NIDA/VA

Cooperative Study #1033

IND Number: 124,980

PHASE 2, MULTI-CENTER TRIAL OF LORCASERIN IN THE TREATMENT OF COCAINE USE DISORDER

PROTOCOL

Version 3

April 17, 2017

Privileged & Confidential

STUDY #: NIDA/VA CSP-1033

PHASE 2, MULTI-CENTER TRIAL OF LORCASERIN IN THE TREATMENT OF COCAINE USE DISORDER

Investigational New Drug Application **(IND) Number:** 124,980

NIDA Protocol Chairman:	**David McCann, Ph.D.,** Tel: 301-827-5934
VA Protocol Chairperson:	**TBD**
NIDA Principal Investigator:	**Shwe Gyaw, M.D.,** Tel: 301-827-5924
NIDA Medical Monitor:	**Tanya Ramey, M.D., Ph.D.,** Tel: 301-827-5944
NIDA Project Manager:	**Liza Zeinert, M.A.,** Tel: 301-443-1138
Funding Agency:	**Division of Therapeutics and Medical Consequences (DTMC)** National Institute on Drug Abuse (NIDA), NIH 6001 Executive Boulevard Bethesda, MD 20892
VA Data Coordinating Center:	**VA Cooperative Studies Program Coordinating Center** VA CSPCC – 151E P.O. Box 1010 Perry Point, MD 21902
VA Biostatistician:	**Joe Collins, Sc.D.,** Tel: 410-642-2411, ex. 5308
VA Research Pharmacy:	**VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center** VA CSPCRPCC 2401 Centre Avenue, SE Albuquerque, NM 87106-4180
VA Research Pharmacist:	**Kathy Boardman, R.Ph., M.S.** Tel: 505-248-3203

TABLE OF CONTENTS

TABLE OF CONTENTS **2**

LIST OF ABBREVIATIONS **6**

1 STUDY SCHEMA **8**

2 SYNOPSIS **9**

3 INTRODUCTION AND RATIONALE **12**

3.1 THERAPEUTIC STRATEGIES FOR TREATING COCAINE ABUSE 12
3.2 USE OF SEROTONERGIC AGENTS TO TREAT COCAINE DEPENDENCY 12
3.3 RATIONALE FOR USE OF PREDICTIVE ENRICHMENT STRATEGIES 13
3.4 LORCASERIN 14
3.4.1 FDA Label Indication 14
3.4.2 Receptor Pharmacology 14
3.4.3 Pre-Clinical Experience with Lorcaserin Relevant to Substance Abuse Treatment 14
3.4.4 Clinical Experience with Lorcaserin Relevant to Substance Abuse Treatment 15
3.4.5 Pharmacokinetics 16
3.4.6 Dose Justification 17
3.4.7 Lorcaserin Safety 17
3.5 ACETAZOLAMIDE SAFETY/DOSE JUSTIFICATION 19

4 STUDY OBJECTIVE **19**

5 IND HOLDER **19**

6 STUDY SITES **19**

7 STUDY DESIGN **19**

8 SUBJECT SELECTION **20**

8.1 ELIGIBLE SUBJECTS 20
8.2 INCLUSION CRITERIA 21
8.3 EXCLUSION CRITERIA 21

9 INVESTIGATIONAL PRODUCTS **23**

9.1 LORCASERIN 23
9.2 LORCASERIN PLACEBO 23
9.3 ACETAZOLAMIDE (ACZM) 23
9.4 PACKAGING AND LABELING 24
9.5 DRUG STORAGE 24
9.6 DISPENSING RECORD 24
9.7 USED/UNUSED INVESTIGATIONAL PRODUCTS 24

10 INTERVENTIONS **24**

10.1 STUDY DRUG 24
10.2 COUNSELOR GUIDED BEHAVIORAL THERAPY (COCAINE) 25

10.3 COMPUTER-BASED THERAPY (ALCOHOL) 25
11 STUDY PROCEDURES 25
11.1 SUBJECT RECRUITMENT 28
11.2 SCREENING (STUDY DAYS -21 TO -1) 28
11.3 SCHEDULING OF STUDY DAY 1 VISIT 28
11.4 STUDY DAY 1 (WEEK 1) – ENROLLMENT 28
11.5 STUDY DAY 8 (WEEK 2) – RANDOMIZATION 29
11.6 STUDY VISITS (WEEKS 2 TO 13) 29
11.7 FOLLOW-UP VISITS (WEEKS 14 AND 16) 29
11.8 EARLY TERMINATION VISIT – PRIOR TO DOSING COMPLETION 29
11.9 SITUATIONS REQUIRING STUDY DRUG DISCONTINUATION 30
11.10 EARLY STUDY TERMINATION 31
11.11 PREVENTING STUDY DROP-OUTS 31
11.12 SUBJECT COMPENSATION 31
11.13 MAINTAINING AND BREAKING STUDY BLIND 34
12 ASSESSMENT METHODS 34
12.1 SUBJECT LOCATOR FORM 34
12.2 MEDICAL HISTORY 34
12.3 SMOKING AND ALCOHOL HISTORY 35
12.4 PSYCHIATRIC HISTORY 35
12.5 DEMOGRAPHICS 35
12.6 ADDICTION SEVERITY INDEX-LITE (ASI-LITE) 35
12.7 PHYSICAL EXAM 35
12.8 VITAL SIGNS AND WEIGHT 35
12.9 PREGNANCY TEST 35
12.10 12-LEAD ECG 36
12.11 BECK DEPRESSION INVENTORY-SECOND EDITION (BDI-II) 36
12.12 COLUMBIA SUICIDE SEVERITY RATING SCALE (C-SSRS) 36
12.13 BLOOD CHEMISTRIES 37
12.14 HEMATOLOGY 37
12.15 URINALYSIS 37
12.16 URINE DRUG SCREEN 37
12.17 URINE FENTANYL 37
12.18 URINE COTININE 37
12.19 ETG URINE ALCOHOL TEST 37
12.20 URINE BE TESTING 38
12.21 BLOOD COLLECTIONS FOR MEDICATION ADHERENCE 38
12.22 COGNITIVE BEHAVIORAL THERAPY (CBT) 38
12.23 ALCOHOL INTERVENTION: QUIT TO QUIT 38
12.24 AIVIEW ADHERENCE MONITORING 38
12.25 CONCOMITANT MEDICATIONS 38
12.25.1 Concomitant Medications Always Excluded 39
12.25.2 Allowable Concomitant Medications with Limitations 39
12.26 SUBSTANCE USE REPORT (SUR) 40
12.27 BRIEF SUBSTANCE CRAVING SCALE (BSCS) 40

