening: up to approximately 30 days Baseline: 1 day Treatment : 6 days Follow-up: 8 days Note: Safety/PK Testing Weeks may be separated by up to approximately 14 days in order to better accommodate participant schedules. The total duration of the study is expected to be 18 months.

CONCOMMITANT MEDICATIONS	Allowed: Non-CNS Active medications Prohibited: CNS active medications that in the opinion of the PI may affect interpretation of the study. Medications which could potentially have clinically significant interactions with buprenorphine or lemborexant, notably drugs significantly inhibiting CYP3A (such as Clarithromycin, telithromycin, nefazodone, itraconazole, ketoconazole, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir)), or CYP3A4 inducers (such as phenobarbital, phenytoin, rifampicin, St. John's Wort, and glucocorticoids). ***Concurrent Medications:*** All participants should be maintained on the same medications throughout the entire study period, as medically feasible, with no introduction of new chronic therapies. Non-CNS active medications which are known not to have any potential interaction with either buprenorphine or lemborexant would be allowed in this study. The following medications are prohibited during the study: Medications that may affect buprenorphine plasma levels; rifampin, phenobarbital, and phenytoin (CYP450 3A4 inducers) or such as ketoconazole, erythromycin, and saquinavir (enzyme inhibitors) that could affect the levels of parent drug or its active metabolites. Lemborexant is not thought to have any significant pharmacokinetic drug-drug interaction other than those that would inhibit CYP450 3A4, and thus would already be excluded based on the above criteria.
EFFICACY EVALUATIONS	**Primary outcome measures:** 1. Safety: Heart rate (HR), blood pressure (BP), respiration (pulse oximetry, end tidal CO2 (EtCO2,) respiratory rate), agitation and sedation (Richmond Agitation Sedation Scale). 2. Buprenorphine PK: Plasma concentration-time profiles of buprenorphine and its metabolite norbuprenorphine 3. Lemborexant PK: Plasma concentration-time profiles of lemborexant and its major metabolite M10. Adverse event data will be compiled for lemborexant and placebo cohorts and presented as summary statistics. **Secondary Outcome Measures:** 1. Subjective effects on opioid craving, anxiety and lemborexant drug liking as measured by a visual analog scale (VAS), and Brief Substance craving scale (BSCS), and opioid withdrawal based on the Subjective Opioid Withdrawal Scale (SOWS). 2. Objective opioid withdrawal based on the Clinical Opioid Withdrawal Scale (COWS). 3. Impulsivity as measured by a delayed discounting task (DDT).

	Exploratory Outcome Measures: 1. Change in pupil size, as measured by single pupil measurements at scheduled times. using a pupillometer. 2. Behavioral/clinical profiles correlated with treatment response generated from PhAB application. 3. Change in sleep, as measured by self-reported sleep measures Pittsburg Sleep Quality Index and Sleep Diary.
PLANNED INTERIM ANALYSES	There will be no formal interim analysis.
STATISTICS Primary Analysis Plan	Initial analyses will evaluate group differences on demographic and baseline variables, will use contingency tables with chi-square testing, ANOVA's, and examination of correlations between baseline variables, subjective responses, and clinical results. General data analysis procedures: Prior to data analysis procedures, groups will be examined for differences in baseline characteristics that could potentially influence treatment outcome. Any variables that differ between groups and are related to outcome measures will be examined as potential covariates in subsequent data analyses. **Primary outcome measures:** 1. Safety: Heart rate (HR), blood pressure (BP), respiratory rate, agitation and sedation (Richmond Agitation-Sedation Scale) and pulse oximetry during a placebo dose will be compared to HR and BP during each lemborexant dose (5 mg and 10mg doses). Changes in safety measures induced by lemborexant dose along with buprenorphine will be compared to those without lemborexant, by lemborexant dose level (5 mg and 10 mg doses), using a generalized linear mixed model analysis with the participant as a random effect for each outcome. Adverse event data will be compiled for lemborexant and placebo cohorts and presented as summary statistics. 2. Buprenorphine PK: Plasma concentration-time profiles of buprenorphine and its metabolite norbuprenorphine after doses during the lemborexant placebo/administration (Day 0,1, 2) will be analyzed to obtain pharmacokinetic parameter estimates of buprenorphine (Cmax, Tmax, AUC, apparent t½, CL/F for parent buprenorphine and metabolic (AUC) ratios for metabolites) by individual.These parameters will be compared within subjects on sessions with lemborexant. 3. Changes in secondary outcome and exploratory outcome measures induced by lemborexant dose along with buprenorphine will be compared to those without lemborexant, by lemborexant dose level (5 mg and 10 mg doses), using a generalized linear mixed model analysis with the participant as a random effect for each outcome.

RATIONALE FOR NUMBER OF SUBJECTS	Projected sample size is 18 subjects who have completed at least one drug-drug interaction treatment session with primary endpoint data– 12 lemborexant-treated subjects, 6 placebo treated subjects. Sample size was determined based on primary outcome safety and PK measures.

BACKGROUND

The US opioid epidemic has reached an alarming scale, with more than 72,000 drug overdose deaths occurring across the US in 2017, and the majority of these deaths due to opioids (CDC 2018). Medication-assisted treatment (MAT), utilizing methadone, buprenorphine, or naltrexone in addition to behavioral interventions has proven to be effective at reducing all-cause mortality and overdose deaths in patients with opioid use disorder (Ma, Bao et al. 2018). However, retention in MAT is problematic, with controlled trials showing a 20-30% patient dropout rate or more in the first 12 weeks of treatment (Johnson, Chutuape et al. 2000, Tanum, Solli et al. 2017). Factors associated with dropout from MAT treatment include continued opioid and other drug use, as well as behavioral factors, including insomnia, impulsivity and anxiety (Marcovitz, McHugh et al. 2016, Hui, Weinstein et al. 2017, Zhu, Evans et al. 2018). Likewise, in conjunction with the opioid epidemic, there has been a resurgence of other drug abuse, including cocaine and methamphetamine, leading to a dramatic increase in overdose deaths with psychostimulants (CDC 2018). ***Hence, there is a significant need for novel pharmacotherapy that could enhance the effects of MAT on reducing opioid and other drug use, reduce behavioral problems and symptoms such as impulsivity, and insomnia, thus improving treatment retention and long-term outcome for MAT in opioid use disorder and opioid use disorder comorbid with other drug use.***

OREXIN 1 AND 2 RECEPTOR Antagonists to treat addiction:

Preclinical research on orexin receptor antagonists has shown that they may have powerful antiaddictive effects and may contribute to attenuation of several addictive behaviors. Additionally, insomnia is thought to contribute to relapse risk in OUD and is a common complaint even amongst subjects on buprenorphine (Kaplan, McQuaid et al. 2014). Additionally, heroin addiction has been shown to increase the number of orexin producing cells in the brain and thus a hyperorexinergic state may play a role in continued use of opioids (Thannickal, John et al. 2018). Our own NIDA funded deep phenotyping studies show that insomnia and sleep disturbance appears to be a distinct component of a particular translational phenotype of opioid and cocaine use disorder that may be informative for precision medicine approaches.

The orexin 1 receptor antagonist SB-334867 attenuated heroin SA in adult rats and diminished cue-induced, but not prime-induced, reinstatement of heroin-seeking behavior following extinction (Smith and Aston-Jones 2012). Also, orexin 2 receptor antagonists reduce heroin intake in long-access (12 h), but not short-access (2 h), SA paradigms (Schmeichel, Barbier et al. 2015). Orexin 1 receptor antagonists attenuate morphine withdrawal symptoms in rats (Azizi, Mirnajafi-Zadeh et al. 2010, Laorden, Ferenczi et al. 2012). Dual orexin antagonists seem to be particularly well suited to treating OUD. Han et al., (2020) reviewed all similar studies and found that there is evidence from multiple animal models of opioid addiction supporting the use of orexin 1 and 2 receptor antagonists to reduce addictive behaviors. Matzeau and Martin-Fardon et al., (2020) evaluated orexin 1 antagonist SB-334867 and TCSOX229 an orexin 2 receptor antagonist in rats with an oxycodone self-administration model showing that the orexin 1 receptor antagonist suppressed self-administration but not the orexin 2 receoptor antagonist.

As a first step in evaluating the potential for use of the orexin 1 and 2 receptor antagonist lemborexant as an adjunctive treatment for opioid use disorder in patients in MAT with buprenorphine, we propose a phase 1b/2a drug-drug interaction study examining two doses of lemborexant as an add-on to buprenorphine-naloxone

with 18 participants (12 treated with lemborexant and 6 treated with placebo. The lemborexant group will have two lab sessions each; one with each dose of med). All participants will be currently stable in MAT treatment with buprenorphine and have symptoms of insomnia as measured by the Pittsburgh Sleep Quality Index. This is parallel groups ascending dose study.

