Title: Drug Interaction and Subjective Effects of Compounds for Opioid Use Disorder

NCT #: NCT03143855

Document date: 02/12/2018

Document Type: Protocol and SAP

TABLE OF CONTENTS

List of Abbreviations

AE	adverse event
ALT	alanine aminotransferase
ASI-lite	Addiction Severity Index
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
C-SSRS	Columbia Suicide Severity Rating Scale
CGI-I	Clinical Global Impression Improvement
CGI-S	Clinical Global Impression Severity
CNS	Central Nervous System
COWS	Clinical Opiate Withdrawal Scale
CPT	Cold Pressor Test
CRF	Case Report Form
CRP	C-reactive protein
CRSU	Clinical Research Services Unit
DMC	Data Monitoring Committee
DMT	Delayed Memory Task
DSMB	Data Safety Monitoring Board
ESR	erythrocyte sedimentation rate
FDA	Food and Drug Administration
FTND	Fagerstrom Test for Nicotine Dependence
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IL-8	Interleukin-8
IMT	Immediate Memory Task
IRB	Institutional Review Board

IV	intravenous
KMSK	Kreek-McHugh-Schluger-Kellogg Scale
LDH	lactate dehydrogenase
NART	National Adult Reading Test
OCS	Opioid Craving Scale
OPUD	Opioid Use Disorder
PI	Principal Investigator
PK	pharmacokinetic
POMS	Profile of Mood Sates
SAE	serious adverse experience
SCID	The Structured Clinical Interview for DSM-IV
SCID-II	The Structured Clinical Interview for DSM-IV Personality Disorders Module
SOWS	Subjective Opiate Withdrawal Scale
VAS	Visual Analog Scale

PROTOCOL SYNOPSIS

TITLE	Phase I drug interaction and subjective effects of compounds 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., oxycodone) and efficacy (subjective response to oxycodone) in non-treatment seeking opioid use disorder subjects. The compound to be studied will be the 5-HT2CR agonist lorcaserin. Lorcaserin has been shown to reduce oxycodone self-administration and cue reactivity in rodents (described in detail in Background section below).
STUDY DESIGN	This is a randomized, double-blind, placebo-controlled phase 1b/2a study.
PRIMARY OBJECTIVE	1. Assess interaction between lorcaserin and oxycodone in healthy opioid using subjects. 2. Assess effect of lorcaserin on subjective response to oxycodone in healthy opioid using subjects. 3. Assess effect of lorcaserin on oxycodone PK in healthy opioid using subjects.
SECONDARY OBJECTIVES	Assess effect of lorcaserin on response inhibition in healthy opioid using subjects.
NUMBER OF SUBJECTS	18
SUBJECT SELECTION CRITERIA	Inclusion Criteria: In order to participate in this study, subjects must: 1. Males and females between 18 and 70 years-of-age. 2. Understand the study procedures and provide written informed consent. 3. Meet current DSM-5 criteria for opioid use disorder, at least moderate severity, but are not seeking treatment. 4. Have at least one positive urine drug screen for opioids during screening to document opioid use. 5. Have no clinically significant abnormalities in the judgment of the study physician in hematology and chemistry laboratory tests including liver function tests. 6. Have no contraindications for study participation as determined by medical history and physical examination. 7. Be able to demonstrate an understanding of study procedures and follow instructions including behavioral laboratory testing.

	8. No pregnant or nursing women will be permitted in the study, and women must either be unable to conceive (i.e., surgically sterilized, sterile, or postmenopausal) or be using a reliable form of contraception (e.g., abstinence, birth control pills, intrauterine device with spermicide, or condoms). Men will be advised to use condoms. All females must provide negative pregnancy urine tests before study entry, at each visit during the study, and at the end of study participation. Exclusion Criteria: In order to participate in the study, subjects must not: 1. Meet current DSM-5 diagnosis of any psychoactive substance use disorder other than opioids, cocaine, marijuana, or nicotine. Diagnosis of mild to moderate use disorder for alcohol will not be considered exclusionary. 2. Have a current DSM-5 axis I psychiatric disorder other than substance use disorder including but not limited to Bipolar Disorder, Major Depressive Disorder, ADHD, or Schizophrenia or a neurological disorder requiring ongoing treatment and/or making study participation unsafe. 3. Have any previous medically adverse reaction to oxycodone or other opioids or lorcaserin or history of serotonin syndrome. 4. Have any untreated clinically significant medical disorder including cardiovascular, pulmonary, CNS, hepatic, or renal disorder. 5. Have a history of seizures (excluding childhood febrile seizures), or loss of consciousness from traumatic injury for more than 30 minutes. 6. Have significant current suicidal or homicidal ideation or a history of suicide attempt within the past 6 months. 7. Have conditions of probation or parole requiring reports of drug use to officers of the court. 8. Have impending incarceration. 9. Have a positive HIV test by self-report or history. 10. Be pregnant or nursing or not using a reliable form of contraception if able to conceive. All females must provide negative pregnancy urine tests at screening, and daily after hospital admission. 11. Have any other illness, or condition, which in the opinion of the PI would preclude safe and/or successful completion of the study. 12. Have taken any investigational drug within 90 days prior to baseline. 13. Have an allergy to lorcaserin or oxycodone. 14. Have taken or are currently taking drugs that are know to inhibit cytochrome P450, CYP3A or CYP2D6. 15. ECG with QTc > 440ms.

TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	Lorcaserin 10mg Product will be administered orally twice daily for 3 days.
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 28 days (including intervening weekends) Screening: up to 21 days Baseline: 1 day Treatment : 4 days Follow-up: 2 days 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 conduction or interpretation of the study. Medications which could potentially interact with lorcaserin or oxycodone, notably drugs inhibiting CYP3A or CYP2D6
Efficacy Evaluations	Primary outcome measures: 1. Safety: Heart rate (HR), blood pressure (BP), respiratory rate, and pulse oximetry, pupil diameter measures during a placebo dose will be compared to HR and BP after each oxycodone dose (10 mg and 20 mg doses). Changes in HR and BP induced by oxycodone dose along with lorcaserin will be compared to those without lorcaserin, by oxycodone dose level (10 mg and 20 mg doses), using repeated measures analysis of variance (ANOVA). Adverse event data will be compiled for lorcaserin and placebo cohorts and presented as summary statistics. 2. Oxycodone PK: Plasma concentration-time profiles of oxycodone and its metabolites (noroxycodone, oxymorphone and noroxymorphone) after immediate-release oxycodone doses during placebo administration (Day 0,1) will be analyzed to obtain pharmacokinetic parameter estimates of oxycodone (cmax, tmax, AUC, apparent t½, CL/F for parent oxycodone and metabolic (AUC-) ratios for metabolites) by individual. These parameters will be compared within subjects on sessions with lorcaserin (Day 4,5,6). 3. Subjective response to oxycodone: Subjective response measures ((visual analog scale (VAS) and Cold Pressor Test (CPT)) after oxycodone administration on day zero will be compared to same measures after oxycodone administration on day 4 between lorcaserin and placebo treated subjects to determine the extent to which these measures are modified by the administration of lorcaserin using repeated measures ANOVA.

	Secondary Outcome Measures: 1. Attention, Memory, and Response inhibition: Correct detections and commission errors on the Immediate and Delayed Memory Task (IMT/DMT) will be compared between lorcaserin and placebo subjects to determine the extent to which this measure is modified by the administration of oxycodone and lorcaserin using repeated measures ANOVA. 2. Craving as measured by the opioid craving scale and brief substance craving scale will be compared between lorcaserin and placebo subjects to determine the extent to which this measure is modified by the administration of oxycodone and lorcaserin using repeated measures ANOVA.
Planned Interim Analyses	When approximately 50% of patients have completed the study, an interim analysis for safety will be conducted by the DSMB. Serious adverse events will be monitored by the committee on an ongoing basis throughout the study.
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: Urn randomization will be used for gender to reduce any potential between-group differences (lorcaserin vs. placebo) on baseline variables. Prior to data analysis procedures, groups will be examined for differences in other 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), pulse oximetry, pupil diameter, and respiratory rate measures during a placebo dose will be compared to HR and BP after each oxycodone dose (10 mg and 20 mg doses). Changes in HR and BP induced by oxycodone dose along with lorcaserin will be compared to those without lorcaserin, by oxycodone dose level (10 mg and 20 mg doses), using repeated measures analysis of variance (ANOVA). Adverse event data will be compiled for lorcaserin and placebo cohorts and presented as summary statistics. 2. Oxycodone PK: Plasma concentration-time profiles of oxycodone and its metabolites after oxycodone doses during placebo administration (Day 0,1) will be analyzed to obtain pharmacokinetic parameter estimates(cmax, tmax, AUC, apparent t½, CL/F and metabolic (AUC-) ratios) by individual. These parameters will be compared within subjects on sessions with lorcaserin (Day 4,5,6). 3. Subjective response to oxycodone: Subjective response measures (VAS, CPT) after oxycodone administration on day zero will be

