Title: Phase I Drug Interaction and Self Administration Studies of Compounds for Cocaine Use Disorder

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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
COCUD	Cocaine Use Disorder
COWS	Clinical Opiate Withdrawal Scale
CRF	case report form
CRP	C-reactive protein
CRSU	Clinical Research Services Unit
DMC	Data Monitoring Committee
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
IDAS	Institute for Drug and Alcohol Studies
IEC	Independent Ethics Committee
IL-8	Interleukin-8
IRB	Institutional Review Board
IV	intravenous

KID-SCID	Childhood Disorders Version of the SCID ADHD Module
KMSK	Kreek-McHugh-Schluger-Kellogg Scale
LDH	lactate dehydrogenase
NART	National Adult Reading Test
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
VAS	Visual Analog Scale
WURS	Wender Utah Rating Scale

PROTOCOL SYNOPSIS

TITLE	Phase I drug interaction and self-administration studies of compounds for Cocaine Use Disorder (COCUD)
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 cocaine) and efficacy (subjective response to cocaine and self administration data) in non-treatment seeking cocaine use disorder subjects. The compound to be studied will be the 5-HT2CR agonist lorcaserin. Lorcaserin and other 5-HT2CR agonists have been shown to reduce cocaine self-administration and cue reactivity in rodents (Cunningham et al., 2011; Manvich et al., 2012). In addition there is human safety data in non-cocaine using subjects for lorcaserin as it is currently FDA approved for obesity, and safety data from a cocaine interaction study in rodents (included below), but there is no human cocaine interaction/PK data and no PD data to support potential dosages for phase II clinical trials.
STUDY DESIGN	This is a randomized, double-blind, placebo-controlled phase 1b/2a study.
PRIMARY OBJECTIVE	1. Assess interaction between lorcaserin and cocaine in healthy cocaine using subjects. 2. Assess effects of lorcaserin on cocaine self-administration in healthy cocaine using subjects. 3. Assess effect of lorcaserin on subjective response to cocaine in healthy cocaine using subjects. 4. Assess effect of lorcaserin on cocaine PK in healthy cocaine using subjects.
SECONDARY OBJECTIVES	Assess effect of lorcaserin on response inhibition in healthy cocaine 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 59 years-of-age. 2. Understand the study procedures and provide written informed consent. 3. Meet current DSM-5 criteria for cocaine use disorder, at least moderate severity, and current DSM-IV diagnosis of cocaine dependence, but are not seeking treatment. 4. Currently using cocaine by smoking or intravenous route of administration as determined by self-report and have a positive urine

drug screen for cocaine during screening.

5. Have vital signs as follows: resting pulse below 95 bpm, blood pressures below 140 mm Hg systolic and 90 mm Hg diastolic.

6. Have no clinically significant abnormalities in the judgment of the study physician in hematology and chemistry laboratory tests including liver function tests.

7. Have sinus rhythm with normal conduction (including QTcF less than 440 ms) by ECG.

8. Have no contraindications for study participation as determined by medical history and physical examination.

9. Be able to demonstrate an understanding of study procedures and follow instructions including behavioral laboratory testing.

10. 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.

11. Have hemoglobin/hematocrit values within normal limits based on age and gender.

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 cocaine, opioids, marijuana, or nicotine. Diagnosis of mild to moderate use disorder for alcohol will not be considered exclusionary.

2. Have a 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 cocaine, including loss of consciousness, chest pain, or epileptic seizure.

4. Have any clinically significant medical disorder including cardiovascular (including hypertension), pulmonary, CNS, hepatic, or renal disorder.

5. Have a history of seizures (excluding childhood febrile seizures), or clinically significant head injury.

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 at each study visit. 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 a positive breath alcohol test or urine drug screening positive for drugs of abuse with the exception of cocaine, cocaine metabolites, opioids, and marijuana. 13. Subjects who are allergic to lorcaserin. 14. Subjects who have taken any investigational drug within 90 days prior to baseline. 15. Subjects who have symptoms of opioid withdrawal during screening.
TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	Lorcaserin 10mg Product will be administered orally once daily for 6 days then increasing to 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	Screening: up to 7 days Treatment in CRSU and IDAS: 12 days Follow-up: 7 days The total duration of the study is expected to be 4 years.
CONCOMMITANT MEDICATIONS	Allowed: Non-CNS Active medications Prohibited: CNS active medications Medications which could potentially interact with lorcaserin or cocaine
Efficacy Evaluations	Primary outcome measures: 1. Safety: Heart rate (HR) and blood pressure (BP) measures during saline infusions will be compared to HR and BP after each cocaine infusion (20 mg and 40 mg doses). Changes in HR and BP induced by cocaine infusion along with lorcaserin will be compared to those without lorcaserin, by cocaine dose level (20 mg and 40 mg doses), using repeated measures analysis of variance (ANOVA). Changes in ECG readings during saline infusion as compared to those taken during cocaine infusions will be reported as summary statistics. Adverse event data will be compiled for lorcaserin and placebo

	cohorts and presented as summary statistics. 2. Cocaine Self-administration: Repeated measures ANOVA with cocaine dose (0mg, 25mg) and lorcaserin dose (0mg, 10mg, 20mg) as within subject factors will be used to examine differences in mean cocaine choice selection. In addition, a Bayesian analysis will be carried out as described below. 3. Subjective response to cocaine: Subjective response measures (VAS) obtained during saline infusions will be compared between lorcaserin and placebo subjects to those during cocaine infusions by cocaine dose level to determine the extent to which these measures are modified by the administration of lorcaserin using repeated measures ANOVA. 4. Cocaine PK: Plasma concentration-time profiles of cocaine after cocaine infusion during placebo administration (Day 2) will be analyzed to obtain pharmacokinetic parameter estimates of cocaine (Tmax, AUC, apparent t½, CL) by individual. These parameters will be compared within subjects on sessions with lorcaserin (Days 6 and 10). Secondary Outcome Measure: Response inhibition: Commission errors on the IMT 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.
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) and blood pressure (BP) measures during saline infusions will be compared to HR and BP after each cocaine infusion (20 mg and 40 mg doses). Changes in HR and BP induced by cocaine infusion along with lorcaserin will be compared to those without lorcaserin, by cocaine dose level (20 mg and 40 mg doses),