Specific Aims:

Primary: Aim 1: To examine safety-tolerability and drug-drug interactions between lemborexant and buprenorphine-naloxone in participants with opioid use disorder and insomnia who are in MAT with buprenorphine-naloxone.

Secondary: Aim 2: To examine lemborexant for an early signal of efficacy (anticraving, anxiolysis, impulsivity, and reduced subjective withdrawal symptoms) in participants with opioid use disorder and insomnia who are in MAT with buprenorphine-naloxone.

Exploratory aim: To determine the effect of lemborexant on central mu receptor function as measured by pupliometry and self-reported sleep measures, and to assess whether behavioral profiles based on a previous factor analysis of a phenotypic database predict behavioral response to lemborexant when added to buprenorphine-naloxone.

STUDY RATIONALE AND HUMAN SUBJECTS PROTECTION

The overall goal of this project is to develop initial human data on effects of novel compounds on safety (interactions with buprenorphine-naloxine) and efficacy (subjective response to lemborexant) in opioid use disorder subjects currently in treatment with buprenorphine-naloxone. The compound to be studied will be lemborexant.

Risk / Benefit Assessment

Potential risks are listed below. The primary risks to participate in this study are those involved from potential unexpected serious adverse events due to receiving lemborexant and buprenorphine. The risks of the medications are provided below. In order to reduce risks associated with exposure to COVID-19, study staff will follow VCU policy regarding COVID-19 safety procedures (e.g., wearing face masks, maintaining social distancing requirements, use of hand sanitizer, etc). Study activities that can be conducted remotely will be completed via zoom and/or phone call (e.g., portions of the screening and/or follow-up visits). Additionally, participants will be tested for COVID-19 prior to each CRU admission based on VCUHS guidance. Outpatient study visits will be scheduled to occur at the time of the patient clinic appointment whenever possible. Finally, in-person research interactions will be reduced to the minimum amount of time needed to complete study procedures and insure participant safety.

Risks of Lemborexant Administration

The most common side effects of lemborexant are somnolence or fatigue (placebo 1.3%, lemborexant 5mg 6.9%, and lemborexant 10mg 9.6%), headache (placebo 3.4%, lemborexant 5mg 5.9%, and lemborexant 10mg 4.5%), and nightmares ore abnormal dreams (placebo 0.9%, lemborexant 5mg 0.9%, and lemborexant 10mg 2.2%). In a controlled study of effects of lemborexant on next day driving ability, at doses of 5 mg and 10 mg compared to placebo there was no statistically significant impairment in next-morning driving performance in participants (compared with placebo), however some participants had impaired driving ability after 10mg of lemborexant (Dayvigo prescribing information). Additional risks associated with lemborexant but uncommon were an increase in suicidal ideation or any suicidal behavior in a controlled clinical trial (0.3% for lemborexant 10mg, 0.4% for lemborexant 5mg, and 0.2% for placebo) (Dayvigo prescribing information).

Combining lemborexant with other sedating medications, such as buprenorphine, could increase the risk of sedation as with other sleeping aids. Likewise, there is evidence that combining lemborexant with alcohol increases impairment of cognitive measures although the clinical significance of this is likely small (Landry, Nakai et al. , Murphy, Kumar et al. 2020).

Lemborexant is a controlled substance (schedule IV) based on a human abuse potential study showing that lemborexant subjective drug liking was similar to zolpidem however, preclinical studies do not show lemborexant to be self-administered and there was no evidence of diversion or withdrawal in clinical studies (Moline, Asakura et al. 2019).

Risks of Buprenorphine Administration

Buprenorphine has been shown to be a very safe medication when used as a maintenance treatment for OUD. The major risks are respiratory depression, although as a partial agonist of the mu receptor this risk is usually limited in persons not-naïve to opioids that have tolerance.

Risks of Lemborexant combined with Buprenorphine

There are no data on this hence the need for the proposed study. Theoretically, an anticonvulsant combined with an opioid partial agonist could lead to increased sedation.

Potential Risks Not Due to Study Medication

Potential risks to participating in this study not involving medication include: unauthorized disclosure of confidential information; discomfort or embarrassment related to urine collection or questionnaires dealing with personal habits, lifestyle, drug or alcohol use; possible unwanted encounters with friends or associates in the treatment setting.

Phlebotomy: There is the potential risk of bruising at the site of the blood draw for the blood chemistries and complete blood count and the intravenous catheter site for PK blood draws. This risk will be minimized by having blood drawn by a trained phlebotomist or nurse.

Adequacy of Protection Against Risks

Informed Consent Procedures. The informed consent process involves a detailed verbal description, provided by a study staff member of the study procedures and the study medication. Staff will emphasize that participation is voluntary. Next, the staff member will conduct an item-by-item reading of the consent form while the participant reads along. The participant then meets with a physician investigator or advance practice provider to ask questions about the risks of the medical procedures in the study. In this initial interview, participants will be informed of the following:

They have an opportunity for research participation involving a program to evaluate effects of the study medication on buprenorphine pharmacokinetics and safety parameters, as well as craving and anxiety. Subjects in the studies will be randomly assigned to receive study medication or placebo. All assignments are based on chance on a 2:1 ration of lemborexant vs. placebo. As with all medications, there are risks to treatment with the study medication. These are enumerated in the section above describing potential risks to the medication. All participants will be asked to complete questionnaires and answer questions related to drug and alcohol use, personal habits, lifestyle and feelings. The initial information collection will take approximately 2 hours; shorter data collection sessions will occur at each visit after the initial screening. All participants will be asked to provide a urine specimen for drug screening and pregnancy test for female participants of child bearing potential at each clinic visit. Participants may drop out at any time without penalty or loss of benefits to which they are otherwise entitled.

Participants will be informed of procedures for ensuring their confidentiality, including: the issuance of a "Certificate of Confidentiality" by the federal government; the use of numbers, codes and/or pseudonyms rather than participants' names; and the placement of all data in locked files. Participants will be informed that, despite participant confidentiality protections, research staff, under current state law, are required to report certain communicable diseases, and any incidents of sexual or physical abuse of a child or elder, and suicidal or homicidal plans. Participants will be given the contact numbers of both the Principal Investigator and IRB to answer questions about the study or one's rights as a human subject.

A copy of the signed form is made and given to the subject, an electronic copy will be uploaded to the electronic medical record system (CERNER), and the original signed consent is kept in a separate, locked file accessible to the Institutional Review Board (IRB) upon request.

Assessment of Adverse Events. Participants will be asked daily how they are doing and if they are having any problems. Any spontaneously reported symptoms or complaints will be recorded and reported to the IRB and NIDA and the FDA if events are classified as serious.

Data monitoring to ensure subject safety and confidentiality. A potential risk in studies involving drug-dependent volunteers is breach of confidentiality. This will be limited by maintaining data files on the medical histories of subjects to be kept in a locked file cabinet in the P.I.'s offices, accessible only to the study P.I. and a study nurse as needed. Electronic data will be stored on OnCore and REDCAP which are password protected. Furthermore, all subject information is coded with a unique numerical identifier. Protections of privacy of subjects' medical information will be described to the prospective subjects as part of the enrollment interview and the informed consent procedures.

As part of the Data and Safety Monitoring Plan, a Data and Safety Monitoring Board (DSMB) will monitor study processes and findings; part of the role of the DSMB will be to intercede to recommend halting enrollment of subjects if results definitively indicate that the study medication or protocol is harmful or in any way would negatively affect those individuals.

Potential Benefits of the Proposed Research to the Subjects and Others

Subjects in the study will receive close medical and psychiatric attention. The potential benefits to society include decreased illicit opioid use if the study medications prove beneficial, with a resultant decrease in opioid morbidity and mortality, as well as a reduction in the overall social costs for opioid dependence. Of note, more Virginians die from opioid overdose than from automobile accidents, highlighting the importance of developing new treatments for opioid use disorder.

Risk-Benefit Ratio

The primary risks to participation to this research are those that result from exposure to the study medications. These risks are seen as reasonable since medication administration will take place under continuous monitoring on the CRU and there are in place numerous procedures, ongoing and periodic, designed to detect adverse experiences that occur both at the level of the individual and at the level of the medication condition. Once detected, there are adequate procedures in place to determine the most appropriate method for addressing adverse events that occur to the individual or to a group of individuals in a specific medication condition. There are few anticipated physical, psychological, social, or legal risks. However, some possible risks to participating in these studies include: unauthorized disclosure of confidential information; discomfort or embarrassment related to questionnaires dealing with personal habits, lifestyle, drug or alcohol use; and possible unwanted encounters with friends or associates in the study setting. If participants were to find any

aspects of their involvement in the study psychologically or otherwise uncomfortable, they will first meet with the study physician to discuss the situation and determine if modifications can be made to accommodate them. If there is no apparent resolution available, the decision will be made whether or not to discontinue the participant from the study.