	compared to VAS and CPT measures after oxycodone administration on day 4 between lorcaserin and placebo treated subjects to determine the extent to which these measures are modified by the administration of lorcaserin using repeated measures ANOVA. Secondary Outcome Measures: 1. Attention, Memory, and Response inhibition: Correct detections and commission errors on the Immediate and Delayed Memory Task (IMT/DMT) will be compared between lorcaserin and placebo subjects to determine the extent to which this measure is modified by the administration of oxycodone and lorcaserin using repeated measures ANOVA. 2. Craving as measured by the opioid craving scale and brief substance craving scale will be compared between lorcaserin and placebo subjects to determine the extent to which this measure is modified by the administration of oxycodone and lorcaserin using repeated measures ANOVA.
Rationale for Number of Subjects	Power Calculation and Sample Size: Rationale for sample size: Sample size for effect of lorcaserin on oxycodone self-administration was based on previous research showing effects of oxycodone on pain and subjective responses in an experimental laboratory session (Jones et al., 2016). In an effort to increase the power of the study, a Bayesian approach will also be utilized that incorporates information from previous studies. This approach will use a Bayesian hierarchical model with subject at the lowest level of the hierarchy and treatment group at the second level. This model is analogous to the repeated measures ANOVA except that prior information will be introduced. Since many similar studies have been conducted with oxycodone users and the same outcome measures we will assign an informative prior distribution on the control group where the mean and standard deviation are educated guesses from the information provided in previous study of Jones et al., (2016). For the treatment group we will assume a priori no change in the mean from the control group and the standard deviation are similar to those as the experimental group of the study by Hart et al. (Hart et al., 2008). The model will be calculated using standard Markov Chain Monte Carlo (MCMC) packages such as WinBUGS, OpenBUGS, JAGS or MCMCpack in R. Because MCMC sampling techniques are being employed the quality of the samples from the posterior distribution will be checked using trace plots, effective sample size, potential scale reduction factor and Hellinger distances (for more on Bayesian analyses and MCMC sampling see (Gelman et al., 2013). As necessary techniques such as discarding burn-in samples, thinning and over-disperse starting points will be employed in order to obtain a set of samples from the posterior distribution that have an effective sample size of 10,000 on all parameters. All inferences will be made from this set of samples from the posterior distribution. To calculate the power for the acute effects of the study three analyses are considered using the paired differences of subjects

at baseline and acute time points.

A two-sample test on the means is performed using: Wilcoxon test (non-parametric), T-test (parametric) and a Bayesian (parametric) approach. While from a Bayesian paradigm the notion of power does not exist in the traditional sense, one can create a decision rule and loss function in such a way that the associated risk is analogous to the notion of power. To understand the power of each of the methods a Monte Carlo study was performed utilizing 1,000 separate datasets for likely effect sizes and sample sizes.

The power was calculated as the proportion of datasets in which the test "rejected" the null hypothesis. The table below gives the power for each test across percent change in effect size and control group sample sizes, here the treatment group sample size was n2 = 12. Based on the table below, an n of 6 was chosen as the sample size for the placebo group.

		Percent Change			
n1	Test	Low (10%)	Medium (25%)	High (50%)	75%
4	T-test	0.116	0.448	0.955	0.998
	Wilcoxon	0.044	0.242	0.855	0.992
	Bayesian	0.249	0.689	0.992	1
6	T-test	0.138	0.528	0.981	0.999
	Wilcoxon	0.079	0.357	0.941	0.997
	Bayesian	0.308	0.782	0.994	1
8	T-test	0.116	0.588	0.986	1
	Wilcoxon	0.096	0.495	0.956	1
	Bayesian	0.309	0.803	0.999	1

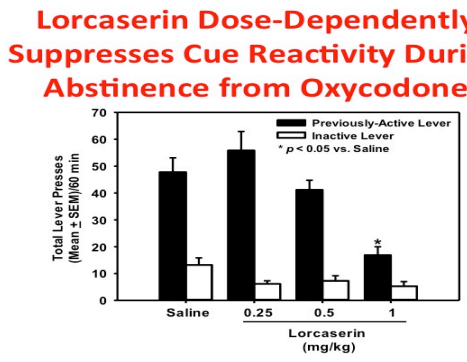
Wilcoxon and Bayesian Power are based off of 1,000 Monte Carlo simulations.

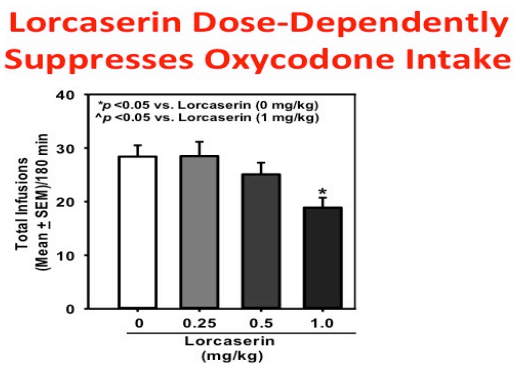
BACKGROUND

Lorcaserin is a serotonin (5-HT) 2C receptor agonist (Trade Name Belviq) approved for treatment of obesity.

Overview of Non-Clinical Studies

Our preclinical research collaborators and others have shown that lorcaserin and other 5-HT2CR agonists have been shown to reduce drugs of abuse self-administration and cue reactivity in rodents including cocaine (Cunningham et al., 2011; Manvich et al., 2012) and nicotine (Levin et al., 2011). Recently, this data has been expanded to opioids. As shown in the figures below, rats trained to self-administer oxycodone showed a significant reduction in self-administration and oxycodone cue induced lever presses after lorcaserin

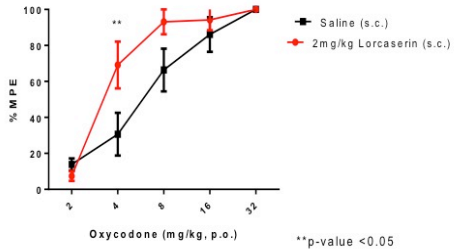




administration (Cunningham et al., unpublished data)

In addition, a study was carried out in mice on the effects of lorcaserin on the oxycodone alteration of pain measures. As shown in the figures below, acute lorcaserin potentiated the effects of oral oxycodone on one measure of pain, the tail flick assay. However, it attenuated the effect of oxycodone on the hot plate assay. The tail flick assay is considered to be a spinal pain pathway, whereas the hot plate assay is considered to be a measure of supraspinal (central) pain response (Le Bars et al., 2001). This preliminary data suggests that lorcaserin may alter the pain reducing effects of oxycodone, which may differ based on whether the pain response is peripheral or central.