	using repeated measures analysis of variance (ANOVA). Changes in ECG readings during saline infusion as compared to those taken during cocaine infusions will be reported as summary statistics. Adverse event data will be compiled for lorcaserin and placebo cohorts and presented as summary statistics. 2. Cocaine Self-administration: Repeated measures ANOVA with cocaine dose (0mg, 25mg) and lorcaserin dose (0mg, 10mg, 20mg) as within subject factors will be used to examine differences in mean cocaine choice selection. In addition, a Bayesian analysis will be carried out as described below. 3. Subjective response to cocaine: Subjective response measures (VAS) obtained during saline infusions will be compared between lorcaserin and placebo subjects to those during cocaine infusions by cocaine dose level to determine the extent to which these measures are modified by the administration of lorcaserin using repeated measures ANOVA. 4. Cocaine PK: Plasma concentration-time profiles of cocaine after cocaine infusion during placebo administration (Day 2) will be analyzed to obtain pharmacokinetic parameter estimates of cocaine (Tmax, AUC, apparent t½, CL) by individual. These parameters will be compared within subjects on sessions with lorcaserin (Day 6 and Day 10). Secondary Outcome Measure: Response inhibition: Commission errors on the IMT 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. .
Rationale for Number of Subjects	Power Calculation and Sample Size: Rationale for sample size: Sample size for effect of lorcaserin on cocaine self-administration was based on previous research showing effects of medication on human cocaine self-administration (Hart et al., 2008). 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 cocaine 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 Hart et al. (2008). 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

		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.

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 at left, an n of 6 was chosen as the sample size for the placebo group.

BACKGROUND

Lorcaserin is a 5-HT2CR agonist (Trade Name Belviq) approved for treatment of obesity.

Overview of Non-Clinical Studies

Lorcaserin and other 5-HT2CR agonists have been shown to reduce cocaine self-administration and cue reactivity in rodents (Cunningham et al., 2011; Manvich et al., 2012). We have collected preliminary data to

indicate that lorcaserin dose-dependently suppresses cue reactivity. Male Sprague-Dawley rats (n=11) were trained to self-administer cocaine on an FR5 schedule of reinforcement (0.75 mg/kg/inf; 3 hrs/d) for 14 days (Anastasio et al, 2014b). Rats were returned to their home cage for 1 day of forced abstinence (no extinction training) and were then reintroduced to the chambers. To assess cue reactivity, presses on the previously active lever were reinforced contingently by the discrete cue complex on an FR1 for one hour (active lever responses); inactive lever presses were recorded but produced no scheduled consequences. As predicted by studies with other selective 5-HT2cR agonists in extinction/reinstatement models, lorcaserin effectively suppressed cue reactivity. In addition there is human safety data in non-cocaine using subjects for lorcaserin as it is currently FDA approved for obesity, and safety data from a cocaine interaction study in rodents (See included full study report).,

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 cocaine) and efficacy (subjective response to cocaine and self- administration data) in non-treatment seeking cocaine use disorder subjects. The compound to be studied will be the 5-HT2CR agonist lorcaserin. Lorcaserin and other 5-HT2CR agonists have been shown to reduce cocaine self-administration and cue reactivity in rodents (Cunningham et al., 2011; Manvich et al., 2012). In addition there is human safety data in non-cocaine using subjects for lorcaserin as it is currently FDA approved for obesity, and safety data from a cocaine interaction study in rodents (included below), but there is no human cocaine interaction/PK data and no PD data to support potential dosages for phase II clinical trials.

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 cocaine 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, as well as the preclinical data on interaction with cocaine described below, a dosage regimen of 10mg daily escalating to a maximum dose of 10mg twice daily was chosen for this study.

Risks of Cocaine Administration

Cocaine exposure: Medical complications that have been reported with cocaine use include heart attack, rupture of major blood vessels, stroke, difficulty breathing, swelling, cessation of bowel function, and death. However, none of these complications have been observed during our previous experience using I.V. cocaine administration for a similar protocol with GBR12909 at the University of Texas Medical Branch, or another study at UTMB using another study medication, SYN117. Cocaine is a potent sympathomimetic and has been associated with adverse cardiovascular events, including myocardial infarction and stroke, when taken illicitly. While these consequences have never been observed following controlled experimental administration, we will limit these potential risks in several ways: (1) We will enroll only physically healthy cocaine using subjects with no evidence of cardiovascular 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 a dose shown to be safe in our hands that was selected to produces scientifically valid results. (3) We will monitor subjects closely in a hospital setting throughout the duration of action of the drug, under the supervision of medical personnel trained in basic and advanced cardiac life support. We will also employ continuous non-invasive hemodynamic monitoring using the Nexfin finger cuff (Edwards Scientific) that provides real-time assessment of blood pressure, heart rate, stroke volume, stroke volume variability, systemic vascular resistance, and cardiac output. Hemodynamic data will be continuously visible at bedside and stored for off-line analysis via the finger cuff. 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 crash cart is located on the unit. Study days 1, 2, 3, 6, 7, 10, and 11 of this study will be conducted at the CRS unit, a specialized research unit at VCU Medical Center. This unit has previously conducted phase I studies, including cocaine studies in humans (Baker et al., 2007). In the highly unlikely event of a suspected of medical emergency (i.e. chest pain, uncontrolled hypertension, cardiac arrhythmia, respiratory distress) 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 possible exposure to intravenous route of cocaine administration. In recruiting our subjects, the inclusion criteria include intravenous and/or smoked cocaine use. It is possible that some subjects might be exposed to intravenous cocaine for the first time. One concern will be whether this experience will lead to a change in route of drug administration, i.e. cocaine smoking subject becoming intravenous drug users. Previous research has shown that this event is not likely to occur. In the case of cocaine, users of smoked cocaine rarely switch to intravenous cocaine use even after exposure to intravenous cocaine.

Thus, we do not think that administering intravenous cocaine to crack users will encourage intravenous drug use. In fact, human laboratory studies comparing the smoked and intravenous administered cocaine have shown that pharmacokinetics are very similar with these routes of administration. That is, time to reach peak plasma levels as well as onset and duration of effect are comparable between intravenous and smoked cocaine administration in humans.