12.28 ADVERSE EVENTS 40
13 REGULATORY AND REPORTING REQUIREMENTS 40
13.1 GOOD CLINICAL PRACTICES 40
13.2 FDA FORM 1572 40
13.3 IRB APPROVAL 41
13.4 INFORMED CONSENT 41
13.5 USE OF PROTECTED HEALTH INFORMATION 41
13.6 DRUG ACCOUNTABILITY 42
13.7 MONITORING 42
13.7.1 Data and Safety Monitoring Board 42
13.7.2 Medical Monitor 42
13.7.3 Clinical Monitors 42
13.8 STUDY OR SITE DISCONTINUATION 43
13.9 RETENTION OF RECORDS 43
13.10 ADVERSE EVENTS REPORTING 43
13.10.1 Pregnancy 44
13.11 SERIOUS ADVERSE EVENTS 44
13.12 SUBJECT CONFIDENTIALITY 45
14 STATISTICAL ANALYSIS 45
14.1 PREDICTIVE ENRICHMENT STRATEGY AND SAMPLE SIZE 46
14.2 DEFINITIONS OF STUDY POPULATIONS 48
14.3 OUTCOME MEASURES 49
14.3.1 Primary Efficacy Outcome Measures 49
14.3.2 Secondary Efficacy Outcome Measures 50
14.3.3 Exploratory Outcome Measures 50
14.4 SAFETY EVALUATIONS 54
15 DATA MANAGEMENT AND ELECTRONIC CASE REPORT FORMS (ECRFS) 55
15.1 DATA COLLECTION 55
15.2 DATA EDITING AND CONTROL 55
15.3 DATA ENTRY, PROCESSING AND ANALYSES 56
16 PUBLICATION OF THE STUDY RESULTS 56
17 SIGNATURES 57
18 REFERENCES 58

LIST OF TABLES

Table 1. Lorcaserin Receptor Affinity 14

Table 2. Adverse Reactions Reported by ≥2% of Lorcaserin-Treated Patients and More Commonly than with Placebo in Patients without Diabetes Mellitus..... 17

Table 3. Schedule of Events..... 26

Table 4. Subject Compensation 33

LIST OF FIGURES

Figure 1. Study Schema 8

Figure 2. Effects of Lorcaserin on Responding for Cocaine or Food in Rhesus Monkeys 15

Figure 3. Enrichment Strategy Study Design 48

LIST OF APPENDICES

APPENDIX I: Instructions for Evaluating and Reporting Adverse Events and Serious Adverse Events

APPENDIX II: Procedure for Applying for Certificate of Confidentiality

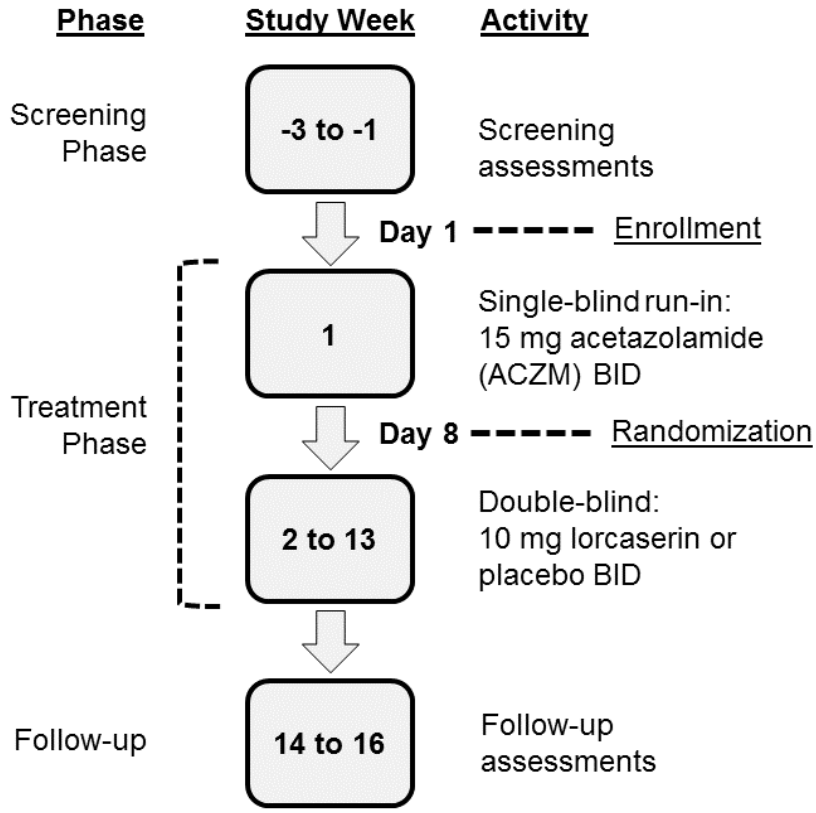
LIST OF ABBREVIATIONS

Abbreviation	Definition
5-HT	serotonin (5-hydroxytryptamine)
AA	Alcoholics Anonymous
AAA	attempting alcohol abstinence
ACZM	Acetazolamide
AE	adverse event
ALP	alkaline phosphatase
ALT/SGPT	alanine aminotransferase/serum glutamate-pyruvate transaminase
ANCOVA	analysis of covariance
ASI	Addiction Severity Index
AST/SGOT	Aspartate aminotransferase/serum glutamic oxaloacetic transaminase
AUC	area under the concentration-time curve
AUD	alcohol use disorder
BDI	Beck Depression Inventory
BE	Benzoylecgonine
BID	twice daily
BP	blood pressure
BSCS	Brief Substance Craving Scale
BUN	blood urea nitrogen
CA	Cocaine Anonymous
CBC	complete blood cell count
CBT	cognitive behavioral therapy
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments of 1988
C_{max}	maximum plasma concentration
CRF	case report form
CSF	cerebrospinal fluid
CSP	Cooperative Studies Program
CSPCC	Cooperative Studies Program Coordinating Center
CSPCRPCC	Cooperative Studies Program Clinical Research Pharmacy Coordinating Center
CYP	cytochrome P450
DA	Dopamine
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DSMB	Data and Safety Monitoring Board
DTMC	Division of Therapeutics and Medical Consequences
EC_{50}	median effective dose
ECG	Electrocardiogram
eCRF	electronic case report form
eDC	electronic data capture
EtG	ethyl glucuronide
FDA	Food and Drug Administration
FMO	flavin containing monooxygenase
GCP	Good Clinical Practice

Abbreviation	Definition
GAD	generalized anxiety disorder
GGT	gamma-glutamyltranspeptidase
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICH	International Conference on Harmonisation
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	intent-to-treat
IWRS	Interactive Web Response System
i.v.	Intravenous
LD_{50}	median lethal dose
MAOI	monoamine oxidase inhibitor
MDD	major depressive disorder
NA	Narcotics Anonymous
NE	Norepinephrine
NDA	New Drug Application
NF	National Formulary
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIDA	National Institute on Drug Abuse
NMS	neuroleptic malignant syndrome
PK	pharmacokinetic(s)
PPEE	prequalified for primary efficacy endpoint
SAE	serious adverse event
SCID-5-RV	Structured Clinical Interview for DSM-5 – Research Version
SD	standard deviation
SI	site investigator
SNRI	selective serotonin-norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
SUR	substance use report
TCA	tricyclic antidepressant
TLFB	timeline followback
T_{max}	time to maximum concentration
UDS	urine drug screen
USP	United States Pharmacopeia
VA	Department of Veterans Affairs
VTA	ventral tegmental area

1 STUDY SCHEMA

Figure 1. Study Schema



2 SYNOPSIS

OBJECTIVE: The objective of this study is to evaluate the efficacy and safety of lorcaserin in the treatment of cocaine use disorder.