Importance of the Knowledge to be Gained

The risks to participants are reasonable in relation to the anticipated benefits because:

The primary risks occur during administration of lemborexant with buprenorphine-naloxone. This will take place on the clinical research unit, under supervision of providers and trained nursing staff who will immediately respond to any adverse event. Participants will spend the night on the CRU prior to lemborexant administration to ensure that they do not take any additional drugs or medications that could interact with lemborexant.

The identification of effective treatments for opioid use disorder would be a great benefit to society.

If any Psychiatric or non-Psychiatric medical illness (other than substance abuse) is discovered during the study, subjects will be referred for additional treatment in the community.

STUDY DESIGN

Overview

We propose a series of experiments to study the safety and target engagement of lemborexant when combined with buprenorphine-naloxone for opioid use disorder.

Study Design: Pharmacokinetic safety and pharmacodynamic efficacy signal trial of combined lemborexant and buprenorphine-naloxone (see Figure 1 below).

STUDY OVERVIEW/SCHEMA

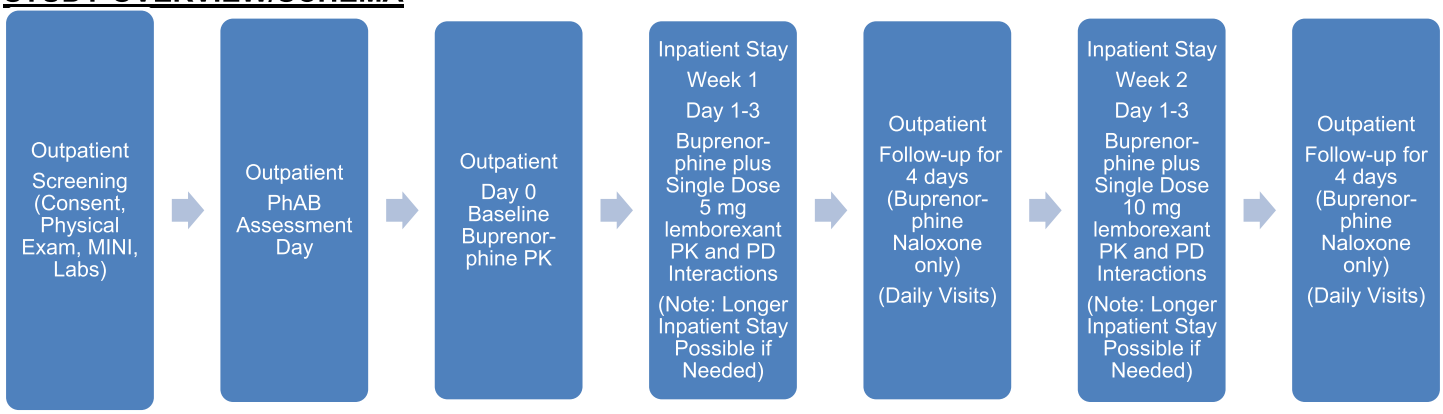


Figure 1. Overall Study Design

Participants will include 18 individuals (goal of 9 male and 9 female) with opioid use disorder in medication assisted treatment who are a buprenorphine-naloxone sublingual film daily dose ranging from 8mg/2mg to 24mg/6mg or buprenorphine sublingual tablet dose ranging from 5.7mg/1.4mg to 17.1/4.3 once daily at the VCU MOTIVATE or other outpatient treatment setting who complete at least one drug-drug interaction treatment session with primary endpoint data (at least 12 lemborexant treated participants and 6 placebo treated subjects).

After a complete screening including the phenotyping assessment battery (PhAB) described in detail below,

participants will be randomized to either lemborexant (12 participants) or placebo (6 participants) and will undergo safety and PK testing on the CRSU at VCU, as described in Tables 1 and 2 below. We will characterize the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of the combined administration of lemborexant with buprenorphine-naloxone including the time to onset, duration of action, magnitude of effects, and the pharmacokinetic disposition of buprenorphine and its major metabolite in plasma.

Study Hypotheses: ***1. Adjunctive lemborexant (compared to placebo) will not alter the PK of buprenorphine-naloxone significantly, nor will it alter the pharmacodynamic properties related to safety (e.g., ECG, pulse oximetry changes, capnography, significant increases in sedation and agitation). Secondary hypothises: 2. Adjunctive lemborexant will reduce subjective opioid craving, anxiety, opioid withdrawal, and impulsivity). Exploratory hypotheses: 3. Adjunctive lemborexant will not affect central mu opioid receptors as measured by pupillometry, but will increase subjective sleep ratings and behavioral effects of lemborexant will be related to behavioral profile measures from the NIDA phenotyping battery.***

Brief description of the protocol: The overall goal of this project is to develop initial human data for lemborexant combined with buprenorphine-naloxone on safety (e.g., interactive effects on cardiovascular and respiratory function, and agitation and sedation) and efficacy (subjective craving and anxiety, opioid withdrawal and impulsivity) in opioid use disorder participants. The sample will be recruited from VCU MOTIVATE clinic and other treatment programs and consist of participants with opioid use disorder of at least moderate severity that have been stabilized on buprenorphine-naloxone sublingual film daily dose ranging from 8mg/2mg to 24mg/6mg or buprenorphine sublingual tablet dose ranging from 5.7mg/1.4mg to 17.1/4.3 once daily.

PRIMARY Endpoints:

1. Safety: Heart rate (HR), blood pressure (BP), respiration (pulse oximetry, end tidal CO2 (EtCO2,) respiratory rate), agitation and sedation (Richmond Agitation Sedation Scale).
2. Buprenorphine PK: Plasma concentration-time profiles of buprenorphine and its metabolite norbuprenorphine
3. Lemborexant PK: Plasma concentration-time profiles of lemborexant and its major metabolite M10.

SECONDARY Endpoints:

1. Subjective effects on opioid craving, anxiety and lemborexant drug liking as measured by a visual analog scale (VAS), and Brief Substance craving scale (BSCS), and opioid withdrawal based on the Subjective Opioid Withdrawal Scale (SOWS).
2. Objective opioid withdrawal based on the Clinical Opioid Withdrawal Scale (COWS).
3. Impulsivity as measured by a delayed discounting task (DDT).

EXPLORATORY Endpoints:

1. Change in pupil size as an indicator of central nervous system mu-opioid pharmacological effects (Rollins, Feiner et al. 2014, measured by pupillometry.).
2. Behavioral/clinical profiles correlated with treatment response generated from PhAB application.
3. Self-reported sleep measures.

SUBJECT SELECTION

Study Population

Subjects with a diagnosis of opioid use disorder who meet all of the inclusion and none of the exclusion criteria will be eligible for participation in this study.

N=18 (nine men and nine women) will be recruited from the VCU MOTIVATE or other outpatient treatment setting (note that we anticipate recruitment and randomization of up to 64 participants to complete 18 participants, see recruitment and enrollment figure at end of protocol).

INCLUSION/EXCLUSION CRITERIA

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom this clinical trial is considered appropriate. All relevant medical and non-medical conditions will be taken into consideration when deciding whether this protocol is suitable for a particular subject.

Inclusion Criteria:

1) Males and females between 18 - 65 years-of-age;

2) Understand the study procedures and provide written informed consent in English language;

3) Meet current DSM-5 criteria for opioid use disorder, of at least moderate severity, currently engaged in buprenorphine-naloxone treatment at a sublingual film daily dose ranging from 8mg/2mg to 24mg/6mg or buprenorphine sublingual tablet dose ranging from 5.7mg/1.4mg to 17.1/4.3 once daily;

4) Have a positive urine drug screen for buprenorphine during screening and on admission to the clinical research unit to document buprenorphine use;

5) Have a Pittsburgh Sleep Quality Index (PSQI) Total Score of 6 or higher.

Exclusion Criteria:

1) Contraindications for participation as determined by medical history and physical exam performed by study NP or study physician;

2) Pregnant or nursing women;

3) Baseline ECG with clinically significant abnormal conduction;

4) Uncontrolled serious psychiatric or major medical disorder, including COPD. Narcolepsy is also considered exclusionary;

5) Taking prescription or over-the counter drugs or dietary supplements known to significantly inhibit CYP3A4 (such as Clarithromycin, telithromycin, nefazodone, itraconazole, ketoconazole, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir), or CYP3A4 inducers (such as phenobarbital, phenytoin, rifampicin, St. John's Wort, and glucocorticoids);

6) Prescribed medications for insomnia, or unable to discontinue over the counter drugs or dietary supplements used to treat insomnia on study days.