In addition, some of subjective effects of cocaine such as feelings of "stimulated" and "high" were greater for smoked than those for intravenous cocaine at comparable plasma levels. In addition, smoked cocaine seems to be associated with more craving than the comparable intravenous dose. Therefore, there is little evidence to support the view that intravenous cocaine is more addicting than smoked cocaine; in fact, the current evidence supports the opposite view. The risk of cocaine administration on craving in general will be minimized through: 1) To enroll in this study, cocaine use disorder subjects must not be seeking treatment. 2) Subjects will remain in the controlled environment after the last dose of cocaine. 3) At the time study completion, risks of ongoing cocaine use and opportunities for treatment are discussed with all subjects.

Risks of Lorcaserin Combined with Cocaine

In a recent NIDA funded preclinical study (NIDA Study Report 1812-12132, Sep. 20, 2013), lorcaserin was administered to rodents in combination with cocaine without any significant toxicity. Final results of this study are summarized here and provided in detail in an attached document. In short, at human equivalent doses in rats (i.e., 5 mg/kg, equivalent to 20 mg/day in humans, based on systemic exposures), there were no additive/synergistic effects of PO lorcaserin on IV cocaine-induced mortality or convulsions. However, at 5-fold higher doses (i.e., 25 mg/kg in rats, equivalent to 100 mg/day in humans – substantially beyond what is proposed in this study), there are indications of increased sensitivity to cocaine-induced convulsions due to lorcaserin. The combination of lorcaserin and cocaine has not been studied in humans. We will guard against potential toxicity of cocaine combined with lorcaserin by dosing cocaine using an ascending dose approach, and we have specific stopping criteria in place to stop the cocaine dose escalation if warranted by excessive cardiovascular responses. If in spite of these precautions cocaine toxicity is observed (significant hypertension, tachycardia, symptoms of ischemia or evidence of arrhythmias) we have established treatment protocols in place and a code team will respond if needed. We have never required such assistance in the past. Moreover, additional blood samples will be drawn 4-6 hours on the days of escalating cocaine infusions to measure high-sensitivity troponin I (hsTnI) and N-terminal pro-brain natriuretic peptide (NT-pro-BNP). Although not routinely utilized in clinical practice, these markers will be stored for batch analysis upon completion of the study to detect the presence cardiac strain and/or stress to the myocardium related to cocaine in the absence of overt clinical disease (Gaggin and Januzzi, 2014; Gualandro et al., 2014). This data will be used as a potential biomarker of subclinical effects of cocaine on heart for future clinical trials. The total amount of blood for the entire study will not exceed 550ml in an 8 week period.

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. This risk will be minimized by having blood drawn by a trained phlebotomist.

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 cocaine in the hospital.

Subjects in the studies will be randomly assigned to receive study medication or placebo. All assignments are based on chance.

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 weekly.

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 cocaine dependence 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 designated study personnel 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 designated 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.

Approval by other interested agencies, including the FDA, is required prior to initiating studies investigating new indications of approved medications. This will provide further safeguard against unanticipated risks. An IND for drug and cocaine administration will be obtained well in advance of project start-up.

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 cocaine use if the study medications prove beneficial, with a resultant decrease in cocaine morbidity and mortality, as well as a reduction in the overall social costs for cocaine dependence.

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 cocaine 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 drug interactions between lorcaserin and cocaine in subjects with cocaine use disorder, to provide information on effects of lorcaserin on subjective response to cocaine and cocaine self-administration in subjects with cocaine use disorder, and to provide safety, PK information, and cocaine self-administration and subjective response to cocaine information for compounds chosen based on results of current project and discussions with NIDA program staff.

Secondary Objectives

The secondary objective is to examine effects of lorcaserin on behavioral laboratory measures of impulsivity in cocaine dependent 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 cocaine) and efficacy (subjective response to cocaine and self-administration data) in non-treatment seeking cocaine use disorder subjects. This project will provide innovative data on effects of novel compounds on cocaine self-administration in addition to needed safety data on drug interactions with cocaine. This is a Phase I human drug interaction study examining the safety of concurrent administration of cocaine

with novel compounds, and the effects of the novel compounds on subjective response to cocaine and cocaine self-administration in non-treatment seeking cocaine use disorder subjects. This 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 cocaine self-administration and cue reactivity in rodents. In addition there is human safety data in non-cocaine using subjects for lorcaserin as it is currently FDA approved for obesity, but there is no human cocaine 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 10mg once daily increasing to 10mg twice daily.

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

Subject participation will consist of 12 active study days and 2 follow-up visits, divided into multiple scheduled study visits. Total duration of the study is expected to be 4 years.

Criteria for evaluation

Primary Efficacy Endpoint

1. Safety: Heart rate (HR) and blood pressure (BP) measures during saline infusions will be compared to HR and BP after each cocaine infusion (20 mg and 40 mg doses). Changes in HR and BP induced by cocaine infusion along with lorcaserin will be compared to those without lorcaserin, by cocaine dose level (20 mg and 40 mg doses), using repeated measures analysis of variance (ANOVA). Changes in ECG readings during saline infusion as compared to those taken during cocaine infusions will be reported as summary statistics. Adverse event data will be compiled for lorcaserin and placebo cohorts and presented as summary statistics.

2. Cocaine Self-administration: Repeated measures ANOVA with cocaine dose (0mg, 25mg) and lorcaserin dose (0mg, 10mg, 20mg) as within subject factors will be used to examine differences in mean cocaine choice selection. In addition, a Bayesian analysis will be carried out as described below.

3. Subjective response to cocaine: Subjective response measures (VAS) obtained during saline infusions will be compared between lorcaserin and placebo subjects to those during cocaine infusions by cocaine dose level to determine the extent to which these measures are modified by the administration of lorcaserin using repeated measures ANOVA.

4. Cocaine PK: Plasma concentration-time profiles of cocaine after cocaine infusion during placebo administration (Day 2) will be analyzed to obtain pharmacokinetic parameter estimates of cocaine (Tmax, AUC, apparent t½, CL) by individual. These parameters will be compared within subjects on sessions with lorcaserin (Days 6 and 10).

Secondary Efficacy Endpoints

Response inhibition: Commission errors on the IMT 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.

SUBJECT SELECTION

Study Population

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

Inclusion Criteria

Males and females between 18 and 59 years-of-age.

Understand the study procedures and provide written informed consent.