STUDY DESIGN: This is a 19-week, multi-center, parallel group study that includes: 1) up to 3 weeks for screening; 2) a 13-week Treatment Phase consisting of a 1-week, single-blind run-in period, when all subjects receive twice daily 15 mg acetazolamide capsules (a medication adherence marker), followed by randomization to either twice daily 10 mg lorcaserin or placebo capsules for the remaining 12 weeks; and 3) a 3-week follow-up period, with scheduled visits during Study Weeks 14 and 16.

Beginning on Study Day 1, subjects will visit the clinic on a weekly basis throughout the 13-week Treatment Phase. At weekly clinic visits, subjects will receive study drug, provide urine samples and will participate in other protocol-specified assessments. Subjects will also take part in a weekly one-hour, manualized individual cognitive behavioral therapy session (CBT) to facilitate avoidance of cocaine use.

On Study Day 1, all subjects will view the first module of a computer-based alcohol intervention that describes the potential benefits of abstaining from alcohol during the trial. Though the module encourages abstinence from alcohol, each subject will determine for him/herself whether this will also be one of their goals during this trial. On Study Day 8, prior to randomization, subjects will be given the option of viewing the second module of the alcohol intervention. Each subject's decision (yes or no) to continue viewing the alcohol intervention modules will be recorded prior to randomization, and will serve as one of the stratification factors for randomization.

Beginning on Study Day 8, subjects will participate in a medication adherence monitoring procedure. The procedure utilizes a handheld device (smartphone) to record the administration of each dose of study drug and reporting of cocaine and alcohol use. Devices are issued by the site and are pre-programmed with the AiView application, a HIPAA-compliant medication monitoring software program. Use of the device carries associated opportunities to earn rewards contingent upon appropriate performance of tasks.

A randomized block design within each site will be utilized with the following stratification factors:

a. Number of subject-reported cocaine use days during the 30 days immediately prior to screening (<8 days versus 8 or more days);

b. Continued viewing of the computer-based alcohol intervention on Study Day 8 (yes/no);

c. Presence of alcohol and/or benzodiazepine dependence (yes/no).

SAMPLE SIZE: Approximately 272 total subjects will be enrolled across 10 or more clinical sites. Enrolled subjects who do not progress to randomization on Study Day 8 will not be replaced.

DURATION: The enrollment period is anticipated to be approximately 12 months and the total study duration will be approximately 18 months.

STUDY POPULATION: Two hundred seventy-two treatment-seeking males and females who meet Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for cocaine use disorder will be recruited from 10 or more clinical sites. Entry into the study will be open to men and women between 18 to 65 years of age, from all racial and ethnic groups. Only those subjects who authorize their enrollment in the Verified Clinical Trials registry and who provide written informed consent; who report cocaine use during the 30 days prior to screening; who provide at least one urine specimen positive for benzoylecgonine (BE) during screening; and who meet all other eligibility criteria and will be enrolled to receive study drug.

INTERVENTIONS: Beginning on the day of enrollment (Study Day 1), subjects will take acetazolamide (ACZM) 15 mg twice a day (BID) for seven days. Starting on the day of randomization (Study Day 8), subjects will take either lorcaserin 10 mg BID or matched placebo BID for the remaining 12 weeks of the Treatment Phase (Weeks 2-13).

All subjects will participate in weekly, one-hour, individual cognitive behavioral therapy session during the Treatment Phase (Weeks 1-13) which will be conducted as described in the NIDA therapy manual entitled "A Cognitive-Behavioral Approach: Treating Cocaine Addiction" (Carroll *et al*., 1998). A computer-based alcohol intervention, "Quit to Quit", will be viewed by all subjects on Study Day 1 and will be continued on an optional basis at the discretion of each subject (for a total of 4 modules). "Quit to Quit" is a modified version of "Take Control," an interactive set of modules developed by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) for use in medication trials (Devine *et al*., 2016).

SAFETY ASSESSMENTS: During Screening, all subjects who provided informed consent will undergo the following assessments to determine their suitability for enrollment: physical examination, body weight, vital signs (blood pressure [BP], pulse, and respiratory rate), 12-lead electrocardiogram (ECG), clinical laboratory tests (blood chemistry, hematology, and urinalysis), on-site urine drug screen for cocaine and other substances of abuse (methamphetamine, amphetamine, methadone, buprenorphine, oxycodone and other opiates), prior/concomitant medication use and suicidality (using the Columbia Suicide Severity Rating Scale [C-SSRS]). Adverse events will be documented beginning on the day the subject provides Informed Consent. A pregnancy test will be performed during Screening on all female subjects.

Beginning on the day of enrollment (Study Day 1), subjects will attend the clinic once per week during the Treatment Phase (Weeks 1-13) for assessments of vital signs, body weight, concomitant medication use, suicidality (using the C-SSRS), treatment-emergent adverse events (AEs), and a pregnancy test (if female). At the clinic visit during week 7, clinical laboratory tests and an ECG will be performed.

Subjects who completed treatment through Week 13 will return for a follow-up visit during Week 14. Assessments at the Week 14 Follow-Up Visit include: AEs, vital signs, body weight, concomitant medication use, suicidality (using the C-SSRS), and a pregnancy test (if female). A final Follow-Up Visit will occur at the end of the study (Week 16). Subjects will be evaluated for AEs, suicidality , vital signs, physical exam, body weight, clinical laboratory tests, ECG, and

pregnancy (if female). Subjects who terminated earlier than Week 13 will complete these assessments at the time of early termination.

EFFICACY ASSESSMENTS: An enrichment strategy based on pre-randomization data from the run-in phase will be used to define a subpopulation of study participants who are likely to be medication adherent during the Treatment Phase and who are likely to exhibit a low placebo response rate. Data from only this subpopulation, termed the "prequalified for primary efficacy endpoint" (PPEE) population, will be utilized for the primary endpoint success/failure analysis. The PPEE population consists of subjects who have demonstrated adherence to the acetazolamide run-in regimen (based on the plasma sample collected on Study Day 8) and who, on the first day of Screening, reported 8 or more days of cocaine use in the previous 30 days. The primary endpoint is the percentage of subjects successfully achieving abstinence from cocaine during the last three weeks of treatment (Study Weeks 11-13) in the PPEE population.