Acute lorcaserin potentiates oral oxycodone in the tail flick assay at 56C

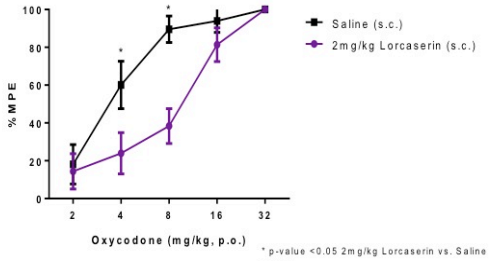


**p-value <0.05

2mg/kg Lorcaserin + Oxycodone ED50 = 3.89 (2.82 – 5.38)

Saline + Oxycodone ED50 = 6.01 (4.73 – 7.63) PR = 1.48 (1.04 – 2.15)

Acute lorcaserin attenuates oral oxycodone-induced antinociception in the hot plat at 56C



* p-value <0.05 2mg/kg Lorcaserin vs. Saline control

2mg/kg Lorcaserin + Oyxcodone ED50 = 7.62 (6.0 – 9.67)

Saline + Oxycodone ED50 = 3.65 (2.7 – 4.93) PR = 1.96 (1.39 – 2.88)

Overview of Clinical Studies

BELVIQ (lorcaserin hydrochloride) tablets, for oral use. BELVIQ is a serotonin 2C receptor agonist indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of: 30 kg/m2 or greater (obese) or 27 kg/m2 or greater (overweight) in the presence of at least one weight-related comorbid condition, (e.g., hypertension, dyslipidemia, type 2 diabetes). In a preliminary report of a smoking cessation study, Eisai Inc. and Arena Pharmaceuticals Inc. announced results from a Phase 2 trial investigating lorcaserin HCl for smoking cessation. The trial demonstrated statistically significant improvement over placebo in reducing the number of patients who smoke after 12 weeks of treatment. Based on Arena media report dated November 3, 2014, the 12-week, randomized, double-blind, placebo-controlled trial assessed the efficacy and safety of lorcaserin as a potential aid to smoking cessation. In the trial, 603 active smokers were randomized to receive lorcaserin 10 mg once daily, 10 mg twice daily or placebo in a 1:1:1 ratio. At baseline subjects were dependent on nicotine averaging 18 cigarettes per day. Patients received medication for two weeks prior to attempting to quit around Day 15 of the trial. Subjects also received smoking cessation counseling during the trial. Results showed that the carbon monoxide confirmed continuous abstinence rate (CAR), was achieved by 5.6%, 8.7%, and 15.3% of patients in the placebo, once daily and twice daily groups, respectively (p-value = 0.003 and odds ratio = 3.02 for twice daily vs. placebo; the result for once daily vs. placebo was not statistically significant).

Safety and tolerability data showed that there was a statistically significant difference in weight between lorcaserin twice daily and placebo (-0.98 kg and -0.01 kg, respectively, p-value = 0.0004). The most common adverse events during the study were headache, nausea, constipation, dizziness and dry mouth, similar to previous trials of lorcaserin. For more detail refer to Belviq prescribing information.

STUDY RATIONALE

The overall goal of this project is to develop initial human data on effects of novel compounds on safety (interactions with oxycodone) and efficacy (subjective response to oxycodone) in non-treatment seeking opioid use disorder subjects. The compound to be studied will be the 5-HT2CR agonist lorcaserin. There are no known or reported adverse interactions between lorcaserin and oxycodone or other opioids.

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 oxycodone or lorcaserin. The risks of the medications are provided below.

Risks of Lorcaserin Administration

Lorcaserin is FDA approved for the treatment of obesity. According to the FDA briefing document on lorcaserin based on the clinical trials in patients with obesity, "the most common adverse events with an incidence in the lorcaserin group that clearly exceeded placebo were headache (16.8 vs. 10.1%), dizziness (8.5 vs. 3.8%), nausea (8.3 vs. 5.3%), fatigue (7.2 vs. 3.6%), and dry mouth (5.3 vs. 2.3%). These events were typically dose-related, mild or moderate in severity and transient. Furthermore, the excess over placebo occurred primarily within the first several days of treatment for headache and dizziness. Rates of discontinuation for adverse events were similar for lorcaserin 10 mg BID (8.6%), 10 mg QD (7.5%), and placebo (6.8%). Serious adverse events were as expected for the population, and similar in both character and frequency in the lorcaserin and placebo populations." Because lorcaserin has the potential to impair cognitive function, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that lorcaserin therapy does not affect them adversely. In preclinical studies abnormalities in thyroid function and liver tests have been seen in animals, but no changes in thyroid function or liver function have been noted in humans. In patients with diabetes, a drop in blood sugar has been seen. Weight loss may increase the risk of hypoglycemia in patients with type 2 diabetes mellitus treated with insulin and/or insulin secretagogues (e.g., sulfonylureas); hypoglycemia was observed in clinical trials with lorcaserin. Lorcaserin has not been studied in combination with insulin. In other populations, lorcaserin has been associated with a modest increase in blood pressure.

Other Potential Risks of Lorcaserin but not seen in Clinical Trials

Risk of serotonin syndrome: As lorcaserin is a serotonergic medication, it carries the risk of serotonin syndrome associated with all serotonergic compounds. This risk could be increased by combining lorcaserin with other serotonergic compounds. Our own research experience using another serotonergic drug, citalopram with cocaine dependent subjects (Moeller et al., 2007) and another ongoing clinical trial has not seen any episodes of serotonin syndrome. Risk of valvular heart disease: Valvular heart disease has been seen in compounds that are 5-HT2B agonists (Hutcheson et al., 2011). Lorcaserin is a 5-HT2C agonist, with minimal affinity for the 5-HT2B receptor (see table 1 below). In addition, occurrence of valvular heart disease was examined in clinical trials with lorcaserin. In 3451 subjects who took lorcaserin 10mg twice daily for 1 year, 2.4% of patients who received lorcaserin and 2.0% of patients who received placebo developed valvular regurgitation on echocardiography (Belviq prescribing information).

Table 1. Lorcaserin 5-HT Receptor Affinity (Belviq Prescribing Information)

Serotonin Receptor Subtype	EC_{50}, nM	Ki, nM
$5\text{-}HT_{2C}$	39	13
$5\text{-}HT_{2B}$	2380	147
$5\text{-}HT_{2A}$	553	92

Risk of Priapism: Other medications that have 5-HT2C receptor affinities have been shown to produce priapism. Due to this risk subjects will be warned regarding the need for prompt treatment of prolonged erections lasting more than four hours.

Abuse Potential: Lorcaserin is a Schedule IV medication due to studies in humans showing that supratherapeutic doses of lorcaserin produced a rating of "high". In a published study (Shram et al., 2011) subjective measures of drug response were obtained in recreational polydrug users after 20mg, 40mg, and 60mg of lorcaserin and compared with zolpidem (15mg and 30mg) and ketamine (100mg). Results of that study showed that on the visual analog scale (VAS) rating of "drug liking", overall, the mean scores for zolpidem and ketamine were in the "liking" range of greater than 50 on a 100 point scale, whereas, ratings for lorcaserin were in the "disliking" range (less than 50). The effects were primarily due to higher doses of lorcaserin. On other VAS ratings, lorcaserin 40mg and 60mg produced a significant increase in the "high" rating but also produced a significant increase in the "feeling sick" rating. In contrast, zolpidem and ketamine were liked by the subjects. The authors' conclusions regarding this study were that "This study demonstrated that lorcaserin has a very low potential for abuse by recreational polydrug users with a history of using perception-altering and central nervous system depressant drugs. Supratherapeutic doses of lorcaserin were significantly disliked, as demonstrated by the bipolar Drug Liking VAS (primary measure), and was associated with prominent negative effects." (Shram et al, 2011). Based on the safety and abuse potential data from human studies described above a dosage regimen of 10mg twice daily was chosen for this study.

Risks of Oxycodone Administration

Primary adverse reactions to oxycodone include constipation, sedation, respiratory depression and hypotension. We will limit these potential risks in several ways: (1) We will enroll only physically healthy opioid using subjects with no evidence of cardiovascular or respiratory disease based on history, physical examination, ECG, and laboratory tests – all prospective subjects will be seen a Cardiologist on staff prior to the initiation of the study. (2) We will administer doses shown to be safe in previous studies that were selected to produces scientifically valid results. (3) We will monitor subjects closely in an outpatient hospital setting throughout the duration of action of the drug, under the supervision of medical personnel trained in basic life support, with immediate availability of physicians trained in advanced cardiac life support and resuscitation if needed. We will also employ a bedside monitor for heart rate, ECG, pulse oximetry and respiratory rate. Blood pressure will be measured non-invasively every 10 minutes for 1 hour after oxycodone treatment. We have an intervention plan in place to deal with any adverse events that may occur, as described in the following paragraph. In the event of an adverse event, the research team and the hospital is fully prepared to respond to any situation that may arise. The general and psychiatric emergency rooms are located minutes away. There is a 24-hour medical emergency code team in the hospital. Physicians and their designated medical staff are fully trained to respond to all types of medical and psychiatric emergencies. A fully equipped resuscitation cart is located on the unit with I.V. naloxone. This study will be conducted at the CRS unit, a specialized inpatient and outpatient research unit at VCU Medical Center. This unit has previously conducted phase I studies, including other drug studies such as cocaine studies in humans (Baker et al., 2007). In the highly unlikely event of a suspected of medical emergency (i.e. respiratory depression, significant hypotension) the subject will be promptly evaluated by one of the research physicians and either transferred to Step Down Unit, ICU or Emergency Department or prescribed the appropriate treatment and monitoring level. Low risk subjects such as those with resolution of symptoms, normalization of vital signs, non-diagnostic ECG, and lack of potentially lethal arrhythmias may be monitored in the CRSU (see Immediate Evaluation of Adverse Event form).