7) Current severe alcohol use disorder or current benzodiazepine use disorder

8) Current DSM-5 diagnosis of any psychoactive substance use disorder other than opioids, cocaine, marijuana, or nicotine, or mild or moderate alcohol use disorder. Diagnosis of mild to moderate use disorder for alcohol will not be considered exclusionary.

9) Any previous medically adverse reaction to opioids or lemborexant:

10) Significant current suicidal or homicidal ideation (C-SSRS “yes” answers on questions 4 or 5) or a history of suicide attempt within the past 6 months.

11) Subjects with Suicidal Behaviors Questionnaire-Revised score ≥8 at the screening visit.

12) Any other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

CONCURRENT MEDICATIONS

Concurrent Medications

All participants should be maintained on the same medications throughout the entire study period, as medically feasible, with no introduction of new chronic therapies. Non-CNS active medications which are known not to have any potential interaction with either buprenorphine or lemborexant would be allowed in this study. The following medications are prohibited during the study: Medications that may affect buprenorphine plasma levels; rifampin, phenobarbital, and phenytoin (CYP450 3A4 inducers) or such as ketoconazole, erythromycin, and saquinavir (enzyme inhibitors) that could affect the levels of parent drug or its active metabolites. Lemborexant is not thought to have any significant pharmacokinetic drug-drug interaction other than those that would inhibit CYP450 3A4, and thus would already be excluded based on the above criteria.

Prohibited

CNS active medications that in the opinion of the PI may affect interpretation of the study.

Medications which could potentially have clinically significant interactions with buprenorphine or lemborexant, notably drugs significantly inhibiting CYP3A.

STUDY TREATMENTS

Method of Assigning Subjects to Treatment Groups

Patients will be randomly assigned to lemborexant or placebo treatment groups in a 2:1 ratio using a randomization scheme overseen by the unblinded research pharmacist, such that 18 patients complete both lemborexant dosing days.

Blinding

Due to the objectives of the study, the identity of test and control treatments will not be known to investigators, research staff, or patients. The following study procedures will be in place to ensure double-blind administration of study treatments:

- Access to the randomization code will be strictly controlled.
- Packaging and labeling of lemborexant and placebo will be identical to maintain the blind. Lemborexant concentrations will not be analyzed until the end of the study.
- The study blind will be broken on completion of the clinical study and after the study database has been locked.

During the study, the blind may be broken only in emergencies when knowledge of the patient's treatment group is necessary for further patient management. Unblinding will occur by the PI contacting the research pharmacy to break the blind in case of emergency.

Formulation of Test Product

Lemborexant 5 mg tablets (Eisai Pharmaceuticals) will be used for this study. To ensure blinding, tablets will be placed in gelatin capsules by the research pharmacist prior to administration.

Buprenoprhine HCl/naloxone films will be used for this study, in unblinded fashion.

Formulation of Control Product: Gelatin placebo capsules identical to capsules that enclose the study drug will be used for placebo. Dextrose powder will be used as a filling in the capsules.

Packaging and Labeling

Each package of study drug will be labeled with the required FDA warning statement, the protocol number, a treatment number, the name of the study physician, and directions for patient use and storage.

Administration of Study Drug

Dosage/Dosage Regimen

If subjects meet inclusion criteria, they will be admitted as research participants to the clinical research unit (CRU) for a total of up to 4 overnight stays across the two inpatient admission visits to maintain complete monitoring for adverse events. While in the hospital, subjects will undergo procedures as described below. Subjects will not be allowed to smoke cigarettes, as smoking is not allowed in the hospital or anywhere on the VCU campus. Subjects who are identified as current smokers will have the option to use a nicotine patch dosed based on the amount of daily cigarettes smoked. Subjects will not be allowed to leave the CRU nor receive visitors if they wish to remain in the study. Subjects who are unable to comply with these restrictions will be dropped from the study. Eligible subjects will be randomized to Group A –placebo only or Group B – lemborexant. Six subjects will be assigned to Group A (placebo) and 12 subjects will be assigned to Group B (active lemborexant).

Study Drug Dosage: 5 mg of lemborexant, and 10 mg of lemborexant, all subjects will receive a dose equivalent to their current prescribed dose of buprenorphine-naloxone sublingually as a film or tablet.

STUDY OUTCOME MEAURES

Primary outcome measures:

1. Safety: Heart rate (HR), blood pressure (BP), respiratory rate, agitation and sedation (Richmond Agitation-Sedation Scale), capnography (EtCO2), and pulse oximetry during placebo administration will be compared to those same measures after lemborexant. Changes in safety measures induced by buprenorphine-naloxone dose along with lemborexant will be compared to those without lemborexant. Adverse event data will be compiled for lemborexant and placebo cohorts and presented as summary statistics.

2. Buprenorphine PK: Plasma concentration-time profiles of buprenorphine and its metabolite norbuprenorphine and after doses during the lemborexant placebo/administration (Day 0,1, 2) will be analyzed to obtain pharmacokinetic parameter estimates of buprenorphine (Cmax, Tmax, AUC, apparent t½, CL/F for parent buprenorphine and metabolic (AUC) ratios for metabolites) by individual. In addition lemborexant and its main metabolite M10 will be determined after each dose of buprenorphine and compared with published lemborexant PK parameters.

Secondary Outcome Measures:

1. Subjective effects on opioid craving and anxiety as measured by a visual analog scale, and brief substance craving scale, and opioid withdrawal based on the Subjective Opioid Withdrawal Scale.

2. Objective opioid withdrawal based on the Clinical Opioid Withdrawal Scale.

3. Impulsivity as measured by delayed discounting. All measures will be compared between subjects receiving lemborexant versus those on placebo to determine the extent to which this measure is modified by the administration of lemborexant with buprenorphine vs. placebo with buprenorphine.

Exploratory Outcome Measures:

1. Pupillometry is used to measure change in pupil size as an indicator of lemborexant changes in buprenorphine central nervous system mu-opioid pharmacological effects (Rollins, Feiner et al. 2014). Single pupil measurements at scheduled times will be performed using a pupillometer per manufacturer's specification. The light in the measurement room will be maintained at 3.6 to 4.3 lux, using a Lutron light meter. Participants will be allowed to adjust to the room lighting for at least 3 minutes prior to any measurement. Pupillometry will be measured using the right eye for all participants, unless otherwise determined by the Investigator. The same eye will be used for all measurements in the study.

2. Sleep quality as measured by sleep diary and Pittsburgh Sleep Quality Index.

3. Relationship between baseline behavioral profiles as determined by the NIDA Phenotyping Battery and subjective response to lemborexant.

STUDY DRUG AND DOSAGE

On PK/Safety Testing week 1 Study Day 2 lemborexant (or matching placebo) is given as 5 mg at 7:00 AM after an overnight stay on the CRU. On PK/Safety Testing Week 2 Study Day lemborexant (or matching placebo) is given as 10 mg at 7:00 AM. Subjects will be continuously monitored on the CRU for 8 hours after the lemborexant dose, which is past the C_{max} lemborexant concentration, which will occur between 8:00 AM and 10:00 AM. Blood samples for determination of buprenorphine concentration and its major metabolite norbuprenorphine and lemborexant and its major metabolite M10 will be collected pre-dose and specified timepoints during the hospital stay (Table 3). Plasma levels will be utilized to determine AUC (area under the concentration–time curve from Time 0 post-dose to infinity) and T1⁄2 (apparent terminal half-life) using noncompartmental analysis, and Cmax (maximum concentration), C24 (concentration at 24 hours post-dose), and Tmax (time to Cmax). Plasma buprenorphine and norbuprenorphine and lemborexant and M10 levels will be determined in the VCU Department of Pharmacology and Toxicology drug analysis laboratory.

Dispensing: Study drug will be dispensed by the research pharmacist and administered by the research nurse on the CRU.

Supply of Study Drug at the Site: Study drug will be provided to the CRU after an order from the study physician or nurse practitioner. Storage: At the testing facility, all lemborexant, buprenorphine, and placebo must be kept in a secure, locked storage place with access limited to authorized study personnel only.

Study Drug Accountability: All study medication will be administered on the CRU. The study staff will record an accurate accounting of each medication administered.

STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is diagrammed in Tables 1-2. Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject. In order to better accommodate participant schedules, PK/Safety Testing Weeks 1 and 2 may be separated by up to approximately 14 days.

Clinical Assessments:

Concomitant Medications

All concomitant medication and concurrent therapies will be documented during screening, CRU study days, and Follow-Up days. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

Clinical Opiate Withdrawal Scale (COWS) and Subjective Opiate Withdrawal Scale (SOWS)

These scales will be administered each study day during screening, admission to the CRU, and CARI or Motivate clinic study days to determine the presence of symptoms indicative of opiate withdrawal.