At the beginning of Study Day 1, at each weekly clinic visit from Week 1 though Week 14, and at the Week 16 Follow-Up Visit, data for the efficacy endpoints will be collected (including urine BE, cotinine and alcohol).

A subject will be regarded as a treatment success (abstinent from cocaine during the last three weeks of treatment) if:

a. There are self-report data indicating no cocaine use on each day of the 3-week period;

b. There is at least one benzoylecgonine (BE) assay result for a urine sample collected within the 3-week period; and

c. BE assay results are negative (BE <150 ng/mL) for all urine samples collected during the 3-week period.

Subjects not meeting these three criteria (including dropouts) will be regarded as treatment failures.

The secondary endpoint is the proportion of subjects who successfully achieve abstinence from cocaine during the last three weeks of treatment (Study Weeks 11-13) in the subset of the PPEE population who are either Non-Drinkers or who are attempting alcohol abstinence, as evidenced by their decision to continue viewing the alcohol intervention modules on Study Day 8. Comparison of this proportion in subjects receiving lorcaserin vs. placebo will constitute the secondary endpoint analysis. In the analysis, abstinence will be defined as described for the primary endpoint.

An important exploratory endpoint will focus on the efficacy of lorcaserin in facilitation of abstinence from alcohol based on self-reported drinking and urine ethyl glucuronide (EtG) assays.

3 INTRODUCTION AND RATIONALE

3.1 Therapeutic Strategies for Treating Cocaine Abuse

Cocaine dependence is a significant public health problem which is associated with serious medical, psychiatric, social, and economic consequences. The treatment of cocaine dependence can decrease addiction-related health care utilization and costs as well as improve the health and quality of life for those who are addicted to cocaine. In particular, homelessness and unemployment are common in those who are addicted to cocaine. Typically, addiction-related behaviors present significant barriers to securing stable housing and employment.

A variety of neuropharmacological strategies are being pursued in the search for an effective treatment for cocaine abuse. These include: 1) preventing or attenuating cocaine's effects, 2) restoration of central nervous system homeostasis, 3) reducing craving or enhancing the addict's ability to manage his/her response to craving, 4) treating underlying comorbid conditions that may predispose targeted subpopulations toward dependence, and 5) stress reduction to prevent relapse. Although many compounds have been evaluated for the treatment of cocaine dependence, none have been approved by the Food and Drug Administration (FDA) for this indication. Psychosocial and behavioral therapy are currently the treatments of choice for cocaine dependence.

3.2 Use of Serotonergic Agents to Treat Cocaine Dependency

Cocaine has three primary mechanisms of action in the brain. It binds to and inhibits the activity of the dopamine (DA) transporter, the norepinephrine (NE) transporter, and the serotonin (5-HT) transporter. These actions prevent reuptake of the three neurotransmitters after release from neurons, which increases their extracellular concentrations after acute exposure to cocaine. In contrast, the effect of chronic cocaine use is to decrease dopaminergic, noradrenergic, and serotonergic tone (as the brain adapts to the presence of cocaine). Thus, a theoretical rationale can be developed for potential efficacy in the treatment of cocaine use disorder for almost any compound that interacts with one or more of the three neurotransmitter systems. Unfortunately, many clinical trials focusing on the treatment of cocaine use disorder have failed to show robust efficacy for compounds that act to inhibit the activity of the transporters, for compounds that act to stimulate the release of DA and NE, and for compounds that act directly at DA receptors (Castells *et al.*, 2010; Amato *et al.*, 2011).

Preclinical and clinical studies indicate that agents stimulating 5-HT release might be effective in treating cocaine use disorder. For example, the 5-HT releaser fenfluramine has been shown to decrease responding to intravenous cocaine in rhesus monkeys (Negus *et al.,* 2007) and to reduce reported levels of cocaine craving in a human laboratory study of experienced cocaine users (Buydens-Branchey *et al.*, 1998). Unfortunately, fenfluramine (an anorectic agent originally approved by the FDA in 1973) causes valvular abnormalities in the heart (Connolly *et al.*, 1997) and it had to be withdrawn from the United States (U.S.) market. It is likely that all 5-HT releasers would demonstrate this same toxicity, which appears to be medicated by the stimulation of 5-HT (2b) receptors (Roth, 2007). The 5-HT (2b) receptor is 1 of 14 known types of 5-HT receptors, all of which are stimulated by 5-HT releasers, such as fenfluramine. Thus, direct 5-HT receptor agonists that do not stimulate 5-HT (2b) receptors (but stimulate other types of 5-HT receptors) could produce the desirable effects of fenfluramine without the associated cardiac toxicity.

Fletcher *et al.* (2004) summarize early rodent data suggesting a potential role for 5-HT (2c) receptor agonists in the treatment of cocaine use disorder. The 5-HT (2c) receptor has a widespread distribution in mammalian brain tissue, and is especially abundant in dopaminergic cell body regions of the substantia nigra and ventral

tegmental area (VTA) as well as in terminal projection areas of the nucleus accumbens, striatum, and prefrontal cortex. The moderately selective 5-HT (2c) receptor agonist Ro60-0175 reduces the firing rate of mesolimbic DA neurons originating in the VTA, leading to a reduction in DA release in terminal regions of the nucleus accumbens and frontal cortex. Additionally, the selective 5-HT (2c) antagonist SB242,084, by itself, increases the burst-firing of dopaminergic neurons in the VTA, leading to increased release of DA in the nucleus accumbens (Di Matteo *et al.*, 1999). Thus, it appears that 5-HT (2c) receptors may exert a tonic inhibitory influence over the activity of ascending DA neurons. Ro60-0175 reduces cocaine self-administration in rats (Fletcher *et al.*, 2004). It also attenuates the ability of stress or conditioned cues to stimulate cocaine-seeking behavior in rats with a prior history of cocaine self-administration (Fletcher *et al.*, 2008). These promising findings led to the preclinical lorcaserin/cocaine studies described below.