Effects on addiction: An additional concern is exposure to oxycodone increasing opioid use. In recruiting our subjects, the inclusion criteria include current opioid use disorder. The risk of oxycodone administration on craving in general will be minimized through: 1) To enroll in this study, opioid use disorder subjects must not be seeking treatment. 2) Subjects will remain in the controlled outpatient environment for 3 hours after the last

dose of oxycodone. 3) At the time of leaving the hospital, risks of ongoing opioid use and opportunities for treatment are discussed with all subjects.

Risks of Lorcaserin Combined with Oxycodone

Lorcaserin was approved by the FDA for the treatment of obesity in June of 2012. Since that time there have been no reported interactions between lorcaserin and oxycodone or other opioids. There is no known theoretical interaction between 5-HT2CR agonists and mu opioid receptor agonists, either directly or through altering the metabolism of either drug when administered together other than the theoretical possibility of a serotonin syndrome, although this has never been reported.

In a recent NIDA funded preclinical study described above, lorcaserin was administered with oxycodone to rats. No increased sedation was noted in the rodents after lorcaserin administration compared to placebo.

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 of the study, the behavioral intervention, and the study medication provided by a study staff member. Staff will emphasize that participation is voluntary. Next, the Project Director or study coordinator will conduct an item-by-item reading of the consent form while the participant reads along. The participant then meets with a physician investigator 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 effects produced by administration of oxycodone.

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 lorcaserin 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 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.

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, another copy is held in the Principal Investigator's records, and the original signed consent is kept in a separate, locked file accessible to the Institutional Review Board (IRB) upon request. Individuals who decide that they are interested in treatment for opioid use disorder will be assisted in selecting treatment services and self-help meetings from the community resource listings.

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 media (i.e., computer-stored data, and data stored on CDs) will be password protected via encrypted code key known only to the senior study personnel.

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 impact those individuals.

Potential Benefits of the Proposed Research to the Subjects and Others

Subjects in the study will receive close psychiatric attention. The potential benefits to society include decreased oxycodone and other 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 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 urine collection or 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:

Staff will be trained and supervised to identify participants who are of danger to themselves or others. Those participants found to be seeking treatment will be referred for appropriate care.

The identification of effective treatments for oxycodone dependence 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 OBJECTIVES

Primary Objective

The primary objectives are to provide safety and PK information on potential drug interactions between lorcaserin and oxycodone in subjects with opioid use disorder, to provide information on effects of lorcaserin on subjective response to oxycodone.

Secondary Objectives

The secondary objective is to examine effects of lorcaserin and oxycodone on behavioral laboratory measures of attention, memory, and impulsivity in oxycodone use disorder subjects.

STUDY DESIGN

Study Overview

The overall goal of this project is to develop initial human data on effects of novel compounds on safety (interactions with oxycodone) and efficacy (subjective response to oxycodone) in non-treatment seeking opioid use disorder subjects. This is a Phase I human drug interaction study examining the safety of concurrent administration of oxycodone with novel compounds, and the effects of the novel compounds on subjective response to oxycodone in non-treatment seeking opioid use disorder subjects. These data will provide important information for go/no-go decisions on phase II clinical trials using medications as a tool to enhance abstinence. The initial compound to be studied will be the 5-HT2CR agonist lorcaserin, which has been shown to reduce oxycodone self-administration and cue reactivity in rodents. In addition there is human safety data in obese subjects for lorcaserin as it is currently FDA approved for obesity, but there is no human opioid interaction/PK data and no PD data to support potential dosages for phase II clinical trials.

This is a single center, double-blind, placebo-controlled, randomized, 1b/2a study. 18 subjects are planned.

Screening data will be reviewed to determine subject eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria will be entered into the study.

The following treatment regimens will be used:

Lorcaserin will be administered at a dose of 10mg twice daily.

Placebo or Comparator – identical placebo capsules administered at the same time as lorcaserin.

Total duration of subject participation will be up to 28 days. Total duration of the study is expected to be 18 months.

Criteria for evaluation

Primary Efficacy Endpoint

1. Safety: Heart rate (HR), blood pressure (BP), pulse oximetry, pupil diameter, and respiratory rate measures prior to oxycodone dosing will be compared to these measures after each immediate release oxycodone dose (10 mg and 20 mg doses). Changes in these measures induced by oxycodone along with lorcaserin will be compared to those without lorcaserin, by oxycodone dose level (10 mg and 20 mg doses), using repeated measures analysis of variance (ANOVA). Changes in ECG readings taken prior to dosing as compared to those

taken during/following oxycodone dosing will be reported as summary statistics. Adverse event data will be compiled for lorcaserin and placebo cohorts and presented as summary statistics.

2. Subjective response to oxycodone: Subjective response measures (VAS and CPT) obtained prior to dosing will be compared between lorcaserin and placebo subjects to those during oxycodone dosing by oxycodone dose level to determine the extent to which these measures are modified by the administration of lorcaserin using repeated measures ANOVA.

4. Oxycodone PK: Plasma concentration-time profiles of oxycodone after oxycodone dosing during placebo administration (Day 0,1) will be analyzed to obtain pharmacokinetic parameter estimates for oxycodone and its circulating metabolites, norxycodone, oxymorphone and noroxymporphone (cmx, tmax, AUC, apparent t½, CL/F and metabolic (AUC-) ratios for each metabolite) by individual. These parameters will be compared within subjects during treatment with lorcaserin (Day 4, 5, 6).

Secondary Efficacy Endpoints

1. Attention, Memory, and Response inhibition: Correct detections and Commission errors on the IMT/DMT will be compared between lorcaserin and placebo subjects to determine the extent to which this measure is modified by the administration of lorcaserin using repeated measures ANOVA.
2. Craving as measured by the opioid craving scale and brief substance craving scale will be compared between lorcaserin and placebo subjects to determine the extent to which this measure is modified by the administration of oxycodone and lorcaserin using repeated measures ANOVA.

SUBJECT SELECTION

Study Population

Subjects with a diagnosis of opioid use disorder who meet the inclusion and exclusion criteria will be eligible for participation in this study.

Inclusion Criteria

1. Males and females between 18 and 70 years-of-age.
2. Understand the study procedures and provide written informed consent.
3. Meet current DSM-5 criteria for opioid use disorder, at least moderate severity, not seeking treatment.
4. Have at least one positive urine drug screen for opioids during screening to document opioid use. Have no clinically significant abnormalities in the judgment of the study physician in hematology and chemistry laboratory tests including liver function tests.
5. Have no contraindications for study participation as determined by medical history and physical examination.
6. Be able to demonstrate an understanding of study procedures and follow instructions including behavioral laboratory testing.
7. No pregnant or nursing women will be permitted in the study, and women must either be unable to conceive (i.e., surgically sterilized, sterile, or postmenopausal) or be using a reliable form of contraception (e.g., abstinence, birth control pills, intrauterine device with spermicide, or condoms). Men will be advised to use condoms. All females must provide negative pregnancy urine tests before study entry, at each visit during the study, and at the end of study participation.

Exclusion Criteria

1. Meet current DSM-5 diagnosis of any psychoactive substance use disorder other than opioids, cocaine, marijuana, or nicotine. Diagnosis of mild to moderate use disorder for alcohol will not be considered exclusionary.
2. Have a current DSM-5 axis I psychiatric disorder other than substance use disorder including but not limited to Bipolar Disorder, Major Depressive Disorder, ADHD, or Schizophrenia or a neurological disorder requiring ongoing treatment and/or making study participation unsafe.

3. Have any previous medically adverse reaction to oxycodone or lorcaserin or history of serotonin syndrome.
4. Have any untreated clinically significant medical disorder including cardiovascular, pulmonary, CNS, hepatic, or renal disorder.
5. Have a history of seizures (excluding childhood febrile seizures), or loss of consciousness from traumatic injury for more than 30 minutes.
6. Have significant current suicidal or homicidal ideation or a history of suicide attempt within the past 6 months.
7. Have conditions of probation or parole requiring reports of drug use to officers of the court.
8. Have impending incarceration.
9. Have a positive HIV test by self-report or history.
10. Be pregnant or nursing or not using a reliable form of contraception if able to conceive. All females must provide negative pregnancy urine tests at screening, and daily after hospital admission.
11. Have any other illness, or condition, which in the opinion of the PI would preclude safe and/or successful completion of the study.
12. Have taken any investigational drug within 90 days prior to baseline.
13. Have an allergy to lorcaserin or oxycodone.
14. Have taken or currently taking prescription or over-the counter drugs know to inhibit CYP3A or CYP2D6.
15. ECG with QTc > 440ms.