Demographics

Demographic information (date of birth, gender, race) will be recorded at screening.

Medical History

Relevant medical history, including history of current disease, other pertinent history, and information regarding underlying diseases will be recorded at screening.

Physical Examination

A complete physical examination will be performed by qualified staff (MD, DO, NP). New abnormal physical exam findings must be documented and will be followed by a physician or other qualified staff at the next scheduled visit.

Table 1. Procedures by Day			
OVERVIEW			
Days -30 to Day 0 (approx.)	Day 0 Baseline buprenorphine PK		
Screening and assessment at CARI/Motivate facility including phenotyping battery (PhAB)	Outpatient visit to CRU for baseline buprenorphine PK measurement		
	PK/Safety Testing Week 1, Day 1	PK/Safety Testing Week 1, Day 2 - Day 3	PK /Safety Testing Week 1, Day 4-7
	Admit to CRU for overnight stay, urine drug screen, vital signs, physical examination, COWS	Lemborexant 5mg or placebo plus Buprenorphine-naloxone safety including pulse oximetry, agitation and sedation, PK, pupillometry, withdrawal, impulsivity measures, and subjective effects.	Follow-up at CARI/MOTIVATE for withdrawal, impulsivity measures, subjective effects, and side effects.
	PK/Safety Testing Week 2, Day 1	PK/Safety Testing Week 2, Day 2 - Day 3	PK/Safety Testing Week 2, Day 4-7
	Admit to CRU, urine drug screen, vital signs, physical examination, COWS. Also stay overnight for safety and observation.	Lemborexant 10mg or placebo plus Buprenorphine-naloxone safety including pulse oximetry, agitation and sedation, PK, pupillometry, withdrawal, impulsivity measures, and subjective effects.	Follow-up at CARI/MOTIVATE for withdrawal, impulsivity measures, subjective effects, and side effects.

Schedule of Procedures and Assessments:

(Week 2 Days 1-6 are essentially identical to Week 1 Days 1-6, and the screening measures are only obtained once in the beginning).

TABLE 2: Schedule of Procedures and Assessments:

Study Day	Screening & PhAB -30 to 0 (approx.)	Baseline Day 0	PK/ Safety Week 1 Study Days 1 & Week 2 Study Days 1	PK/Safety Week 1 Study Day 2 & Week 2 Study Day 2	PK/Safety Week 1 Study Day 3 & Week 2 Study Day 3	PK/Safety Week 1 Study Day 4-7 & Week 2 Study Day 4-7
Location	CARI/ MOTIVATE	CRSU	CRSU	CRSU	CRSU if needed, CARI/Motivate otherwise	CARI/ MOTIVATE
Procedure						
Informed Consent	X					
Serum Chemistry	X					
Serum Hematology	X					
Admission to Unit		X	X			
Discharge from Unit		X		X (if medically stable without motor and cognitive impairment)	X	
History, Physical Exam, and Neurological Exam	X	X	X			
Urine Pregnancy test (females)	X	X	X	X		X
Psychiatric Interview (MINI)	X					
PhAB assessment battery and platform instruments	X					
Addiction Severity Index (ASI-lite)	X					
Brief Substance Craving Scale	X	X	X	X	X	X

Study Day	Screening & PhAB -30 to 0 (approx.)	Baseline Day 0	PK/Safety Week 1 Study Days 1 & PK/Safety Week 2 Study Days 1	PK/Safety Week 1 Study Day 2 & PK/Safety Week 2 Study Day 2	PK/Safety Week 1 Study Day 3 & PK/Safety Week 2 Study Day 3	PK/Safety Week 1 Study Day 4-7 & PK/Safety Week 2 Study Day 4-7
Timeline Follow Back Drug Use	**X**	**X**	**X**			**X**
Drug Use History	**X**					
Concomitant Medications	**X**	**X**	**X**			**X**
Clinical Opiate Withdrawal Scale (COWS)	X	X	X	X	X	X
Subjective Opiate Withdrawal Scale (SOWS)	X	X	X	X	X	X
Urine drug screen	X	X	X	X	X	X
Breathalyzer or Salivary Alcohol Level	X	X	X	X	X	X
Verify Inclusion & Exclusion	X	X	X			
Vital Signs	X	X	X	X	X	X
12-Lead ECG (baseline triplicate) and singlet thereafter)	X	X	X	X	X	
Brief Physical Exam	X			X	X	X
Continuous pulse oximetry, capnography, and physiological monitoring		X		X		
Pupil Measurement		X		X		
Adverse Events Inventory		X	X	X	X	X
Visual Analog Scales (VAS)		X		X		
Delay Discounting Task		X		X		X

Study Day	**Screening & PhAB -30 to 0 (approx.)**	**Baseline Day 0**	**PK/Safety Week 1 Study Days 1 & Week 2 Study Days 1**	**PK/Safety Week 1 Study Day 2 & Week 2 Study Day 2**	**PK/Safety Week 1 Study Day 3 & Week 2 Study Day 3**	**PK/Safety Week 1 Study Day 4-7 & Week 2 Study Day 4-7**
Clinical Global Impression Severity & Improvement (CGI-S&I) (baseline CGI-S, and CGI-I thereafter)	X	X		X		X
Richmond Agitation-Sedation Scale		X		X		X
Sleep Diary	X	X	X	X	X	X
Columbia Suicide Severity Rating Scale (C-SSRS) (Lifetime version at screening and since last visit version thereafter)	X	X		X		X
Suicide Behaviors Questionnaire-Revised (SBQ-R).	X					
Daily screening for symptoms of COVID-19,	X	X	X	X	X	X
Testing for SARS-CoV-2			X (prior to CRU admission)			
Lemborexant or Placebo				X		
Buprenorphine-naloxone		X		X		

- Note: Screening and/or baseline procedures may be repeated (and the participant will receive appropriate compensation) if they are not able to be completed in their entirety. Additionally, participants who report obstacles which prevent them from completing any of the in-person outpatient follow-up visits may be offered the option to complete the visit virtually (without the option of providing biological samples for urine drug screen and pregnancy testing, alcohol testing, or collecting of vital signs).

Vital Signs

Body temperature, blood pressure, pulse and respirations will be performed after resting for 5 minutes at each study day.

The Mini International Neuropsychiatric Interview V 7.0.2 (MINI) (Sheehan et al, 1998) will be used to collect diagnostic information used to make eligibility determinations. DSM-5 diagnoses will be ascertained for all subjects. Interviews will be conducted by experienced research personnel who have successfully completed

standardized training in the administration and scoring of the MINI.

PhAB Platform Instrument Measures. Platform instruments will not be administered in the fixed sequence as in below. Efforts will be made to administer as many of the Platform Instruments marked with an asterisk (*) at the time of the Screening Visit (as time permits). Otherwise, they will be administered during the Phenotyping Visit.

* Adult Self-Report Symptom (ASRA) Checklist (ADHD). A brief self-administered inventory consisting of 18 questions which aids in assessing symptoms of ADHD/ADD. Estimated time to complete is 1-5 minutes. It has demonstrated high rates of internal consistency for both self-report and rater-administered versions (Cronbach's alpha 0.88, 0.89, respectively) and high concurrent validity with the rater administered ADHD RS (Adler, Spencer, et al, 2006)

* Family Tree Questionnaire (FTQ) for Substance Use. A self-report family history measure that assists in identifying of first- and second-degree relatives with alcohol and other substance use-related problems (Mann, Sobell, Sobell, & Sobell, 1985). Reliability studies have demonstrated good test-retest reliability, and validity studies have shown criterion and concurrent validity of the instrument.

* Trauma History Questionnaire (THQ). A 24-item self report measure of physical and sexual abuse (ever in lifetime), which includes items related to crime-related events and general disaster/trauma. Respondents are asked to provide the frequency of the event and their age at the time of the event. The THQ has been found to be psychometrically sound with regard to both reliability and validity (Hooper, Stockton, Krupnick, & Green, 2011)

* Relationship Scale Questionnaire (RSQ) A 30-item self-report questionnaire that assesses attachment style. Subjects rate on a 5 point scale, the extent to which each statement describes them in close relationships from "Not at all like me" to "Very much like me". (Griffin and Bartholomew, 1994). Previous research has suggested that the RSQ demonstrates good test-retest reliability and internal consistency (Guédeney, Fermanian, & Bifulco 2010).