3.3 Rationale for Use of Predictive Enrichment Strategies

Evaluation and selection of safe and effective medications for drug abuse and addiction through clinical trials is an important public health objective. Unfortunately, deception to gain enrollment has been well documented in repeat clinical trial participants (Devine *et al.,* 2013; Shiovitz *et al.,* 2013), which can lead to low medication compliance as the subjects may not be truly seeking treatment. In one recent placebo-controlled study, oral vigabatrin was examined as a treatment for cocaine dependence with a primary outcome measure of 2-week cocaine abstinence (Somoza *et al.,* 2013). No significant difference was found between the placebo and vigabatrin groups; however, post hoc measures of urine vigabatrin levels suggested that only 40-60% of patients were fully adherent to the protocol-specified vigabatrin regimen. In a National Institute on Drug Abuse (NIDA) trial evaluating modafinil for the treatment of methamphetamine dependence (Anderson *et al.,* 2012), 10% of subjects in the active treatment groups never had any detectable modafinil in their urine samples from Week 1 through the end of the 12-week trial. One concern is the existence of "professional subjects," who may participate in clinical trials due to the financial incentives but are not truly treatment-seeking and have no intention of ingesting study medications (McCann *et al*., 2015). These subjects can alter clinical outcomes, masking any genuine therapeutic effect. This can result in the failure to develop potentially effective medicines, or result in additional cost and delay in the drug development cycle.

One difficulty with "professional subjects" is the possibility that, if they are made aware (via informed consent) of a monitored run-in phase with the possibility of study termination for non-compliant subjects, they will change their normal behavior and comply to avoid detection. For this reason, in part, study drug non-adherence during the run-in phase of the current study will not result in early termination. Instead, a predictive enrichment strategy based on pre-randomization data will be used to define a subpopulation of study participants who are likely to be medication adherent during the treatment phase of the trial and likely to exhibit a low placebo response rate. Data from only this subpopulation, termed the "prequalified for primary efficacy endpoint" (PPEE) population, will be utilized for the primary efficacy endpoint. Predictive enrichment strategies have been endorsed by the FDA (Food and Drug Administration, Guidance for Industry: Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products, December, 2012), and their use has been suggested as a means to address the overlapping issues of medication nonadherence, "professional subjects," and increasing placebo response rates (McCann *et al.,* 2015).

Specific details of the enrichment strategy used in this study are described in Section 14.1

3.4 Lorcaserin

3.4.1 FDA Label Indication

Lorcaserin (trade name Belviq®) is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients who are obese or who are overweight with at least one related co-morbid condition (Belviq® Product Label, 2012).

3.4.2 Receptor Pharmacology

Lorcaserin binds more tightly to and is much more potent an agonist for 5-HT (2c) receptors than for 5-HT (2a) or 5-HT (2b) receptors, whether human or rat (Thomsen *et al*., 2008) (**Table 1**).

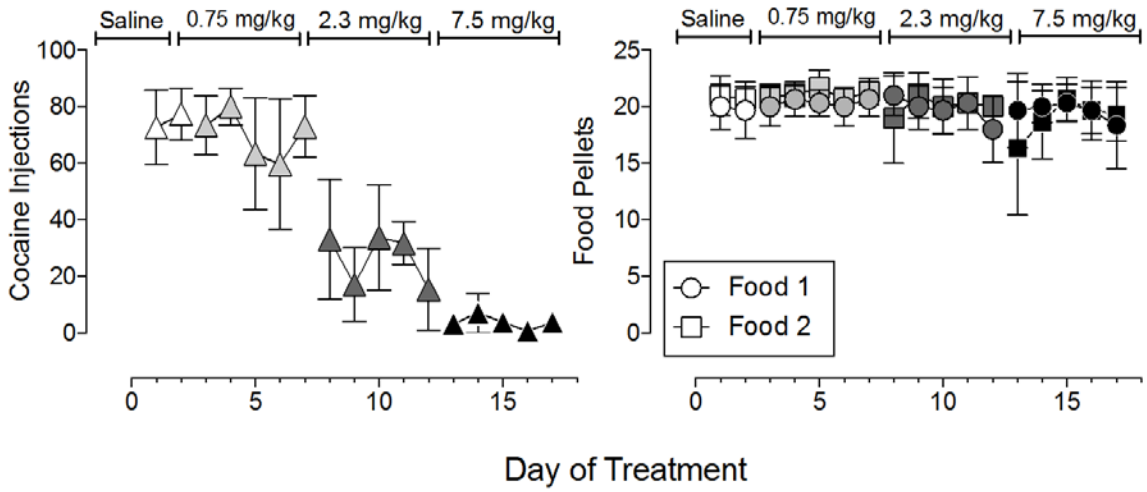
Table 1. Lorcaserin Receptor Affinity

Receptor	Affinity K_I (nM)
Human 5-HT (2c)	15 ± 1
Human 5-HT (2a)	112 ± 7
Human 5-HT (2b)	174 ± 32
Rat 5-HT (2c)	29 ± 7
Rat 5-HT (2a)	159 ± 27
Rat 5-HT (2b)	190 ± 5

3.4.3 Pre-Clinical Experience with Lorcaserin Relevant to Substance Abuse Treatment

Lorcaserin has shown activity in animal models that are relevant to the treatment of multiple substance use disorders. For example, lorcaserin reduces nicotine self-administration and blunts the subjective effects of nicotine in rats (Levin *et al*., 2011; Higgins *et al*., 2012). It also reduces the self-administration of alcohol (Rezvani *et al.*, 2014) and cocaine (Harvey-Lewis *et al.*, 2016) in rats. In a recently published study in rhesus monkeys, lorcaserin was shown to both reduce cocaine self-administration and blunt the subjective effects of cocaine (Collins *et al.*, 2016). In addition, unpublished studies of lorcaserin in rhesus monkeys have generated similar findings in a second laboratory (Bergman *et al.*; presented at the 78th Annual Scientific Meeting of the College on Problems of Drug Dependence, 2016). From these unpublished studies, **Figure 2** shows the effect of chronic lorcaserin treatment on responding for intravenous cocaine (left panel) or food pellets (right panel). The monkeys received constant intravenous infusions of saline or lorcaserin through one lumen of a double-lumen catheter (the total daily dose of lorcaserin is indicated above each panel), and the dose of lorcaserin was escalated every 5 days. Once daily, in 100 minute sessions, the monkeys had an opportunity to press a key to receive injections of cocaine through the other lumen of their catheters (30 key presses were required and 0.01 mg/kg cocaine was delivered per injection). Immediately prior to and immediately after each cocaine session, the monkeys had an opportunity to press a different key to obtain food pellets. Chronic treatment with lorcaserin produced a persistent reduction in cocaine self-administration with limited effects on food-maintained behavior. The selectivity of this effect rules out sedation or impairment of responding as an explanation for the reductions in cocaine self-administration. Different conditions (e.g., unlimited availability of highly palatable food) would have been required to observe the well-established ability of lorcaserin to decrease food consumption.