Concurrent Medications

All subjects should be maintained on the same medications throughout the entire study period, as medically feasible, with no introduction of new chronic therapies.

Allowed Medications and Treatments

Non-CNS active medications which are not known to have a potential interaction with oxycodone or lorcaserin would be allowed in this study.

Prohibited Medications and Treatments

The following medications are prohibited during the study and administration will be considered a protocol violation.

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

Any medications with a known interaction with oxycodone or lorcaserin (see 14 above)

STUDY TREATMENTS

Method of Assigning Subjects to Treatment Groups

Up to 18 eligible patients will be randomly assigned to lorcaserin or placebo treatment groups in a 1:2 ratio using a SAS-based computer-generated randomization scheme developed by the study data management provider.

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 lorcaserin and placebo will be identical to maintain the blind.

Lorcaserin concentrations will not be analyzed till 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

Lorcaserin HCL 10mg tablets (Belviq, Arena Pharmaceuticals) will be used for this study. To ensure blinding, tablets will be placed in gelatin capsules by the research pharmacist prior to administration.

Oxycodone HCL 10mg IR tablets (generic OxyIR) .To ensure blinding, tablets will be placed in gelatin capsules by the research pharmacist prior to administration.

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 pill bottle 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 hospital outpatients for a total of 2 study days to maintain complete monitoring for adverse events. In addition, the outpatient oxycodone administration procedures will reduce the likelihood of increased oxycodone craving after oxycodone administration. 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 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 CRS Unit nor receive visitors. Subjects who are unable to comply with these restrictions will be dropped from the study. After a screening oxycodone dosing to determine safety, eligible subjects will be randomized to Group A –placebo only or Group B –lorcaserin (10mg BID). Six subjects will be assigned to Group A (placebo) and 12 subjects will be assigned to Group B (active lorcaserin).

Study Drug Dosage: Lorcaserin will be 10mg twice daily.

Study Objectives and Outcome Measures

Objectives

Primary Objectives:

1. Assess interaction between lorcaserin and oxycodone in healthy opioid using subjects.
2. Assess effect of lorcaserin on subjective response to oxycodone in healthy opioid using subjects.
3. Assess effect of lorcaserin on oxycodone PK in healthy opioid using subjects.

Secondary Objectives:

1. Assess effect of lorcaserin on response inhibition in healthy opioid using subjects.
2. Assess effect of lorcaserin on opioid craving in healthy opioid using subjects.

Outcome Measures

The primary outcome measures are adverse events, respiratory responses (pulse oximetry and respiratory rate), cardiovascular responses (Heart rate (HR), blood pressure (BP), ECG measurements, pupil diameter, subjective response to oxycodone (visual analog scale and cold pressor test), and oxycodone blood PK.

Secondary outcome measures: attention, memory and impulsivity as measured by the immediate memory task (IMT) and delayed memory task (DMT), and Responses to Opioid Craving Scale and Brief Substance Craving Scale.

Study Drug Administration

1) Day 0: All subjects will be admitted to the CRSU for Oxycodone Dosing Session 1 (Baseline). All subjects will receive placebo on Day 0 in a single blind fashion. All subjects will undergo an ascending dose oxycodone administration (10 and 20mg OxyIR) to ensure safety of later oxycodone studies. Vital signs including heart rate, blood pressure, respiration rate and pupil diameter, pulse oximetry will be obtained after placebo administration. Day 0 will be single-blind placebo, whereas all remaining study days will be double-blind. All subjects will be discharged from the CRSU at the end of study day 0.

2) Days 1-3: All subjects will come to the CARI clinic for drug dispensing/monitoring. On days 1-3, subject group A will receive one placebo pill twice daily, and group B will receive one lorcaserin 10 mg pill in the morning while in the clinic and one matching lorcaserin 10 mg pill will be dispensed to the participant to take in the evening, for a total dose of 20 mg daily.

3) Day 4: All subjects will be re-admitted to the CRSU on Day 4 for Oxycodone Dosing Session 2. To assess the safety and subjective effects of oxycodone in the presence of lorcaserin, subjects will receive ascending doses of oxycodone (0, 10 mg, 20 mg), with each oxycodone administration separated by 45 minutes Monitoring will be continued for 3 hours after the last dose of oxycodone.

Dispensing

Study drug will be dispensed by the research pharmacist and administered by the research nurse on the CRS unit.

Supply of Study Drug at the Site

Study drug will be provided to the CRS research unit after an order from the study physician.

Storage

At the testing facility, all lorcaserin and placebo must be kept in a secure, locked storage place with access limited to authorized study personnel only. Lorcaserin bottles must be kept at room temperature (15°C–25°C) until ready for administration with controlled access.

Study Drug Accountability

An accurate and current accounting of the dispensing and return of study drug for each subject will be maintained on an ongoing basis by a member of the study site staff. The number of study drug dispensed and returned by the subject will be recorded on the Investigational Drug Accountability Record. The study staff must record an accurate accounting of each lorcaserin, and Oxycodone/placebo dispensation and assignment number, as well as the date dispensed.

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 Appendix 1.

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. If appropriate, assent must also be obtained prior to conducting any study-related activities.

Clinical Assessments

Concomitant Medications

All concomitant medication and concurrent therapies will be documented during screening at Outpatient Hospital study days, CARI clinic 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 CRSU, and CARI clinic study days to determine the presence of symptoms indicative of opiate withdrawal. A score > 5 on the scale would prohibit study participation. In the event of a positive urine drug screen for opiates the study physician will review the COWS/SOWS and the subject's drug use history to determine the likelihood of opiate withdrawal which would also prohibit study participation.

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 respiratory 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.

Vital Signs

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

The Structured Clinical Interview for DSM-IV (SCID)

The SCID (First et al, 2002) will be used to collect diagnostic information used to make eligibility determinations. This interview will be conducted by staff who will be trained by experienced SCID interviewers using standardized training videotapes from Biometrics Research, NY. This interview will be conducted at screening.

Structured Clinical Interview for DSM-IV Personality Disorders Module (SCID-II)

This instrument provides a DSM-IV axis II diagnosis, and will be used to determine a diagnosis of Antisocial Personality Disorder and Borderline Personality Disorder (First et al, 1997). This interview will be conducted at screening by trained staff.

Kreek-McHugh-Schluger-Kellogg Scale (KMSK)

This scale (Kellogg et al, 2003) will be used to quantify use of opioids, cocaine, marijuana, alcohol, and other substances of abuse by assessing the frequency, amount, and duration of use of the particular substance during the individual's period of greatest consumption. The scale also assesses the mode of use, whether the substance use is current or past, and whether each substance is the substance of choice. This will be conducted at screening by trained staff.

Addiction Severity Index (ASI-lite)

This scale (Cacciola et al, 2007) will be used in conjunction with the KMSK as measures of baseline severity of substance use. This will be conducted at screening by trained staff.

Fagerström Test for Nicotine Dependence (FTND)

This is a short self-report questionnaire (Heatherton et al, 1991) designed to measure the construct of nicotine dependence, will be included to explore the potential moderating effects of tobacco dependence in relation to opioid use and response to treatment. This will be conducted at screening by trained staff.

National Adult Reading Test (NART)

The NART-R is a 61-item vocabulary test (Nelson and O'Connell, 1978) will be used to estimate general intellectual ability and to control for individual differences in subject's premorbid level of intelligence. This test has been shown to have high inter-rater (.96-.98) and test-retest reliability (.98) and predictive validity (.74) with the WAIS-R IQ. This will be conducted at screening.

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).

Immediate Memory Task (IMT)

The Immediate Memory Task (IMT) is a behavioral task designed to measure a subject's ability to retain and subsequently identify a stimulus kept in memory. As well as the ability to inhibit impulsive responding. The task is computer driven and takes approximately 20 minutes to complete. A series of 5-digit numbers are displayed on the monitor for a 0.5 s blackout period.