Meet current DSM-5 criteria for cocaine use disorder, at least moderate severity, and current DSM-IV diagnosis of cocaine dependence, but are not seeking treatment.

Currently using cocaine by smoking or intravenous route of administration as determined by self-report and have a positive urine drug screen for cocaine during screening.

Have vital signs as follows: resting pulse below 95 bpm, blood pressures below 140 mm Hg systolic and 90 mm Hg diastolic.

Have no clinically significant abnormalities in the judgment of the study physician in hematology and chemistry laboratory tests including liver function tests.

Have sinus rhythm with normal conduction (including QTcF less than 440 ms) by ECG.

Have no contraindications for study participation as determined by medical history and physical examination.

Be able to demonstrate an understanding of study procedures and follow instructions including behavioral laboratory testing.

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.

Have hemoglobin/hematocrit values within normal limits based on age and gender.

Exclusion Criteria

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

Have a DSM-5 diagnosis of any psychoactive 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.

Have any previous medically adverse reaction to cocaine, including loss of consciousness, chest pain, or epileptic seizure.

Have any clinically significant medical disorder including cardiovascular (including hypertension), pulmonary, CNS, hepatic, or renal disorder.

Have a history of seizures (excluding childhood febrile seizures), or clinically significant head injury.

Have significant current suicidal or homicidal ideation or a history of suicide attempt within the past 6 months.

Have conditions of probation or parole requiring reports of drug use to officers of the court.

Have impending incarceration.

Have a positive HIV test by self-report or history.

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 at each study visit.

Have any other illness, or condition, which in the opinion of the PI would preclude safe and/or successful completion of the study.

Have a positive breath alcohol test or urine drug screening positive for drugs of abuse with the exception of cocaine, cocaine metabolites, opiates and marijuana.

Have a score > 5 on the Clinical Opiate Withdrawal Scale on any screening, monitoring, or study visit.

Subjects who are allergic to lorcaserin.

Subjects who have taken any investigational drug within 90 days prior to baseline.

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 cocaine 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

Any medications with a known interaction with cocaine or lorcaserin

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.

Commercially available sterile normal saline for human use will be used as a matched placebo for cocaine. Cocaine is packaged in 2 mL vials containing 20 mg per mL.

Cocaine for IV human use will be obtained from a NIDA contractor under a letter of authorization to allow cross reference to NIDA's DMF for cocaine obtained and submitted to the IND.

The pharmacist will prepare the cocaine according to instructions supplied by the NIDA contractor and dispense according to the randomization. The labels on the cassettes of cocaine and matching placebo will conform to internal Pharmacy and CRSU SOPs and instructions.

The doses of cocaine will be prepared by diluting cocaine with 20 mL normal saline.

Cocaine administration: Cocaine will be administered by a study nurse under the direct supervision of a physician. The drug is given intravenously (IV) over a 2 minute period in a cassette via a pump delivery system.

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 seen both in the hospital and at IDAS clinic for a total of 12 active study days and monitoring procedures will be in place to detect drug and alcohol use and assess for adverse events at each visit. In addition, the hospital cocaine administration procedures will reduce the likelihood of increased cocaine craving after cocaine administration. 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 during their study visits. Subjects who are unable to comply with these restrictions will be dropped from the study. After a screening cocaine infusion to determine safety, eligible subjects will be randomized to Group A –placebo only or Group B –placebo followed by an ascending dose of lorcaserin. 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 once daily increasing to 10mg twice daily.

Outcome Measures: The primary outcome measures are adverse events, cardiovascular responses (Heart rate (HR), blood pressure (BP), ECG measurements, subjective response to cocaine, cocaine self-administration, and cocaine blood PK. Secondary outcome measures will be impulsivity as measured by the immediate memory task (IMT).

1) Days 1-2: All subjects will be seen on the CRSU. All subjects will receive placebo on days 1-2 in a single blind fashion. Vital signs including heart rate, blood pressure and respiration rate will be obtained after placebo administration. Days 1-2 will be single-blind placebo, whereas all remaining study days will be double-blind. All subjects will leave the CRSU at the end of each study day.

2) Days 3-6: All subjects will be seen on the CRSU on days 3 and 6, and at the IDAS clinic on days 4 and 5. On days 3-6, subject group A will receive one placebo pill twice daily, and group B will receive one placebo pill in the morning and one matching lorcaserin 10 mg pill in the evening, for a total dose of 10 mg daily. ECG with QTc will be performed daily. If the QTc is prolonged greater than 30ms over baseline lorcaserin dosage will be held.

3) Day 7: All subjects will receive one placebo pill in the morning in single blind fashion. Following Cocaine Self-administration sessions and impulsivity testing the subjects will leave the unit.

4) Days 8-10: All subjects will be seen at the IDAS clinic on Days 8 and 9 and subjects in group B will have a blinded dosage increase to 10 mg of lorcaserin twice daily for Days 8-11 (Days 10 and 11 will take place at the CRSU). Vital signs including heart rate, blood pressure and respiration rate will be obtained before placebo/lorcaserin administration. ECG with QTc will be performed daily under the supervision of a study physician. If the QTc is prolonged greater than 30ms over baseline lorcaserin dosage will be held.

5) Day 11: All subjects will be seen on the CRSU and receive placebo/lorcaserin in the morning followed by the last cocaine self-administration session.

6) Day 12: Subjects will be seen at IDAS for study procedures.

5) Cocaine Infusion Sessions (Days 1, 2, 6, and 10): All subjects will undergo an ascending dose intravenous cocaine administration after admission on day 1 to ensure safety of later cocaine studies.

To assess the safety and subjective effects of cocaine in the presence of lorcaserin, subjects will receive ascending doses of intravenous cocaine (10 mg, 20 mg, 40 mg), with each cocaine administration separated by

one hour. In addition, 0 mg cocaine (saline) infusion will be randomly given after the first dose of cocaine in order to aid in blinding investigators and subjects to the order of drug administration. Infusions will be carried out hourly starting from 1 hour after placebo/lorcaserin for 4 times (on Day 1, 2, 6, and 10). An example dose by session diagram is shown below. Note that the 0 mg dose is randomly given after the first dose of cocaine. Monitoring will be continued for 1 hour after the last dose of cocaine.