Figure 2. Effects of Lorcaserin on Responding for Cocaine or Food in Rhesus Monkeys



Related to safety, NIDA conducted a lorcaserin/cocaine interaction study in rats (Smithers Avanza Study No. 1812-12132). In this study, Sprague Dawley rats were given oral doses of lorcaserin at 5 mg/kg (a dosage yielding peak plasma levels in rats that are similar to peak plasma levels in humans taking 10 mg twice daily) and 25 mg/kg (a 5-fold safety margin). Cocaine was administered at doses of 3.2, 5.6, 10.0, and 17.5 mg/kg. Lorcaserin was administered 30 min ± 5 min prior to intravenous (i.v.) cocaine (this pretreatment time corresponded to the time to maximum plasma concentration [T_{max}] of oral lorcaserin in rats). There was a dose-dependent mortality due to cocaine, and all deaths occurred by 9 min after cocaine administration. The cocaine median lethal dose (LD_{50}) was 8.58 mg/kg (95% confidence interval [CI] 6.50-11.31 mg/kg), 12.47 mg/kg (CI 9.30-16.71 mg/kg), and 10.54 mg/kg (CI 7.43-14.94 mg/kg) after lorcaserin dose levels of 0, 5 mg/kg, and 25 mg/kg, respectively. Cocaine treatment also increased convulsions in a dose-related manner. The cocaine median effective dose (ED_{50}) values as a convulsant were 6.58 mg/kg (CI 5.12-8.47 mg/kg), 7.25 mg/kg (CI 2.43-21.62 mg/kg), and 5.38 mg/kg (CI 3.71-7.79 mg/kg) at lorcaserin dose levels of 0, 5 mg/kg, and 25 mg/kg, respectively. The mortality, convulsions, and clinical observations noted in Sprague Dawley rats challenged with i.v. cocaine after oral administration of lorcaserin were consistent with the known effects of cocaine, and the data did not reveal a substantive increase in cocaine toxicity following lorcaserin treatment.

3.4.4 Clinical Experience with Lorcaserin Relevant to Substance Abuse Treatment

In 2014, Arena Pharmaceuticals, with study design guidance from NIDA, conducted an outpatient trial to evaluate the efficacy of lorcaserin in smoking cessation (Shanahan, Rose, Glicklich, Stubbe & Sanchez-Kam, 2016). In this study, 603 smokers were randomized (1:1:1) to receive 10 mg lorcaserin once daily, 10 mg lorcaserin twice daily (BID), or placebo for 12 weeks. The primary endpoint was the proportion of subjects in each group achieving abstinence from smoking during the last 4 weeks of treatment (Study Weeks 9-12). The primary endpoint of smoking abstinence was achieved by 5.6% of subjects in the placebo group, 8.7% of subjects in the lorcaserin 10 mg once daily group, and 15.3% of subjects in the lorcaserin 10 mg BID group (p=0.003 and odds ratio=3.02 for BID lorcaserin vs. placebo). It was reported that the adverse event profile appeared "…similar to the profile in previous trials of lorcaserin, with the most common adverse events being headache, nausea, constipation, dizziness and dry mouth." To date, the efficacy of lorcaserin vs. other substance abuse disorders has not been evaluated in clinical trials, and it is anticipated that the current study will be the first evaluation of lorcaserin in the treatment of cocaine use disorder.

In 2015, in anticipation of the current study, NIDA conducted a human laboratory study under a contract with Vince & Associates Clinical Research (Overland Park, KS) with a primary focus on the safety of the lorcaserin/cocaine combination (ClinicalTrials.Gov/National Library of Medicine Identifier: NCT02393599). This unpublished, double-blind, parallel-group study in non-treatment seeking cocaine users assessed the safety and potential pharmacokinetic (PK) interactions of lorcaserin (10 mg BID) vs. placebo when combined with intravenous infusions of saline or cocaine doses of 20 or 40 mg. Of the 26 subjects exposed to either lorcaserin or placebo, 20 subjects (11 receiving lorcaserin, 9 receiving placebo) completed the 7-day, 13-dose treatment regimen and all PK assessments. Steady-state lorcaserin plasma concentrations were attained starting on the fifth day of study drug administration (Study Day 8), with plasma concentrations of approximately 35 ng/mL. The administered dose of 10 mg BID lorcaserin was safe and tolerable. All 26 participants in the study experienced at least one AE. All but one AE was mild in severity. There were no severe AEs and only one moderate AE, a case of euphoria subsequent to cocaine infusion that was judged to be cocaine-related/lorcaserin-unrelated in a participant receiving lorcaserin. Of the subjects receiving lorcaserin (n=11), the only lorcaserin-related AEs were mild headaches in 2 subjects (13%). The frequency and severity of cocaine-related AEs reported in all 20 study completers coincided with the scheduled cocaine infusions and were consistent with the risk-profile of cocaine administration. These events included euphoric mood (96%), abnormal feelings (42%), hyperhidrosis (38%), feeling hot (38%), tachycardia (23%), and paresthesia (19%). As compared to placebo, vital signs recorded before, during, and after cocaine infusion were not affected in a statistically significant manner in subjects receiving lorcaserin. One subject in each treatment group experienced an electrocardiogram (ECG) abnormality; both spontaneously resolved, and the abnormality experienced by the subject in the lorcaserin group occurred prior to lorcaserin dosing (during a baseline cocaine infusion). Lorcaserin did not appear to affect cocaine's subjective effects, as measured by a visual analog scale assessment, but there was a nonsignificant trend towards a reduction in the cocaine craving increase from baseline (pre-infusion) to 125 min after 40 mg cocaine infusion, as measured by the Brief Substance Craving Scale (p=0.0952, difference between lorcaserin and placebo craving score change = -0.8 or -80%). A between-group analysis of covariance (ANCOVA) comparing baseline (Day 2) to post-treatment (final dose taken approximately 2 hours prior to cocaine infusion) showed that lorcaserin had no statistically significant effect on the plasma PK of cocaine or its primary metabolite, BE.

3.4.5 Pharmacokinetics

Lorcaserin is absorbed from the gastrointestinal tract with peak plasma concentration occurring 1.5 to 2 hours after oral dosing and can be administered with or without food (Belviq® Product Label, 2012). Lorcaserin has a plasma half-life of approximately 11 hours; steady state is reached within 3 days after BID dosing, and accumulation is estimated to be approximately 70%.

Lorcaserin hydrochloride is moderately bound (~70%) to human plasma proteins and distributes to the cerebrospinal fluid (CSF) and central nervous system in humans. Although in rats the ratio of brain-to-plasma exposure (exposure expressed as the area under the concentration-time curve [AUC]) was 13.3 (Thomson *et al*., 2008), in humans the ratio of CSF-to-plasma exposure (AUC) was 0.017. After 10 mg BID for 7 days, the mean human CSF and plasma AUC values were 8.6 ng·hr/mL vs. 520 ng·hr/mL, respectively (Lorcaserin Clinical Pharmacology Review, 2012). Although the CSF levels are low compared to plasma levels in humans, human CSF levels nevertheless approximate the ED_{50} against the 5-HT (2c) receptor.