Delayed Memory Task (DMT)

The Delayed Memory Task (DMT) similar to the IMT involves responding to matching numbers, but the numbers to be compared are separated by a filler sequence (e.g. 12345).

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.

Opioid Craving Scale (OCS)

The Opioid Craving Scale, a modification of the Cocaine Craving Scale, is a brief, 3-item measure used to measure opioid craving. The scale consists of 3 items rated on a visual analogue scale from 0-10.

Cold Pressor Test (CPT)

The analgesic effects of oxycodone will be evaluated with experimentally induced pain using the cold pressor test (CPT), a commonly used and well-established model for producing pain. Methods for the cold pressor test will be the same as previously published (Jones et al., 2016). Crushed ice is added to a cold tank, and warm water was placed in a warm tank. The temperature in the cold talk will be maintained at 4 °C in and the temperature in the warm tank will be maintained at 37°C. Each participant is asked to immerse a hand in the warm tank for 2 min (to equalize baseline skin temperature across participants), afterwards participants are asked to immerse the same hand in the cold tank for up to 2 minutes. During the cold water immersion subjective measures of pain are collected using a visual analog scale. Objective measures of pain during the cold water immersion include pain threshold (time in seconds to the first report of pain) and pain tolerance (time until removal of the hand from water). Immediately following the CPT, subjective ratings of pain will be measured using a shortened version of the McGill Pain Questionnaire and a visual analog scale.

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).

Clinical Laboratory Measurements

Hematology

Blood will be obtained and sent to each site's 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 each site's 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 each site's 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, amphetamine, methamphetamine, and THC.

Breathalyzer

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

Pharmacokinetic Measurements

Pharmacokinetic samples for analysis of oxycodone and its metabolites: Blood samples for analysis of the pharmacokinetics of 10/20mg oxycodone will be collected during treatment with 0 mg Lorcaserin (on Study Day 0,1) and during treatment with lorcaserin at 10mg twice daily (Study Day 4,5,6). Plasma oxycodone levels at these time points for each of those days: 0, 45, 90, 135, 180, 195, 330, 600, and 1440 minutes (on the following day). After separation of plasma by routine methods, samples will be frozen at -70°C until ready for analysis. Plasma concentrations of oxycodone and metabolites (noroxycodone, oxymorphone and noroxymorphone) will be assayed by liquid chromatography-tandem mass spectrometry.

EVALUATIONS BY VISIT (see Table 2. below for overview of study time course)

Screening Conducted at CARI clinic (Days -21 to -1, can be extended based on ability to schedule day 0)

Review the study with the subject and obtain written informed consent.

Assign the subject a unique screening number.

Record demographics data.

Record medical history.

Record concomitant medications.

Administer COWS

Administer SOWS

Perform a complete physical examination (once during screening).

Perform a complete neurological exam (once during screening).

Perform a 12-Lead ECG (once during screening).

Collect urine for clinical laboratory tests (urine drug screen, pregnancy test, urinalysis).

Perform and record vital signs.

Perform and record Breathalyzer.
Collect blood for clinical laboratory tests (serum chemistry and hematology) (once during screening).
Perform psychiatric interviews (SCID, SCID-II) (once during screening).
Conduct clinical assessments (KMSK, FTND, NART, ASI-lite, POMS, C-SSRS) (once during screening).
Record brief substance craving scale, timeline follow back oxycodone use, and drug use history.
Verify inclusion and exclusion.
Schedule subject for Day 0 visit as soon as possible.

Outpatient Hospital Visit 1 (Day 0)
Report to CRS unit.
Collect urine for pregnancy test and urine drug screen.
Perform and record Breathalyzer.
Administer COWS.
Administer SOWS
Perform and record vital signs.
Perform a 12-Lead ECG.
Perform a brief physical exam.
Begin continuous pulse oximetry and physiological monitoring, pupils, subjective effects, CPT
Administer placebo in morning.
Administer IMT/DMT.
Administer oxycodone for Dosing session 1.
Collect blood samples for oxycodone pK.
Update concomitant medications.
Record Visual Analog Scale (VAS).
Record adverse events.
Conduct clinical assessments (POMS, CGI-S, C-SSRS, OCS).
Administer IMT/DMT.
Administer Delay Discounting Task
Perform a 12-Lead ECG.
Perform sobriety test, leave CRS unit.

Study Days Conducted at CARI clinic (Days 1-3)
Collect urine for pregnancy test and urine drug screen.
Blood draw for oxycodone and metabolite levels 24 hours post oxycodone dose (day 1 only)
Perform and record Breathalyzer and vital signs.
Record adverse events.
Administer COWS.
Administer SOWS
Document drug use by self-report over last 24 hours.
Update concomitant medications.
Conduct clinical assessments (POMS, CGI-I, C-SSRS, OCS).

Dispense study drugs (AM dose taken in clinic, PM dose given to participant)

Outpatient Hospital Visit 2 (Day 4)
Report to CRS unit.
Collect urine for pregnancy test and urine drug screen.
Perform and record Breathalyzer.
Administer COWS.
Administer SOWS
Perform and record vital signs.
Perform a 12-Lead ECG.
Perform a brief physical exam and continuous cardiovascular monitoring.
Begin continuous physiological monitoring, pupils, subjective effects, CPT
Administer study drug in morning.
Administer IMT/DMT.
Administer oxycodone for Dosing session 2.
Collect blood samples for oxycodone/lorcaserin pK.
Update concomitant medications.
Record Visual Analog Scale (VAS).
Record adverse events.
Conduct clinical assessments (POMS, CGI-S, C-SSRS, OCS).
Administer IMT/DMT.
Administer Delay Discounting Task
Perform a 12-Lead ECG.
Perform Sobriety test
Leave CRS unit.

Follow-Up Conducted at CARI clinic (Days 5, 6)
Collect urine for pregnancy test and urine drug screen.
Blood draw for oxycodone and metabolite levels 24 hours post oxycodone dose (Day 5)
Perform and record Breathalyzer and vital signs.
Perform a 12-Lead ECG and brief physical exam (Day 6 only).
Record OCS and timeline follow back opioid use.
Administer COWS
Administer SOWS
Update concomitant medication.
Conduct clinical assessments (POMS, CGI-I (only Day 6), and C-SSRS).
Record adverse events.

Table 2. Time Course of Study

	Screening (up to six visits Days -21 to -1)	Baseline (Day 0 Week 1)	Day 1 Week 2	Day 2 Week 2	Day 3 Week 2	Day 4 Week 2	Day 5 Week 2	Day 6 Week 3
Location	**CARI**	**CRSU**	**CARI**	**CARI**	**CARI**	**CRSU**	**CARI**	**CARI**
Test Drug		Placebo	Lorcaserin 10mg BID or Placebo	Lorcaserin 10mg BID or Placebo	Lorcaserin 10mg BID or Placebo	Lorcaserin 10mg in AM or Placebo		
Oxycodone Dose		0, 10, 20mg				0, 10, 20mg		
Behavioral Measures	Self-report Drug Use	Subjective responses, Cold pressor tests, IMT/DMT Delay Discounting				Subjective responses, Cold pressor tests, IMT/DMT Delay Discounting		
Other	Once during screening ECG and Routine Blood work	Blood samples for PK for oxycodone	Blood sample for PK for oxycodone			Blood samples for PK for oxycodone	Blood samples for PK for oxycodone Follow-up for side effects	Follow-up for side effects
UDS	Obtained	Obtained	Daily	Daily	Daily	Daily	Obtained	Obtained

On each day of oxycodone administration, the following schedule will be used for procedures:

Time	Procedure
-15	Begin continuous physiological monitoring, pupils, subjective effects, CPT, ECG
0	Lorcaserin or placebo, IMT/DMT
30	Subjective effects, pupils
45	Subjective effects, pupils, blood, CPT

60	OXY 0 mg, PO
75	Subjective effects, pupils
90	Subjective effects, pupils, blood, CPT
105	OXY 10 mg, PO: Subjective effects, pupils
120	Subjective effects, pupils
135	Subjective effects, pupils, blood, CPT
150	OXY 20 mg, PO (cumulative dose of 30 mg): Subjective effects, pupils
165	Subjective effects, pupils
180	Subjective effects, pupils, blood, CPT
195	Subjective effects, pupils, blood
210	IMT/DMT, Delay Discounting
225	Subjective effects, pupils, CPT
270	Subjective effects, pupils, CPT
315	Subjective effects, pupils, CPT
330	Subjective effects, pupils, blood, CPT, ECG
600	Subjective effects, pupils, blood, Sobriety test

Criteria for withholding Oxycodone Administration

Oxycodone administration will not be initiated if:

- Heart rate less than 50/min or abnormal cardiac rhythm
- Blood pressure less than 90/60mmHg
- Pulse Oximetry of 92% or less
- Respiratory Rate < 6/min
- Behavioral manifestations of oxycodone toxicity (moderate sedation or greater, inability to cooperate with study procedures).