Dose	Dose Session 1	Dose Session 2	Dose Session 3	Dose Session 4
1	10 mg Cocaine	10 mg Cocaine	10 mg Cocaine	10 mg Cocaine
2	20 mg Cocaine	0 mg Cocaine	20 mg Cocaine	0 mg Cocaine
3	0 mg Cocaine	20 mg Cocaine	40 mg Cocaine	20 mg Cocaine
4	40 mg Cocaine	40 mg Cocaine	0 mg Cocaine	40 mg Cocaine

Dispensing

Study drugs will be dispensed by the research pharmacist and administered by the research nurse on the CRS unit (cocaine) or trained research personnel (lorcaserin) at IDAS.

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, placebo, and cocaine 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. Cocaine must be

stored in accordance with regulations for controlled substances and per pharmacy

policy.

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 Cocaine/placebo dispensation and assignment number, as well as the date dispensed.

Both used and cocaine/placebo cassettes and IV cocaine vials must be accounted for on a drug disposition and accountability form, including the amount of cocaine that was not dispensed and was wasted from the 2mg/mL vial.

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. While it will be preferable to schedule all of the study days consecutively, the modular design allows Day 1 and Day 2 to be scheduled independently in advance of the Day 3-7 and Day 8-12 study visits. The Day 3-7 and Day 8-12 hospital visits will be for 5 days each. In addition these 2 study visits may be scheduled separately to accommodate the availability of participants. However, all study days must be completed with a 90-day period. In the event that all study days are not scheduled consecutively, participants will be required to come into the research clinic for weekly monitoring (including UDS, vitals, and questionnaires).

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 at screening and study days (Days 1-11) and Follow-Up days (Days 12, 15 and 19). Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

Clinical Opiate Withdrawal Scale (COWS)

This scale will be administered each study day during screening, monitoring and at each of the study visits for subjects who meet criteria for opioid dependence 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 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, 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 screening and at study visits (Days 1-12) and Follow-Up visits (Days 15 and 19).

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.

Childhood Disorders Version of the SCID (KID-SCID) ADHD Module

A version of the KID-SCID modified for adults will be used to aid in the determination of a diagnosis of adult attention deficit hyperactivity disorder (ADHD). This interview will be conducted at screening by trained staff.

Wender Utah Rating Scale (WURS)

This 61-item scale for adults (Almaric and Koob, 1993) describes their own childhood behavior to aid in the determination of ADHD in adults. This 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 cocaine 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.

Attentional Bias (modified Stroop task)

This is a widely-used implicit task in which the subject is presented with words printed in color, and asked to discriminate the color of each stimulus and to ignore the meaning of the words. There are ten cocaine-related words (e.g., "cocaine", "crack"), and ten neutral words consisting of household features (eg., "table", "kitchen"). The word sets are matched in length or frequency of use using typical procedures. Subjects are instructed that words written in different colors (blue, green, or red) will be presented on the screen, one after the other, and that their task is to indicate the color in which the word is written as quickly and as accurately as possible, ignoring the meaning of the word itself. A new word is presented 500ms after a response (or 500ms after the timeout of 3 sec). In this block design protocol a block (60s) of neutral words alternates with a block (60s) of cocaine words and each run is approximately 10 min. Subjects first respond to a practice sequence (50 trials) of letter strings (e.g, HHHH). Within each Stroop task, the program randomly determines the presentation order of words and colors for each participant under the constraint that the same color does not appear on two consecutive trials.

Conditioned Distracter XY Go-No Go task

This task is based on the XY-GoNo Task of Hugh Garavan and colleagues:

http://www.ncbi.nlm.nih.gov/pubmed/12944513

In this task, the subject sees the letters X and Y alternating once per second (white letter on black background) in a large font, e.g. 400 ms of letter presentation, alternating with 600 ms blank screen. The subject is to emit a press each time the letter is different from the one before (an alternation). Since most of the time X alternates with Y, this builds up a prepotent tendency of the subject to press every second. However, the subject is to NOT press if the same letter is presented twice in a row,
e.g. ..X.…Y…..X….X..... or X….Y…..X….Y….X….Y….Y… The presentation of the same letter twice in a row in the series is a called a LURE, and these represent 10% of the stimuli, and lures never occur in rapid succession. The task will be divided into 15 blocks, each 30 seconds long. Each block will thus have 30 letters shown, three of which will be identical to the letter before it (i.e. three lures per block. Five blocks will be "non-distractor" control blocks, where the background will be black as in the original Garavan task. Five blocks will be "unconditioned distractor) control blocks, where the subject will see a continuous thick yellow border at the periphery of the screen. Five blocks will be the "conditioned distractor" blocks, where the subject will see a continuous teal-colored thick border that was previously seen in the cocaine self-administration task.

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 cocaine (PK): Blood samples for analysis of the pharmacokinetics of 10 mg IV cocaine will be collected during treatment with 0 mg Lorcaserin (on study day 2) and during treatment with lorcaserin at 10 mg once daily (study day 6) and lorcaserin 10mg twice daily (study day 10). Plasma cocaine levels at these time points for each of those days: -15, 5, 10, 20, 30, 45 60, 90, 120, 180, 240 minutes. Plasma levels of cocaine and metabolites will be assayed by liquid chromatography-tandem mass spectrometry. Benzoylecgonine and ecgonine methyl ester both peak at approximately 120 minutes, with expected concentrations of 170 and 15 ng/mL at 480 minutes, respectively. Determinations of cocaine, benzoylecgonine, ecgonine methyl ester, and norcocaine (if detectible) will be measured. Blood will be collected into Vacutainer tubes that contain fluoride to inhibit hydrolysis of cocaine by plasma cholinesterases. After separation of plasma by routine methods, samples will be frozen at -70°C until ready for analysis.

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

Screening (Days -7 to 0) Conducted at IDAS

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 if opioid user
Perform a complete physical examination.
Perform a complete neurological exam.
Perform a 12-Lead ECG.
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).
Perform psychiatric interviews (SCID, SCID-II, KID-SCID).
Conduct clinical assessments (KMSK, FTND, NART, ASI-lite, POMS, CGI-S, C-SSRS).
Record brief substance craving scale, timeline follow back cocaine use, and drug use history.
Verify inclusion and exclusion.
Schedule subject for Day 1 visit as soon as possible.