* Visual Analog Scale for Pain (VAS-pain). 100mm visual analog scale used to obtain patient rating for current magnitude of pain experienced, with endpoints defining extreme limits such as 'no pain at all' and 'pain as bad as it could be' (Wewers & Lowe, 1990)

Timeline Follow Back for Drug, Alcohol, Tobacco use (Sobell and Sobell, 1996). Structured interview that queries quantity of daily drug,alcohol and tobacco use over a specified time period. Using a calendar, respondents provide retrospective estimates of their tobacco, alcohol and/or drug use. This method has demonstrated solid psychometric properties across a variety of populations (Robinson, Sobell, Sobell, & Leo, 2014).

Fagerström Test for Nicotine Dependence (FTND) (Heatherton et al, 1991; available in the Millisecond Test Library). A widely used 6-item self-report questionnaire designed to measure nicotine dependence, The items are summed to yield a total score of 0-10, with higher scores indicating greater nicotine dependence.

Brief Substance Craving Scale (BSCS; available in the Millisecond Test Library). The BSCS is a 16 item, self-report instrument assesses craving intensity and frequency of craving for cocaine and other substances of abuse over a 24-hour period. Items are rated on a five-point Likert-type scale (Somoza, Dyrenforth, Goldsmith, Mezinskis, & Cohen, 1995).

PTSD Checklist for DSM5. (PCL5; available in the Millisecond Test Library) A 20-item questionnaire based on DSM5 criteria for PTSD**,with each item being assigned a severity score of 0-4, yielding** a total symptom severity score ranging from 0-80 The PCL5 has been shown to exhibit strong internal consistency (α = .94), and test-retest reliability (r = .82), as well as convergent and discriminant validity (Blevins, Weathers, Davis, Witte, & Domino, 2015).

WHO QOL Bref. (available in the Millisecond Test Library). A 26-item questionnaire assessing quality of life in 4 domains: physical, psychological, social and environmental (WHOQOL Group, 1998). Reliability and validity data indicate that the WHOQOL-BREF has good to excellent internal consistency, item–total correlations, and discriminant validity and construct validity (Skevington, Lotfy, & O'Connell, 2004)

Positive and Negative Affect Schedule (PANAS-20; available in the Millisecond Test Library). A 20-item measure assessing positive and negative affect, on a scale from 1 to 5 (Watson et al.1988). Reliability and validity reported by Watson (1988) was moderately good, with the Cronbach alpha coefficient ranging from 0.84 to 0.90, and test-retest correlations ranging from 0.39-0.71 over a 8-week time period.

Toronto Alexithymia Scale (TAS-20; available in the Millisecond Test Library). A 20-item self-report questionnaire to assess emotional awareness. The measure is divided into three subscales: Difficulty Describing Feelings, Difficulty Identifying Feelings, and Externally-Oriented Thinking. Items are rated on a 5 point Likert-type scale, from 1 (strongly disagree) to 5 (strongly agree). The TAS-20 demonstrates good internal consistency (Cronbach's alpha = .81) and test-retest reliability (.77, p<.01), as well as adequate levels of convergent and concurrent validity (Bagby, Parker & Taylor, 1994).

WHO Disability Assessment Schedule (WHO-DAS; available in the Millisecond Test Library). A 12 item generic assessment for health and disability linked to ICF (International Classification of Functioning, Disability and Health). A Normative data for the 12 item version of the WHO-DAS 2.0. found that scores of 10–48 accurately identify individuals with a clinically significant disability (Andrews, Kemp, Sunderland, VonKorf, & Ustun, 2009).

Levenson Self-Report Psychopathy Scale (LSRP; available in the Millisecond Test Library). A 26 item self-report scale, in which respondents rate each item on a scale from 1 (strongly disagree) to 4 (strongly agree. Items included in the scale reflect both primary psychopathy (callous, manipulative, and selfish use of others) and secondary psychopathy (impulsivity and poor behavioral controls; Levenson et al, 1995).

Phenotyping Assessment Battery (PhAB) Measures.

Measures will be administered in non-fixed order.

Attentional Network Test (ANT; available in the Millisecond Test Library): Cue-target test using reaction time to measure Alerting, Orienting, Executive Control. Our focus is on Executive Control. Single testing session, 1 block test 9 min, connects with neuronal networks. (Fan, McCandliss, Sommer, Raz & Posner, 2002). This measure cannot be administered virtually. Therefore, it will only be administered during on-site screening visits under circumstances where the additional time on-site is not deemed to increase risk of COVID-19 exposure.

Stop Signal Reaction Task ((SST) available in the Millisecond Test Library) A measure of response inhibition in which subjects perform a "go *task"* in response to a stimulus, and occasionally the go stimulus is followed by a "*stop signal"*, which requires subjects to withhold the go response (Verbruggen et al, 2008). This measure cannot be administered virtually. Therefore, it will only be administered during on-site screening visits under circumstances where the additional time on-site is not deemed to increase risk of COVID-19 exposure.

Hypothetical Purchase Task. A time- and cost-efficient simulation procedure to assess reinforcement efficacy in humans. Respondents answer questionnaires asking how much of a particular substance (e.g., bags of heroin) they would purchase across a range of prices within a fixed period of time. (Jacobs & Bickel, 1993).

Visual Digit Span (backward recall; available in the Millisecond Test Library): Brief (approximately 5 minutes) commonly used test of working memory, in which subjects are tasked to recall (in reverse order) a sequence of numerical digits presented to them via computer. Increasingly longer sequences are presented in each subsequent trial. (Wechsler, 1997).

5-Trial Adjusting Delay Discounting task (available in the Millisecond Test Library; Koffarnus & Bickel, 2014). A brief task designed to obtain a subject's discount rate in less than one minute. Based on the premise that individuals tend to value rewards less as the amount of time increases until those rewards would be received.

SUPPS-P (available in the Millisecond Test Library). A 20-item version of the original UPPS-P questionnaire, used to assess self-reported personality traits associated with impulsive behavior across five dimensions: urgency, premeditation, perseverance, sensation seeking, and positive urgency (Whiteside & Lynam, 2001)

Distress Tolerance Scale (DTS) (available in the Millisecond Test Library). A 15-item self report measure of emotional distress tolerance. Items are loaded across 4 factors: tolerance, absorption, appraisal, regulation (Simons & Gaher, 2005)

PROMIS- Depression scale. A brief (4-item) self-report measure which assesses four domains of depression: negative mood, views of self, social cognition, and decreased positive affect and engagement. With regard to psychometric characteristics, Choi and colleagues (2010), found that the short form scores were highly correlated with the longer PROMIS measures.

PROMIS- Anxiety. A brief (4-item) self-report measure which assesses anxiety symptoms (e.g., hyperarousal), experienced in the past 7 days. Subjects rate the frequency of experiencing each symptom, on a 5-point Likert-type scale, from 1 (never) to 5 (always).

Buss Perry Aggression Questionnaire- 29 item self measure of aggression. Participants rank statements along a 7-point Likert-type scale, ranging from 1 (extremely uncharacteristic of me) to 7 (extremely characteristic of me). The measure includes four subscales: physical aggression, verbal aggression, anger, and hostility (Buss & Perry, 1992).

Snaith-Hamilton Pleasure Scale (SHAPS; Snaith et al, 1995). Available in the Millisecond Test Library. A 14-item scale which measures anhedonia. Previous research has found the SHAPS has adequate construct validity and test-retest reliability (ICC=0.70) as well as high internal consistency (Cronbach's alpha of 0.94) among both clinical and nonclinical populations (Franken et al, 2007).

Metacognitions Questionnaire-30 (MCQ-30; available in the Millisecond Test Library). A brief (approximately 5 minutes) self-report measure of metacognitive beliefs associated with the five-factor metacognitive model of psychological disorders, including: cognitive confidence, positive beliefs about worry, cognitive self-consciousness, negative beliefs about uncontrollability of thoughts and danger, and beliefs about the need to control thoughts. The MCQ-30 has demonstrated good internal consistency, convergent validity, and test-retest reliability (Wells and Cartwright-Hatton 2004).

Multidimensional Assessment of of Interoceptive Awareness (MAIA; available in the Millisecond Test Library). A 32-item self-report measure that assesses awareness of body sensations, including the emotional/physiological state, physical discomfort and pain. Items are rated on a 6 point Likert-type scale, ranging from 0 (never) to 5 (always) (Mehling, Price et al. 2012).

Pittsburgh Sleep Quality Index-Revised ((PSQI) available in the Millisecond Test Library) A brief questionnaire assessing sleep habits, including disruptions in sleep and influence of sleep on daily functioning during the past week. (Buysse et al.,1989).

Addiction Severity Index (ASI-lite)

A shortened version of the Addiction Severity Index (ASI) (McClellan, et al., 1980), a semi-structured instrument which covers 7 psychosocial domains, including: medical, employment, drug and alcohol use, legal, family/social, and psychiatric functioning. This will be conducted at screening by trained staff.