Stopping Criteria for Subject Participation

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 abnormal cardiac rhythm
- Blood pressure less than 90/60mmHg
- Pulse Oximetry of 92% or less
- Respiratory Rate < 6/min
- Behavioral manifestations of oxycodone toxicity (moderate sedation or greater, inability to cooperate with study procedures).
- QTc increase of more than 30ms from baseline on repeat ECG
- Symptoms of serotonin syndrome (fever, agitation, confusion, rapid heart rate and high blood pressure

ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

Adverse Events

Adverse Events (AEs) will be identified through daily interviews with participants and noted at any visit. The data will be entered on the standard VCU IRB AE and SAE forms. Continuous logs of all SAEs and AEs will be maintained. SAEs will be reported to the VCU IRB, the NIDA PO, the DSMB and the US FDA (when appropriate) as described above. 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 Program Officer (Aidan Hampson, and the FDA (when appropriate) within 24-48 hours. A full written report to all institutions will follow as soon as possible but in no more than three 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 (Lorcaserin)

A subject may be discontinued from study treatment at any time if the subject, the investigator, or the Sponsor 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

Protocol violation requiring discontinuation of study treatment

Lost to follow-up

Sponsor request for early termination of study

Positive pregnancy test (females)

Chest discomfort or shortness of breath consistent with ischemia or other cardiac abnormality

Systolic BP > 180 mmHg

Diastolic BP > 110 mmHg

Heart rate > Maximum predicted heart rate (> 220 – age x 0.85) bpm.

Symptoms of serotonin syndrome (fever, agitation, confusion, rapid heart rate, and high blood pressure

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 Refer to Section 10 for early termination procedures.

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

Failure to meet inclusion/exclusion criteria

Use of a prohibited concomitant medication

Failure to follow study procedures as described in the study protocol.

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.

DATA SAFETY MONITORING

a. The Data Safety and Monitoring Board includes, Michael J. Lennon (M.D., Richmond VA Hospital), and Ananda Pandurangi (M.D., VCU school of Medicine), and John M. Hettema (M.D., Ph.D., VCU school of Medicine), Roshanak Markley, (M.D. Cardiology VCU school of Medicine), Brandon Willis (DO, Emergency

medicine and toxicology VCU school of medicine), Spencer Hays, (statistician, VCU department of statistics). Members are 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.

b. Frequency of meetings

The first meeting will take place face-to-face to discuss the protocol, any modifications of the trial, and to establish guidelines to monitor the study. The DSMB Chairperson and the PI will prepare the agenda to address the review of manual of operating procedures, modification of the study design, initiation of the trial, reporting of adverse events, stopping rules, interim analysis plan, etc.

Meetings of the DSMB will be held at time points corresponding with annual progress reports. Open DSMB meetings will be attended by the PI, co-investigators, and research staff member (as appropriate). A closed DSMB session will be held at study completion and attendance will be limited to DSMB members and the PI. Meetings may be convened as conference calls as well as in person, although the initial meeting and meetings to discuss interim analysis will be face-to-face. An emergency meeting of the DSMB (open, closed, or executive session) may be called at any time by the Chairperson should questions of patient safety arise.

Issues discussed at DSMB sessions will include conduct and progress of the study, patient accrual, compliance with protocol, and problems encountered. As patient-specific data and treatment group data may be presented at DSMB sessions, the discussion will be regarded as completely confidential.

c. Conflict of interest

All participating investigators and DSMB members will declare any conflicts of interest before the study is initiated, annually, and in the event of changing circumstances. Beyond this, the investigators are blind to the conditions and the PI does not make active decisions about assignment or subject care or participation. This separation of activities diminishes the risk of harm to either science or subjects due to conflicts of interest.

d. Protection of confidentiality

All materials, discussions and proceedings of the DSMB are completely confidential. Members and other participants in DSMB meetings will be expected to maintain confidentiality.

e. Monitoring activities

After initial review and approval of the project, the monitoring activities of the DSMB will be to evaluate the progress of the trial, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of the trial site, and other factors that can affect study outcome.

f. Communication plans to IRB, NIDA, and FDA

The DSMB will make recommendations to the PI, who will then communicate the recommendations to the NIDA PO, and if necessary, to the FDA. Recommendations of the DSMB will be sent to the IRB as well.

STATISTICAL METHODS AND CONSIDERATIONS

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below.

Data Sets Analyzed

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: Urn randomization will be used for gender to reduce any potential between-group differences (lorcaserin vs. placebo) on baseline variables. Prior to data analysis procedures, groups will be examined for differences in other 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.

Demographic and Baseline Characteristics

Women, minorities, and children (18-21 years of age) will be included to the extent they are reflected in this non-treatment seeking population. In our previous oxycodone clinical trials, the percentage of females and males is approximately 30% and 70% respectively. We will continue recruitment efforts to achieve a 50-50 balance and thus permit meaningful analyses by sex across groups.

The ethnic representation has been 55% Black, 44% White, 15% Hispanic, and <1% Asian in previous research by our group. Nevertheless, we are prepared to implement recruitment procedures to ensure a more diverse patient population. These procedures include: 1) Targeted advertising in newspapers which serve minority communities (e.g., Hispanic or Latino communities). 2) Distribution of flyers and notices in neighborhoods known to have a high minority population. 3) Engaging in outreach activities on an ongoing basis, e.g., contacting church and community leaders in the Hispanic communities to provide educational material about oxycodone dependence and its consequences; providing contact information to aid in referrals to our clinic.

Children as defined by NIH (age 18-21years) will be included in this research. The incidence of severe oxycodone abuse/dependence is relatively small in the population of youth less than 18 years old. From a safety perspective, risks of exposure to the proposed study medication and oxycodone administration in substance-dependent children under 18 have not been established.

Analysis of Primary Endpoint

1. Safety: Heart rate (HR), blood pressure (BP), pulse oximetry, pupil diameter, and respiratory rate measures during a placebo dose will be compared to these measures after each oxycodone dose (10 mg and 20 mg doses). Changes in these measures induced by oxycodone dose along with lorcaserin will be compared to those without lorcaserin, by oxycodone dose level (10 mg and 20 mg doses), using repeated measures analysis of variance (ANOVA). Adverse event data will be compiled for lorcaserin and placebo cohorts and presented as summary statistics.

2. Oxycodone PK: Plasma concentration-time profiles of oxycodone after oxycodone doses during placebo administration (Day zero) will be analyzed to obtain pharmacokinetic parameter estimates of oxycodone (Tmax, AUC, apparent t½, CL) by individual. These parameters will be compared within subjects on sessions with lorcaserin (Day 5).

3. Subjective response to oxycodone: Subjective response measures (VAS, CPT) after oxycodone administration on day zero will be compared to VAS, CPT measures after oxycodone administration on day 4 between lorcaserin and placebo treated subjects to determine the extent to which these measures are modified by the administration of lorcaserin using repeated measures ANOVA.

Analysis of Secondary Endpoints

1. Response inhibition: Commission errors on the IMT/DMT will be compared between lorcaserin and placebo subjects to determine the extent to which this measure is modified by the administration of lorcaserin using repeated measures ANOVA.
2. Craving as measured by the opioid craving scale and brief substance craving scale will be compared between lorcaserin and placebo subjects to determine the extent to which this measure is modified by the administration of oxycodone and lorcaserin using repeated measures ANOVA.

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

When approximately 50% of patients have completed the study, an interim analysis for safety will be conducted by the DSMB. Serious adverse events will be monitored by the committee on an ongoing basis throughout the study.