Study Day 1
Arrive at CRS unit.
Collect urine for pregnancy test and urine drug screen.
Perform and record Breathalyzer.
Administer COWS if opioid user.
Perform and record vital signs.
Perform a 12-Lead ECG.
Perform a brief physical exam and continuous cardiovascular monitoring.
Administer placebo in morning.
Administer cocaine for Dosing session 1.
Record brief substance craving scale.
Update concomitant medications.
Record Visual Analog Scale (VAS).
Record adverse events.
Conduct clinical assessments (POMS, CGI-I, C-SSRS).
Administer Immediate Memory Task (IMT).
Leave CRS unit.

Study Day 2
Arrive on CRS unit.
Collect urine for pregnancy test and urine drug screen.
Perform and record Breathalyzer and vital signs.
Administer COWS if opioid user.
Perform a 12-Lead ECG.
Perform a brief physical exam and continuous cardiovascular monitoring.

Administer placebo in morning.
Administer cocaine for PK.
Record brief substance craving scale.
Update concomitant medications.
Record VAS and adverse events.
Administer cocaine for Dosing session 2.
Conduct clinical assessments (POMS, CGI-I).
Leave CRS unit.

Study Day 3
Arrive on CRS unit.
Collect urine for pregnancy test and urine drug screen.
Perform and record Breathalyzer and vital signs.
Administer COWS if opioid user.
Perform a 12-Lead ECG, brief physical exam, and continuous cardiovascular monitoring.
Administer placebo in morning
Self -Administered cocaine session 1 in morning.
Self-Administered cocaine session 2 in afternoon.
Record brief substance craving scale.
Update concomitant medications.
Record VAS and AE.
Conduct clinical assessments (POMS, CGI-I).
Administer placebo/lorcaserin in evening
Leave CRS unit.

Study Day 4
Arrive at IDAS
Administer placebo in morning
Collect urine for pregnancy test and urine drug screen
Perform and record Breathalyzer and vital signs.
Perform a 12-Lead ECG.
Record brief substance craving scale and AE.
Administer COWS if opioid user.
Update concomitant medications.
Conduct clinical assessments (POMS, CGI-I).
Administer IMT task
Administer placebo/lorcaserin in evening
Leave IDAS.

Study Day 5
Arrive at IDAS

Administer placebo in morning
Collect urine for pregnancy test and urine drug screen.
Perform and record Breathalyzer and vital signs.
Perform a 12-Lead ECG.
Record brief substance craving scale and AE.
Administer COWS if opioid user.
Update concomitant medications.
Conduct clinical assessments (POMS, CGI-I, and C-SSRS).
Administer placebo/lorcaserin in evening
Leave IDAS.

Study Day 6
Arrive on CRS unit
Administer placebo in morning
Collect urine for pregnancy test and urine drug screen.
Perform and record Breathalyzer and vital signs.
Perform a 12-Lead ECG and continuous cardiovascular monitoring.
Record brief substance craving scale, VAS, and AE.
Administer COWS if opioid user.
Update concomitant medications.
Administer cocaine for PK.
Measure lorcaserin PK
Administer cocaine for Dosing session 3.
Conduct clinical assessments (POMS, CGI-I).
Administer placebo/lorcaserin in evening
Leave CRS unit.

Study Day 7
Arrive on CRS unit
Administer placebo in morning
Collect urine for pregnancy test and urine drug screen.
Perform and record Breathalyzer and vital signs.
Perform a 12-Lead ECG and brief physical exam.
Record brief substance craving scale, VAS and AE.
Administer COWS if opioid user.
Update concomitant medication.
Self -Administered cocaine session 3 in morning.
Self -Administered cocaine session 4 in afternoon.
Conduct clinical assessments (POMS, CGI-I).
Administer IMT task.
Leave CRS unit

Study Day 8
Arrive at IDAS
Administer placebo/lorcaserin in morning
Collect urine for pregnancy test and urine drug screen.
Perform and record Breathalyzer and vital signs.
Administer COWS if opioid user.
Perform a 12-Lead ECG and brief physical exam.
Record brief substance craving scale, VAS and AE.
Update concomitant medications.
Conduct clinical assessments (POMS, CGI-I, and C-SSRS).
Administer placebo/lorcaserin in evening.
Leave IDAS.

Study Day 9
Arrive at IDAS
Administer placebo/lorcaserin in morning
Collect urine for pregnancy test and urine drug screen.
Perform and record Breathalyzer and vital signs.
Perform a 12-Lead ECG.
Record brief substance craving scale and AE.
Administer COWS if opioid user.
Update concomitant medications.
Conduct clinical assessments (POMS, CGI-I, and C-SSRS).
Administer placebo/lorcaserin in evening.
Leave IDAS.

Study Day 10
Arrive on CRS unit
Administer placebo/lorcaserin in morning
Collect urine for pregnancy test and urine drug screen.
Perform and record Breathalyzer and vital signs.
Perform a 12-Lead ECGand continuous cardiovascular monitoring.
Record brief substance craving scale, VAS, and AE.
Administer COWS if opioid user.
Update concomitant medications.
Administer cocaine for PK.
Measure lorcaserin PK.
Conduct clinical assessments (POMS, CGI-I).
Administer cocaine for Dosing session 4.
Administer IMT task

Administer placebo/lorcaserin in evening
Leave CRS unit.

Study Day 11
Arrive on CRS unit
Administer placebo/lorcaserin in morning
Collect urine for pregnancy test and urine drug screen.
Collect blood for clinical laboratory tests (serum chemistry and hematology).
Perform and record Breathalyzer and vital signs.
Perform a 12-Lead ECG and continuous cardiovascular monitoring.
Record brief substance craving scale, VAS and AE.
Administer COWS if opioid user.
Update concomitant medication.
Self -Administered cocaine session 5 in morning.
Self -Administered cocaine session 6 in afternoon.
Conduct clinical assessments (POMS, CGI-I).
Leave CRS unit.

Study Day 12
Arrive at IDAS
Collect urine for pregnancy test and urine drug screen.
Perform and record Breathalyzer and vital signs.
Perform a 12-Lead ECG.
Record brief substance craving scale and AE.
Administer COWS if opioid user.
Update concomitant medication.
Conduct clinical assessments (POMS,CGI-I, Stroop, and XY Go-No Go).
PI (or designee) conduct assessment for lorcaserin side effects.
Leave IDAS

Follow-Up Days (Day 15, 19) Conducted at IDAS
Collect urine for pregnancy test and urine drug screen.
Perform and record Breathalyzer and vital signs.
Perform a 12-Lead ECG and brief physical exam (Day 19 only).
Record brief substance craving scale and timeline follow back cocaine use.
Update concomitant medication.
Conduct clinical assessments (POMS, CGI-I, and C-SSRS).