Lorcaserin is extensively metabolized in the liver by multiple enzymatic pathways (Belviq® Product Label, 2012). The primary oxidative metabolites are *N*-hydroxylorcaserin, 7-hydroxylorcaserin, 5-hydroxylorcaserin, and 1-hydroxylorcaserin (Usmani *et al*., 2012). Human CYP1A2, CYP2A6, CYP2B6,

CYP2C19, CYP2D6, CYP3A4, and FMO1 are involved in *N*-hydroxylorcaserin formation; CYP2D6 and CYP3A4 are involved in 7-hydroxylorcaserin formation; CYP1A1, CYP1A2, CYP2D6, and CYP3A4 are involved in 5-hydroxylorcaserin formation; and CYP3A4 is involved in 1-hydroxylorcaserin formation.

The major circulating metabolite is lorcaserin sulfamate, with a maximum plasma concentration (C_{max}) that exceeds lorcaserin C_{max} by 1- to 5-fold. *N*-carbamoyl glucuronide lorcaserin is the major metabolite in urine; lorcaserin sulfamate is a minor metabolite in urine, representing approximately 3% of dose. Unchanged lorcaserin in urine accounted for only 2.5% of an oral dose in normal subjects. Other minor metabolites excreted in urine were identified as glucuronide or sulfate conjugates of oxidative metabolites. The principal circulating metabolites exert no pharmacological activity at 5-HT receptors. In a human mass balance study in which healthy subjects ingested radiolabeled lorcaserin, 94.5% of radiolabeled material was recovered, with 92.3% and 2.2% recovered from urine and feces, respectively.

Lorcaserin is not recommended for patients with severe renal impairment (creatinine clearance <30 mL/min) or patients with end stage renal disease. Dose adjustment is not required for patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment on lorcaserin was not evaluated.

No dosage adjustment is required based on age, gender, or race.

3.4.6 Dose Justification

This study will use the approved lorcaserin dose for weight loss, 10 mg BID, during Weeks 2-13 of the Treatment Phase. As mentioned above, this same 10 mg BID dose of lorcaserin demonstrated significant efficacy in a smoking cessation trial, whereas 10 mg once daily lorcaserin did not yield a significant effect. Moreover, as summarized above, a previous human laboratory study demonstrated that the 10 mg BID lorcaserin dose was safe and tolerable when administered for 1 week to non-treatment seeking cocaine users, and there was no evidence of an adverse interaction with intravenous cocaine infusions.

3.4.7 Lorcaserin Safety

3.4.7.1 Common Adverse Reactions

The most common adverse reactions for non-diabetic patients treated with lorcaserin compared to placebo were headache, dizziness, fatigue, nausea, dry mouth, and constipation. The incidence of these side effects is shown in **Table 2.**

Table 2. Adverse Reactions Reported by ≥2% of Lorcaserin-Treated Patients and More Commonly than with Placebo in Patients without Diabetes Mellitus

Adverse Reactions	Lorcaserin 10 mg BID N=3195	Placebo N=3185
Gastrointestinal Disorders		
Nausea	264 (8.3)	170 (5.3)
Diarrhea	207 (6.5)	179 (5.6)
Constipation	186 (5.8)	125 (3.9)
Dry Mouth	169 (5.3)	74 (2.3)
Vomiting	122 (3.8)	83 (2.6)
General Disorders and Administration Site Conditions		
Fatigue	229 (7.2)	114 (3.6)
Infections and Infestations		

Adverse Reactions	Lorcaserin 10 mg BID N=3195	Placebo N=3185
Upper respiratory tract infections	439 (13.7)	391 (12.3)
Nasopharyngitis	414 (13.0)	381 (12.0)
Urinary tract infection	207 (6.5)	171 (5.4)
Musculoskeletal and Connective Tissue Disorders		
Back pain	201 (6.3)	178 (5.6)
Musculoskeletal pain	65 (2.0)	43 (1.4)
Nervous System Disorders		
Headache	537 (16.8)	321 (10.1)
Dizziness	270 (8.5)	122 (3.8)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	136 (4.3)	109 (3.4)
Oropharyngeal pain	111 (3.5)	80 (2.5)
Sinus congestion	93 (2.9)	78 (2.4)
Skin and Subcutaneous Tissue Disorders		
Rash	67 (2.1)	58 (1.8)

The most common adverse reactions leading to discontinuation more often among lorcaserin-treated patients than placebo were headache (1.3% vs. 0.8%), depression (0.9% vs. 0.5%) and dizziness (0.7% vs. 0.2%).

3.4.7.2 Potential for Serotonin or Neuroleptic Malignant Syndrome (NMS)-like Reactions

In the prescribing information for lorcaserin (Belviq® Product Label, 2012), under "WARNINGS AND PRECAUTIONS," it is noted that: 1) lorcaserin is a serotonergic drug and 2) "development of a potentially life-threatening serotonin syndrome or neuroleptic malignant syndrome (NMS)-like reactions have been reported during use of serotonergic drugs, including, but not limited to, selective serotonin-norepinephrine reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), bupropion, triptans, dietary supplements such as St. John's Wort and tryptophan, drugs that impair metabolism of serotonin (including monoamine oxidase inhibitors [MAOIs]), dextromethorphan, lithium, tramadol, antipsychotics or other dopamine antagonists, particularly when used in combination." The use of serotonergic drugs is not contraindicated in patients receiving lorcaserin (in fact, no medications are contraindicated); however, in the "DRUG INTERACTIONS" section of the prescribing information (Belviq® Product Label, 2012), it is stated that "based on the mechanism of action of Belviq and the theoretical potential for serotonin syndrome" lorcaserin should be "used with extreme caution in combination with other drugs that may affect the serotonergic neurotransmitter systems." This legitimate concern is entirely theoretical. During three phase 3 trials, in which a total of 4,347 patients received lorcaserin, no subjects met the clinical criteria for diagnosis of serotonin syndrome (Nguyen *et al.*, 2016), and from the time of FDA approval (February, 2012) to the time of this writing (August, 2016), there have been no published case reports suggesting serotonin syndrome in patients receiving lorcaserin. In addition, during the course of the phase 3 studies, 814 patients receiving lorcaserin and 624 patients receiving placebo were found to be taking a wide range of serotonergic agents (some that were protocol-allowed, such as dextromethorphan, and some that were protocol-prohibited, such as antidepressants), and an evaluation of adverse events in these subpopulations revealed no signal of serotonin toxicity with the concurrent use of lorcaserin and the serotonergic agents (Nguyen *et al.*, 2016). The number of co-exposures to lorcaserin and other serotonergic agents during the phase 3 studies (814) was much greater than the total number of subjects who will receive lorcaserin in the current study (up to 136). Thus, even though depression is a common comorbidity in patients with cocaine use disorder, and a subset of subjects in the current study will almost certainly be taking antidepressants, it appears unlikely that any subjects will experience serotonin syndrome.