Sample Size and Randomization

Rationale for sample size: Sample size for effect of lorcaserin on oxycodone self-administration was based on previous research showing effects of oxycodone on pain and subjective responses in an experimental laboratory session (Jones et al., 2016). In an effort to increase the power of the study, a Bayesian approach will also be utilized that incorporates information from previous studies. This approach will use a Bayesian hierarchical model with subject at the lowest level of the hierarchy and treatment group at the second level. This model is analogous to the repeated measures ANOVA except that prior information will be introduced. Since many similar studies have been conducted with oxycodone users and the same outcome measures we will assign an informative prior distribution on the control group where the mean and standard deviation are educated guesses from the information provided in previous study of Jones et al., (2016). For the treatment group we will assume a priori no change in the mean from the control group and the standard deviation are similar to those as the experimental group of the study by Hart et al. (Hart et al., 2008). The model will be calculated using standard Markov Chain Monte Carlo (MCMC) packages such as WinBUGS, OpenBUGS, JAGS or MCMCpack in R. Because MCMC sampling techniques are being employed the quality of the samples from the posterior distribution will be checked using trace plots, effective sample size, potential scale reduction factor and Hellinger distances (for more on Bayesian analyses and MCMC sampling see (Gelman et al., 2013). As necessary techniques such as discarding burn-in samples, thinning and over-disperse starting points will be employed in order to obtain a set of samples from the posterior distribution that have an effective sample size of 10,000 on all parameters. All inferences will be made from this set of samples from the posterior distribution.

To calculate the power for the acute effects of the study three analyses are considered using the paired differences of subjects at baseline and acute time points. A two-sample test on the means is performed using: Wilcoxon test (non-parametric), T-test (parametric) and a Bayesian (parametric) approach. While from a Bayesian paradigm the notion of power does not exist in the traditional sense, one can create a decision rule and loss function in such a way that the associated risk is analogous to the notion of power. To understand the power of each of the methods a Monte Carlo study was performed utilizing 1,000 separate datasets for likely effect sizes and sample sizes.

The power was calculated as the proportion of datasets in which the test "rejected" the null hypothesis. The table below gives the power for each test across percent change in effect size and control group sample sizes, here the treatment group sample size was n2 = 12. Based on the table below, an n of 6 was chosen as the sample size for the placebo group.

		Percent Change				
n1	Test	Low (10%)	Medium (25%)	High (50%)	75%	100%
4	T-test	0.116	0.448	0.955	0.998	1
	Wilcoxon	0.044	0.242	0.855	0.992	1
	Bayesian	0.249	0.689	0.992	1	1
6	T-test	0.138	0.528	0.981	0.999	1
	Wilcoxon	0.079	0.357	0.941	0.997	1
	Bayesian	0.308	0.782	0.994	1	1
8	T-test	0.116	0.588	0.986	1	1
	Wilcoxon	0.096	0.495	0.956	1	1
	Bayesian	0.309	0.803	0.999	1	1
Wilcoxon and Bayesian Power are based off of 1,000 Monte Carlo simulations.						

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 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. 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 obtained from 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 IRBs are notified within five working days.

Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the VCU 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.

References:

Baker, J.R., Jatlow, P., McCance-Katz, E.F., 2007. Disulfiram effects on responses to intravenous cocaine administration. Drug Alcohol Depend 87, 202-209.

Cunningham, K.A., Fox, R.G., Anastasio, N.C., Bubar, M.J., Stutz, S.J., Moeller, F.G., Gilbertson, S.R., Rosenzweig-Lipson, S., 2011. Selective serotonin 5-HT(2C) receptor activation suppresses the reinforcing efficacy of cocaine and sucrose but differentially affects the incentive-salience value of cocaine- vs. sucrose-associated cues. Neuropharmacology.

Gelman, A., Carlin, J., Stern, H., Dunson, D.B., Vehtari, A., Rubin, D.B., 2013. Bayesian Data Analysis, Third Edition. Chapman and Hall/CRC, Boca Raton, Florida.

Hart, C.L., Haney, M., Vosburg, S.K., Rubin, E., Foltin, R.W., 2008. Smoked cocaine self-administration is decreased by modafinil. Neuropsychopharmacology 33, 761-768.

Hutcheson, J.D., Setola, V., Roth, B.L., Merryman, W.D., 2011. Serotonin receptors and heart valve disease--it was meant 2B. Pharmacol Ther 132, 146-157.

Jones, J.D., Sullivan, M.A., Manubay, J.M., Mogali, S., Metz, V.E., Ciccocioppo, R., Comer, S.D., 2016. The effects of pioglitazone, a PPARgamma receptor agonist, on the abuse liability of oxycodone among nondependent opioid users. Physiol Behav 159, 33-39.

Le Bars, D., Gozariu, M., Cadden, S.W., 2001. Animal models of nociception. Pharmacol Rev 53, 597-652.

Levin, E.D., Johnson, J.E., Slade, S., Wells, C., Cauley, M., Petro, A., Rose, J.E., 2011. Lorcaserin, a 5-HT2C agonist, decreases nicotine self-administration in female rats. J Pharmacol Exp Ther 338, 890-896.

Manvich, D.F., Kimmel, H.L., Howell, L.L., 2012. Effects of serotonin 2C receptor agonists on the behavioral and neurochemical effects of cocaine in squirrel monkeys. J Pharmacol Exp Ther 341, 424-434.

Moeller, F.G., Schmitz, J.M., Steinberg, J.L., Green, C.M., Reist, C., Lai, L.Y., Swann, A.C., Grabowski, J., 2007. Citalopram combined with behavioral therapy reduces cocaine use: a double-blind, placebo-controlled trial. American Journal of Drug and Alcohol Abuse 33, 367-378.

Shram, M.J., Schoedel, K.A., Bartlett, C., Shazer, R.L., Anderson, C.M., Sellers, E.M., 2011. Evaluation of the abuse potential of lorcaserin, a serotonin 2C (5-HT2C) receptor agonist, in recreational polydrug users. Clin Pharmacol Ther 89, 683-692.

APPENDIX 1. DETAILED TIMELINE OF MEASURES

Study Day	Screening -21 to -1	Baseline Day 0	Study Day 1	Study Day 2	Study Day 3	Study Day 4	Follow Up Day 5	Follow Up Day 6
Location	CARI	CRSU	CARI	CARI	CARI	CRSU	CARI	CARI
Procedure								
Informed Consent	X							
Serum Chemistry	X							
Hematology	X							
Admission to Unit		X				X		
Discharge from Unit		X				X		
History, Physical Exam, and Neurological Exam	X							
Urine Pregnancy test (females)	X	X	X	X	X	X	X	X
Psychiatric Interview (SCID)	X							
Psychiatric Interview (SCID-II)	X							
Psychiatric Interview (KID-SCID)	X							
Kreek-McHugh-Schluger-Kellogg scale (KMSK)	X							
Fagerstrom Test for Nicotine Dependence (FTND)	X							
National Adult Reading Test (NART)	X							
Addiction Severity Index (ASI-lite)	X							

Brief Substance Craving Scale	X	X	X	X	X	X	X	X
Opioid Craving Scale (OCS)	X	X	X	X	X	X	X	X
Timeline Follow Back Opiate Use	X							X
Drug Use History	X							
Concomitant Medications	X	X	X	X	X	X	X	X
Clinical Opiate Withdrawal Scale (COWS)	X	X	X	X	X	X	X	X
Subjective Opiate Withdrawal Scale (SOWS)	X	X	X	X	X	X	X	X
Urine drug screen	X	X	X	X	X	X	X	X
Breathalyzer	X	X	X	X	X	X	X	X
Verify Inclusion & Exclusion	X	X						
Vital Signs	X	X	X	X	X	X	X	X
12-Lead ECG (baseline triplicate) and singlet thereafter)	X	X				X		
Brief Physical Exam		X				X		X
Oxycodone Administration for 3 Doses		X				X		
Continuous pulse oximetry and physiological monitoring		X				X		
Cold Pressor Test (CPT)		X				X		
Pupil Measurement		X				X		
Adverse Events		X	X	X	X	X	X	**X**

Inventory								
Visual Analog Scale (VAS)		X				**X**		
Profile of Mood States (POMS)	X	X	X	X	X	X	X	X
Delayed Memory Task (DMT)		X				X		
Immediate Memory Task (IMT)		X				X		
Delay Discounting Task		X				X		
Clinical Global Impression Severity & Improvement (CGI-S&I) (baseline CGI-S, and CGI-I thereafter)	X	X	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	X	X	X	X
Blood Draw for Oxycodone PK		X	X			X	X	
Blood Draw for Lorcaserin PK measurement						X	X	
Lorcaserin or Placebo		X	X	X	X	X		