Table 2. Overview of Study Procedures

Study Day	Day 1	Day 2
Study Visit	One	Two
Procedure Morning Session	Arrive at CRS, Three Screening Doses of Cocaine (NexFin monitoring)	Arrive at CRS 10mg Cocaine for PK
Procedure Afternoon Session	Impulsivity Testing Depart from CRS	Three Doses of Cocaine, Cardiovascular (NexFin monitoring) Cardiac Biomarkers (4-6 hrs from last dose) Subjective Ratings Depart from CRS
Study Drug	Placebo 8:00 a.m.	Placebo 8:00 a.m

Study Day	Day 3	Day 4	Day 5	Day 6	Day 7
Study Visit	Three	Four	Five	Six	Seven Arrive at CRS ECG
Procedure Morning Session	Arrive at CRS Cocaine Self Administration	Arrive at IDAS ECG Impulsivity Testing	Arrive at IDAS ECG	Arrive at CRS ECG 10mg Cocaine for PK, Lorcaserin blood levels	Cocaine Self Administration
Procedure Afternoon Session	Cocaine Self Administration Depart from CRS			Three Doses of Cocaine (NexFin monitoring) Cardiovascular& Subjective Ratings Cardiac Biomarkers (4-6 hrs from last dose) Depart from CRS	Cocaine Self Administration Impulsivity Testing Depart from CRS
Study Drug	Placebo 8:00 a.m., Lorcaserin 10mg p.m. prior to departure or Placebo 8:00 a.m., Placebo p.m. prior to	Placebo 8:00 a.m., Lorcaserin 10mg p.m. prior to departure or Placebo 8:00	Placebo 8:00 a.m., Lorcaserin 10mg p.m. prior to departure or Placebo	Placebo 8:00 a.m., Lorcaserin 10mg p.m. prior to departure, or Placebo 8:00 a.m., placebo p.m. prior to departure	Placebo 8:00 a.m.

	departure	a.m., placebo p.m. prior to departure	8:00 a.m., placebo p.m. prior to departure		

Study Day	Day 8	Day 9	Day 10	Day 11	Day 12
Study Visit	Eight	Nine	Ten	Eleven	Twelve
Procedure Morning Session	Arrive at IDAS ECG	Arrive at IDAS ECG	Arrive at CRS ECG 10mg Cocaine for PK, Lorcaserin blood levels	Arrive at CRS ECG Cocaine Self Administration	Arrive at IDAS ECG Impulsivity Testing
Procedure Afternoon Session			Three Doses of Cocaine (NexFin monitoring) Cardiovascular & Subjective Ratings Cardiac Biomarkers (4-6 hrs from last dose) Impulsivity Testing Depart from CRS	Cocaine Self Administration Depart from CRS	Physical exam
Study Drug	Lorcaserin 10mg 8:00 a.m., Lorcaserin 10mg p.m. prior to departure. or Placebo 8:00 a.m., placebo p.m. prior to departure	Lorcaserin 10mg 8:00 a.m., Lorcaserin 10mg p.m. prior to departure or Placebo 8:00 a.m., placebo p.m. prior to departure	Lorcaserin 10mg 8:00 a.m., Lorcaserin 10mg p.m. prior to departure or Placebo 8:00 a.m., placebo p.m. prior to departure	Lorcaserin 10mg 8:00 a.m. or Placebo 8:00 a.m.,	

Self-Administration Session (Days 3, 7, and 11)

On days 3, 7, and 11, subjects participate in two self-administrative sessions and will make six choices for cocaine or $5. The first session will begin at 10 am and the second at 1 pm (see Table 3 below), with each session being 2.5 hours long.

Table 3. Schedule of Cocaine Self Administration Procedure

Time	Choices	8 patients	8 patients
10:00 am	Baseline: VAS, BP/HR, EKG		
10:20 am	Choice 1	0 mg cocaine IV or $ 5	25 mg cocaine IV or $ 5
10:35 am	Choice 2	0 mg cocaine IV or $ 5	25 mg cocaine IV or $ 5

10:50 am	Choice 3	0 mg cocaine IV or $ 5	25 mg cocaine IV or $ 5
11:05 am	Choice 4	0 mg cocaine IV or $ 5	25 mg cocaine IV or $ 5
11:20 am	Choice 5	0 mg cocaine IV or $ 5	25 mg cocaine IV or $ 5
11:35 am	Choice 6	0 mg cocaine IV or $ 5	25 mg cocaine IV or $ 5
1:00 pm	Baseline: VAS, BP/HR, EKG		
1:20 pm	Choice 1	25 mg cocaine IV or $ 5	0 mg cocaine IV or $ 5
1:35 pm	Choice 2	25 mg cocaine IV or $ 5	0 mg cocaine IV or $ 5
1:50 pm	Choice 3	25 mg cocaine IV or $ 5	0 mg cocaine IV or $ 5
2:05 pm	Choice 4	25 mg cocaine IV or $ 5	0 mg cocaine IV or $ 5
2:20 pm	Choice 5	25 mg cocaine IV or $ 5	0 mg cocaine IV or $ 5
2:35 pm	Choice 6	25 mg cocaine IV or $ 5	0 mg cocaine IV or $ 5

In one session subjects will make six choices between 0 mg i.v. cocaine or money. During the other self-administration session, subjects will make six choices between 25 mg i.v. cocaine or money. The dose of cocaine was chosen based on previous studies showing a significant medication effect on cocaine self-administration (Hart *et al*, 2008). Sessions begin with a baseline period in which participants complete computerized subjective-effects questionnaires, and vital signs are monitored.

The session begins with one “sample” choice, where participant respond on a keyboard under a fixed ratio schedule (FR200; participants are required to press the spacebar 200 times to receive the option). The subsequent five trials are spaced 15-min apart, in which participants had the opportunity to self-administer the same dose of cocaine as the sample dose, or to receive money. A modified progressive ratio of responding is used, in which the first response requirement is a FR200. Following each choice, the response requirement for the chosen option increases by 400, while the response requirement for the non-chosen option does not change. Thus, if a participant only chose cocaine or only chose money, the response requirements would escalate progressively through 600, 1,000, 1,400,1,800, and 2,200 bar presses (Haney *et al*, 2011).