Sleep Diary: Based on prior studies and recommended by the National Sleep Foundation, this calendar based sleep diary helps subjects record their nightly sleep time. This will be used to retrospectively assess sleep habits/quality occurring approximately 2 weeks prior to screening, and then for each interval in between the following visits.

Clinical Opiate Withdrawal Scale (COWS)

The COWS is an 11-item scale (Wesson and Ling, 2003) designed to be administered by a clinician. This tool can be use in both outpatient and outpatients settings to reproducibly rate common signs and symptoms of opiate withdrawal and monitor symptoms over time. The summed score for the complete scale can be used to help clinicians determined the stage or severity of opiate withdrawal and assess the level of physical dependence on opioids.

Subjective Opiate Withdrawal Scale (SOWS)

The SOWS contains 16 symptoms whose intensity the patient rates on a scale of 0 (not at all) to 4 (extremely).

Adjusting Delay Discounting Task

Adjusting Delay Discounting Task- This task is designed to measure participants' discounting rate when they are presented with the possibility of receiving a real reward.

Visual Analog Scale

A 100mm visual analog scale for craving, anxiety, drug liking, good drug effect, bad drug effect, and drug disliking will be collected during each lemborexant administration session.

Richmond Agitation Sedation Scale

RASS was designed to have precise, unambiguous definitions for levels of sedation that rely on an assessment of arousal, cognition, and sustainability using common responses common stimuli presented in a logical progression. Scores range from +4 (combative) to 0 (alert and calm) and -5 (unarousable).

Columbia Suicide Severity Rating Scale (C-SSRS) (Posner et al., 2009) is an interview measure used to assess suicidal ideation and behavior. The *Baseline* version is used during screening and collects information related to lifetime suicidal ideation and behavior. The *Since Last Visit* version assesses suicidal ideation and behavior in the time since the last patient visit, and will be used at the subsequent study visit.

Suicide Behaviors Questionnaire-Revised (SBQ-R). This is a four item questionnaire that assesses past suicide attempts, suicidal ideation, and self reported likelihood of future suicide. A score $\geq$ 8 on this measure identifies at risk individuals.

Adverse Events

Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates and times), severity, outcome, treatment and relation to study drug will be recorded on the case report form (CRF).

COVID-19 Safety Measures

All participants will undergo PCR SARS-CoV-2 testing prior to each CRU admission based on VCUHS guidance.

All ambulatory patients and visitors (which are limited) are screened at entry (temperature checks, masks, & questions).

Clinical providers observe a universal masking protocol.

Ambulatory patients and visitors receive wristbands. These badges and wristbands are a signal that the guest has entered through an appropriate screening entrance.

VCUHS is not accepting vendor visitation with only exceptions being specific, critical individual patient case support or critical equipment repair.

All observation rotation/experiences for students that are not part of a formal commitment or contract with an outside institution and require the student to be physically present, have been suspended.

Outpatient screening visits will be done at the same time as a regular clinical visit as much as possible to reduce the number of additional visits to the clinic.

Contraception requirements in women of child-bearing potential and men who have partners that are women of child-bearing potential.

The risks of the study medication to the unborn fetus are presently unknown. We will require men who have partners that are of child-bearing potential and women of child bearing-potential to utilize an effective method of contraception during their study participation.

Clinical Laboratory Measurements

Hematology

Blood will be obtained and sent to the clinical hematology lab a complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count, white blood cell differential, and platelet count).

Blood Chemistry Profile

Blood will be obtained and sent to the clinical chemistry lab for determination of serum sodium, potassium, chloride, bicarbonate, random glucose, BUN, creatinine, aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), alkaline phosphatase, total bilirubin, direct bilirubin, albumin and LDH.

Pregnancy Test

A urine pregnancy test will be obtained from female subjects who are of childbearing age prior to their participation in the study.

Urinalysis

Urine will be obtained and sent to the clinical laboratory for determination of color, specific gravity, pH, protein, glucose, ketones, and blood.

Urine Drug Screen

Urine will be obtained from all subjects to be tested for cocaine (benzoylecgonine), opiates and opioids, benzodiazepines, fentanyl, amphetamine, methamphetamine, and THC.

Breathalyzer or salivary alcohol level

Breath or salivary alcohol level will be obtained from all subjects. Subjects who have a positive breath or salivary alcohol will be told that they must return at a later date with a negative alcohol test in order to take part in study procedures.

Pharmacokinetic Measurements

Pharmacokinetic samples for analysis of buprenorphine and its metabolites: Blood samples for analysis of the pharmacokinetics of buprenorphine-naloxone dose and lemborexant 5 and 10mg will be collected at baseline on day 0, and on PK/Safety Testing week 1, day 2, PK/Safety Testing week 2, day 2. After separation of plasma by routine methods, samples will be frozen at -70°C until ready for analysis. Plasma concentrations of buprenorphine and metabolite (norbuprenorphine) and lemborexant and metabolit (M10) will be assayed by liquid chromatography-tandem mass spectrometry.

Table 3. Schedule for blood samples for PK testing

Day 0 Baseline Buprenorphine PK	PK/Safety Week 1, Day 2 (and similarly Week 2, Day 2)	PK/Safety Week 1, Day 3 (and similarly Week 2, Day 3)
	7:00 am (Pre-lemborexant dose at 7:05)	7:00 am (if still on inpatient unit)
	7:30	
8:00 am (Pre-buprenorphine dose at 8:05)	8:00 am (Pre-buprenorphine dose at 8:05)	8:00 am (pre-buprenorphine dose at 8:05)
8:15	8:15	
8:30	8:30	
8:45	8:45	
9:15	9:15	
9:30	9:30	
10:00	10:00	
10:30	10:30	
11:00	11:00	
11:30	11:30	
12:00	12:00	
2:00	2:00	
4:00	4:00	

Pupilometry measurement

Pupillometry is used to measure change in pupil size as an indicator of central nervous system mu-opioid pharmacological effects (Rollins, Feiner et al. 2014). Change in pupil size, as measured by single pupil measurements at scheduled times. using a pupillometer. The light in the measurement room will be maintained at 3.6 to 4.3 lux, using a Lutron light meter. Participants will be allowed to adjust to the room lighting for at least

3 minutes prior to any measurement. Pupillometry will be measured using the right eye for all participants, unless otherwise determined by the Investigator. The same eye will be used for all measurements in the study.

Assessment of motor and cognitive impairment prior to discharge from research unit

All participants will undergo a bief assessment of motor function and mental status exam prior to discharge from the research unit. Participants who are impaired based on this evaluation will remain on the unit until symptoms have resolved.

Lemborexant Dose Escalation (from 5mg in PK/Safety Testing week one to 10mg in PK/Safety Testing week two) and Stopping Criteria for Subject Participation

Dose escalation for a given participant will be discontinued and subject participation will be terminated if any of the following events occur:

The following values do not return to acceptable limits within appropriate time frames

(approximately 30 minutes);

- Heart rate less than 50/min or clinically significant abnormal cardiac rhythm
- Blood pressure less than 90/60mmHg with symptoms of hypotension
- Pulse Oximetry of 92% or less
- Respiratory Rate < 6/min
- Behavioral manifestations of buprenorphine toxicity (moderate sedation or agitation or greater, inability to cooperate with study procedures).
- Participants with clinically significant worsening depression or sleep disorder, or suicidality as determined by study provider.

  Overall trial hold would take place if IRB, FDA, the DSMB or NIDA place the study on hold through email or written notification.

Trial stopping Criteria:

The trial will be discontinued if the Medical Monitor, DSMB, IRB, or FDA recommend study stopping for any reason. Specifically, the study would be discontinued based on a pattern of adverse events (such as the individual participant study stopping criteria listed above) that are thought to be related to study procedures or study medications.

ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

Adverse Events

Adverse Events (AEs) will be identified through daily interviews with participants and noted at any visit and graded according to the tables below. The data will be entered on the standard AE and SAE forms. Continuous logs of all SAEs and AEs will be maintained. SAEs will be reported to the VCU IRB, the DSMB and the US FDA (when appropriate).SAEs will be reported to NIDA SO and PO within 72 hours after identification by the study team. In addition to immediate reports where appropriate, there will be annual reports and descriptions in the results section of publications.

Table 3. AE Severity Grading

Severity (Toxicity Grade)	Description

Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

AE Relationship to Study Drug

The relationship of an AE to the study drug will be assessed using the following the guidelines in Table 4.

Table 4. AE Relationship to Study Drug

Relationship to Drug	Comment
Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

Serious Adverse Experiences (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening adverse experience
- outpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

Serious Adverse Experience Reporting

All adverse events (AEs) occurring during the course of the study will be collected, documented, and reported to the PI. The occurrence of AEs will be assessed at baseline and each clinic visit during the treatment phase of the study.