The subject would make a series of choices using the PR schedule between ascending value money options ($5) or cocaine (0 mg or 25 mg/i.v. infusion) using a patient controlled (PCA pump). Choices for money will be verbally indicated to the investigator. Infusions will be made over a 2 min period followed by a 13 min time-out period. Subjects will receive the cash or cocaine doses (0 or 25 mg) immediately after they meet the progressive ratio criteria for each choice, providing vital signs remain within the preset intervals. If the subject chooses all cocaine options in the cocaine choice session and no money, they will receive a maximum of 120 mg cocaine, i.v. Money choices will be given directly to the patient after choice session, but this can only be spent after departing from the CRS. All infusions on this day will be double-blinded and counterbalanced in their presentation among subjects.

Cardiovascular Monitoring During Cocaine Infusions and Cocaine Self-Administration Procedure

Cardiovascular monitoring by continuous measuring heart rate/ECG and blood pressure starting 15 minutes prior to each of the 4 cocaine infusions and continued for at least 60 minutes following each dose. PI/Co-I or their medically qualified designees will be present during all cocaine infusions to monitor and intervene if necessary. For the sessions of cocaine infusions on Day 1, 2, 6, and 10, non-invasive monitoring of cardiac hemodynamics will be performed with the NexFin finger cuff system (Edwards Life Sciences).

Criteria for withholding Cocaine Administration

Cocaine administration will not be initiated if:

- Clinically significant arrhythmias
- Resting pulse > 130 bpm
- QTc increase of greater than 30ms over baseline
- Blood pressure above 165mm Hg systolic and 100mm Hg diastolic.
- Behavioral manifestations of cocaine toxicity (agitation, psychosis, inability to cooperate with study procedures).

If cardiovascular measures have not returned to acceptable levels (heart rate <130 bpm, diastolic pressure <100mmHg, and systolic pressure <165 mmHg, QTc <30ms over baseline), the next session will be delayed by 15 min, after which these measures will be repeated.

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);

• Systolic BP > 180 mm Hg
• Diastolic BP > 120 mm Hg
• Heart rate > (220 – age x 0.85) bpm
• QTc > 470ms
• Participants must continue to meet other inclusion criteria in order to remain in the protocol

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 4. 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 5.

Table 5. 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
- inpatient 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

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

Systolic BP > 180 mmHg

Diastolic BP > 110 mmHg

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

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 cocaine 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 cocaine 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 cocaine 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 cocaine administration in substance-dependent children under 18 have not been established.

Analysis of Primary Endpoint

1. Safety: Heart rate (HR) and blood pressure (BP) measures during saline infusions will be compared to HR and BP after each cocaine infusion (20 mg and 40 mg doses). Changes in HR and BP induced by cocaine infusion along with lorcaserin will be compared to those without lorcaserin, by cocaine dose level (20 mg and 40 mg doses), using repeated measures analysis of variance (ANOVA). Changes in ECG readings during saline infusion as compared to those taken during cocaine infusions will be reported as summary statistics. Adverse event data will be compiled for lorcaserin and placebo cohorts and presented as summary statistics.

2. Cocaine Self-administration: Repeated measures ANOVA with cocaine dose (0mg, 25mg) and lorcaserin dose (0mg, 10mg, 20mg) as within subject factors will be used to examine differences in mean cocaine choice selection. In addition, a Bayesian analysis will be carried out as described below.

3. Subjective response to cocaine: Subjective response measures (VAS) obtained during saline infusions will be compared between lorcaserin and placebo subjects to those during cocaine infusions by cocaine dose level to determine the extent to which these measures are modified by the administration of lorcaserin using repeated measures ANOVA.

4. Cocaine PK: Plasma concentration-time profiles of cocaine after cocaine infusion during placebo administration (Day 2) will be analyzed to obtain pharmacokinetic parameter estimates of cocaine (Tmax, AUC, apparent t½, CL) by individual. These parameters will be compared within subjects on sessions with lorcaserin (Day 6 and 10).

Analysis of Secondary Endpoints

Response inhibition: Commission errors on the IMT 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.

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

This project requires a final sample size of 18 subjects (Six subjects assigned to Group A (placebo) and 12 subjects assigned to Group B (active lorcaserin). This sample size for effect of lorcaserin on cocaine self-administration was based on previous research showing effects of medication on human cocaine self-administration (Hart et al, 2008). 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 cocaine 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 Hart et al. (2008). 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 at left, 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.

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APPENDIX 1. DETAILED TIMELINE OF MEASURES

	Screening Day	Study Day												Follow-up
Procedure	-90 to 0	1	2	3	4	5	6	7	8	9	10	11	12	15, 19
Informed Consent	X													
Serum Chemistry	X											X		
Hematology	X											X		
History, Physical Exam, and Neurological Exam	X	X	X									X		
Urine Pregnancy test (females)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Psychiatric Interview (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	X	X	X	X	X	X
Timeline Follow Back Cocaine Use	X													X
Drug Use History	X													
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Opiate Withdrawal Scale (COWS)	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine drug screen	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Breathalyzer	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Verify Inclusion & Exclusion	X	X	X											
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG (baseline triplicate) and singlet thereafter)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Continuous Cardiovascular Monitoring		X	X	X			X			X			X	
Brief Physical Exam		X	X	X					X				X	X (Day 19 only)
Cocaine Administration for 3 Doses		X	X				X				X			

Adverse Events Inventory		X	X	X	X	X	X	X	X	X	X	X	X	
Visual Analog Scale (VAS)		X	X	X			X	X			X	X		
Profile of Mood States (POMS)	X	X	X	X	X	X	X	X	X	X	X	X	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	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
Cocaine for PK			X				X				X			
Lorcaserin PK measurement							X				X			
Cardiac biomarkers (baseline and 4-6 hours after last dose)			X				X				X			

Lorcaserin or Placebo		X	X	X	X	X	X	X	X	X	X			
Cocaine Self-administration				X				X				X		
Immediate Memory Task (IMT)		X			X			X			X			
Stroop													X	
XY Go-NoGo													X	