AE's deemed to be serious (SAEs), as defined by the FDA, will be systematically evaluated at each clinic visit. Any SAE, whether or not related to study, will be reported to the VCU IRB, the NIDA Project Scientist (Tanya Ramey, MD, PhD) and NIDA Program Officer (Kevin Walton, PhD) , and the FDA (when appropriate) within 72 hours of the PI/staff learning of the incident. A full written report to all institutions will follow as soon as possible but in no more than three business days. The written report will be in the format required by the local IRB and will contain information regarding the date of the SAE, description of the SAE, severity rating (Grade 1 to 4), assessment of cause, whether the SAE indicates an increased risk for current or future subjects, and whether changes to the informed consent form will be necessary.

In cases of early termination from the study due to SAE, the participant will have appropriate follow-up medical monitoring. Monitoring will continue until the problem has resolved or stabilized with no further change expected, is clearly unrelated to study medication, or results in death. Outcome of SAEs will be periodically reported to NIDA. A summary of the SAEs that occurred during the previous year will be included in the annual progress report to NIDA.

Medical Monitoring

Dr. F. Gerard Moeller should be contacted directly at these numbers to report medical concerns or questions regarding safety.

Phone: (804) 828-4134

Pager: (804) 828-4999, pager 3479

DISCONTINUATION AND REPLACEMENT OF SUBJECTS

Early Discontinuation of Study Drug (Lemborexant)

A subject may be discontinued from study treatment at any time if the subject or the investigator feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Subject withdrawal of consent (or assent)
- Subject is not compliant with study procedures
- Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment
- Lost to follow-up
- Sponsor request for early termination of study
- Positive pregnancy test (females)
- If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All subjects who discontinue study treatment should come in for an early discontinuation visit as soon as possible and then should be encouraged to complete all remaining scheduled visits and procedures.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents.

Withdrawal of Subjects from the Study

A subject may be withdrawn from the study at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents.

Replacement of Subjects

Subjects who withdraw from the study treatment will be replaced.

Subjects who withdraw from the study will be replaced.

Protocol Violations

A protocol violation occurs when the investigator fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria except when performed for participant safety. Protocol violations for this study include, but are not limited to, the following:

Failure to meet inclusion/exclusion criteria

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The investigator will determine if a protocol violation will result in withdrawal of a subject.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. A copy of the form will be filed in the site's regulatory binder, and these will be reported to VCU IRB and the DSMB.

DATA SAFETY MONITORING

The Data Safety and Monitoring Plan includes establishment of a Data Safety Monitoring Board who will include five individuals who are completely independent of the investigators and who have no financial, scientific, or other conflict of interest with the trial. Each member will provide written documentation attesting to absence of conflict of interest. Additionally, Dr. Moeller will serve as the on site medical monitor for the study. For full data safety monitoring information see the Data Safety Monitoring Plan.

STATISTICAL METHODS AND CONSIDERATIONS

Initial analyses will evaluate group differences on demographic and baseline variables, will use contingency tables with chi-square testing, ANOVA's, and examination of correlations between baseline variables subjective responses and clinical results. General data analysis procedures: Prior to data analysis procedures, groups will be examined for differences in baseline characteristics that could potentially influence treatment outcome. Any variables that differ between groups and are related to outcome measures will be examined as potential covariates in subsequent data analyses.

Primary outcome measures:

1. Safety: Heart rate (HR), blood pressure (BP), respiratory rate, agitation and sedation (Richmond Agitation-Sedation Scale) and pulse oximetry during a placebo dose will be compared to HR and BP after each lemborexant dose (5 mg and 10 mg doses). Changes in safety measures induced by lemborexant dose along with buprenorphine will be compared to those without lemborexant, by lemborexant dose level (5 mg and 10

mg doses), using a generalized linear mixed model analysis with the participant as a random effect for each outcome. Adverse event data will be compiled for lemborexant and placebo cohorts and presented as summary statistics.

2. Buprenorphine PK: Plasma concentration-time profiles of buprenorphine and its metabolite norbuprenorphine after doses during the lemborexant placebo/administration (Day 0,1, 2) will be analyzed to obtain pharmacokinetic parameter estimates of buprenorphine (Cmax, Tmax, AUC, apparent t½, CL/F for parent buprenorphine and metabolic (AUC) ratios for metabolites) by individual. These parameters will be compared within subjects on sessions with lemborexant. Lemborexant PK will be compared with published lemborexant PK data. As it would be unethical to withhold buprenorphine treatment from patients who are on buprenorphine for MAT, there will be no lemborexant dose without buprenorphine.

3. Changes in secondary outcome measures induced by lemborexant dose along with buprenorphine will be compared to those without lemborexant, by lemborexant dose level (5 mg and 10 mg doses), using a generalized linear mixed model analysis with the participant as a random effect for each outcome.

Safety and tolerability data will be summarized by treatment group.

Adverse event rates will be coded by body system and MedDra classification term. Adverse events will be tabulated by treatment group and will include the number of patients for whom the event occurred, the rate of occurrence, and the severity and relationship to study drug.

Interim Analysis

There will be no formal interim analysis.

Rationale for sample size: Sample size for effect of lemborexant on recommendations from the FDA regarding phase I safety studies.

DATA COLLECTION, RETENTION AND MONITORING

Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug.

Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific paper/electronic CRF when the information corresponding to that visit is available. Subjects will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee), but will be identified by a subject number.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator.

Data Management Procedures

The data will be entered into a REDCap database and OnCore. The Data Management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed. All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database. At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

Availability and Retention of Investigational Records

The Investigator will make study data accessible to IRB, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that subject. The Investigator will ensure the reliability and availability of source documents from which the information on the CRF was derived. All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) will be kept secured for a period of six years after study completion and the IND has been discontinued.

Subject Confidentiality

In order to maintain subject confidentiality, only a subject number will identify all study subjects on CRFs and other documentation submitted to the Sponsor. In addition, a Certificate of Confidentiality will be issued by NIDA to protect subject confidentiality.

ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

Protocol Amendments

Any amendment to the protocol will be written by the investigator Protocol amendments cannot be implemented without prior written IRB approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRB is notified subsequently.

Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the VCU IRB or Western IRB prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB in accordance with

the standard operating procedures and policies of the IRB, and the Investigator will keep the IRB informed as to the progress of the study. The Investigator will obtain assurance of IRB compliance with regulations.

Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRBs written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB and written verification that the modification was submitted and subsequently approved should be obtained.

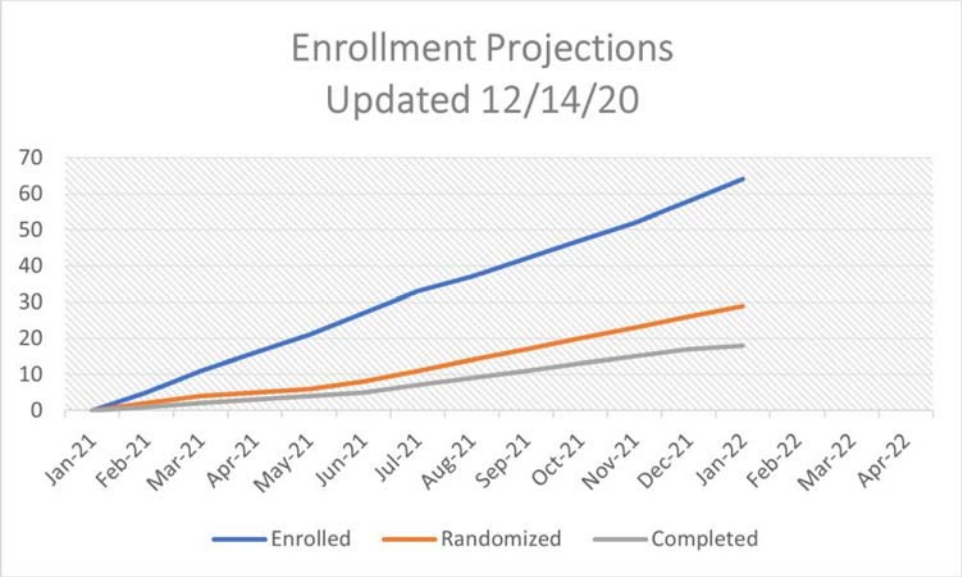
The IRB must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations. The Investigator will prepare the informed consent form and HIPAA authorization. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonization and will also comply with local regulations. A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects must be given ample opportunity to inquire about details of the study. A copy of the signed consent form will be given to the subject and the original will be maintained with the subject's records.

Publications

The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.



TIMELINE:

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