Due to the serious nature of serotonin syndrome and the theoretical possibility of its occurrence, subjects will be closely monitored for signs of serotonin toxicity when adverse events are assessed during each weekly visit.

3.5 Acetazolamide Safety/Dose Justification

Because of its long half-life and other desirable properties, a very low dose of acetazolamide (15 mg, which is just 6% of the recommended starting therapeutic dose) can serve as a useful marker of study drug adherence during clinical trials (Hampson *et al.*, 2016). In the current study, subjects will receive 15 mg capsules of acetazolamide BID during the one-week run-in period (from the evening of Study Day 1 through the morning of Study Day 8) only. This dose is much lower than the therapeutic doses of 250 to 1000 mg daily. Data from a NIDA PK study conducted under a contract with Vince & Associates Clinical Research (Overland Park, KS) indicate that plasma acetazolamide concentrations can be expected to stay above 15 ng/mL for 48 hours after a single 15 mg oral dose in approximately 99.9% of subjects. In the current study, plasma samples will be drawn on Study Day 8 (following 7 days of BID dosing with 15 mg acetazolamide) and the samples will be assayed for acetazolamide. Subjects with plasma levels below 15 ng/mL will be regarded as study-drug non-adherent (they would have to skip at least their last 4 doses of study drug before the Study Day 8 visit to fall below 15 ng/mL) and they will not qualify for the PPEE population.

There are very limited data on adverse events for this low (15 mg) dose of acetazolamide, but it is anticipated that this dose will present minimal risk to subjects. In the NIDA PK study mentioned above, 24 healthy subjects were administered a single 15 mg oral dose of acetazolamide, no moderate or severe AEs were observed, and 3 out of 24 subjects (13%) experienced mild AEs (1 alopecia, 2 headache; unpublished data). In the only relevant published study (Hampson *et al.*, 2016), 10 subjects received 15 mg oral acetazolamide for four consecutive days, and one subject reported a metallic taste in the mouth on one of the four dosing days. That is the only acetazolamide-specific adverse event mentioned in the publication.

4 STUDY OBJECTIVE

The objective of this study is to evaluate the efficacy and safety of lorcaserin in the treatment of cocaine use disorder.

5 IND HOLDER

This study will be conducted under an Investigational New Drug Application (IND) held by the National Institute on Drug Abuse (NIDA).

6 STUDY SITES

This clinical trial will be conducted as a multi-center study at 10 or more clinical sites throughout the United States .

7 STUDY DESIGN

This is a 19-week, multi-center, parallel group study that includes: 1) up to 3 weeks for screening; 2) a 13-week Treatment Phase consisting of a 1-week, single-blind run-in period, when all subjects receive twice daily 15 mg acetazolamide capsules (a medication adherence marker), followed by randomization to either twice daily 10 mg lorcaserin or placebo capsules for the remaining 12 weeks; and 3) a 3-week follow-up period, with scheduled visits during Study Weeks 14 and 16.

Upon providing informed consent, subjects will be screened over a period of up to 21 days and will complete baseline evaluations. Subjects who complete all screening and baseline evaluations and meet the specified inclusion/exclusion criteria will be eligible to enter the treatment phase. Eligible subjects will receive 15 mg BID acetazolamide during the 1-week run-in period, which will be used to define the PPEE population (on the basis of plasma acetazolamide concentrations ≥15 ng/mL and self-report of cocaine use on at least 8 days during the 30 days immediately prior to screening). Following the 1-week run-in period, all subjects will be randomly assigned to receive either placebo or 10 mg BID lorcaserin for 12 weeks, with weekly clinic visits during those 12 weeks, and with follow-up assessments 1 and 3 weeks after treatment completion.

A randomized block design within each site will be utilized with the following stratification factors:

a. Number of subject-reported cocaine use days during the 30 days immediately prior to screening (<8 days versus 8 or more days);
b. Continued viewing of the computer-based alcohol intervention on Study Day 8 (yes/no);
c. Diagnosis of Alcohol Use Disorder and/or Sedative, Hypnotic, or Anxiolytic use disorder (yes/no).

Beginning on Study Day 1, subjects will visit the clinic on a weekly basis throughout the 13-week Treatment Phase. At each weekly clinic visit, subjects will receive study drug, provide urine samples and will participate in other protocol-specified assessments. Subjects will also take part in a weekly one-hour, manualized individual cognitive behavioral therapy session (CBT) to facilitate avoidance of cocaine use. On Study Day 1, all subjects will view the first module of a computer-based alcohol intervention that describes the potential benefits of abstaining from alcohol during the trial. Though the module encourages abstinence from alcohol, each subject will determine for him/herself whether this will also be one of their goals during this trial. On Study Day 8, prior to randomization, subjects will be given the option of viewing the second module of the alcohol intervention. Each subject's decision (yes or no) to continue viewing the alcohol intervention modules will be recorded prior to randomization and will serve as one of the stratification factors for randomization.

Beginning on Study Day 8, subjects will participate in a medication adherence monitoring procedure. Following randomization, subjects will be instructed on the use of a handheld device to log daily use of cocaine and alcohol and to record the daily administration of study drug. The devices are smartphones furnished by the sites and come pre-loaded with the medication monitoring AiView software. These devices are password protected and are programmed with limited functionality so that their use is restricted to study-specific tasks and activities. Use of the device grants subjects associated opportunities to earn rewards contingent upon appropriate performance of tasks.

Two Follow-Up Visits will occur at Week 14 and at Week 16. Subjects will be asked to return to the clinic at these visits to provide self-report data on cocaine use, perform vitals, and provide a urine sample. Additional safety evaluations (physical exam, blood chemistry, hematology, and urinalysis) will occur at the final Follow-up Visit (Week 16), more than two weeks after the last dose of study drug.

8 SUBJECT SELECTION

8.1 Eligible Subjects

Approximately two hundred seventy-two (272) treatment-seeking males and females who meet DSM-5 criteria for cocaine use disorder will be recruited from 10 or more clinical sites. Entry into the study will be

open to men and women, between 18 to 65 years of age, from all racial and ethnic groups. Subjects who are enrolled, but who do not proceed to randomization on Study Day 8 will not be replaced.

8.2 Inclusion Criteria

A subject must meet all of the following criteria in order to be included in the study:

1. Is between 18 to 65 years of age.

2. Has DSM-5 diagnosis of current cocaine use disorder as verified by the Structured Clinical Interview for DSM-5 – Research Version (SCID-5-RV).

3. Is seeking treatment for cocaine use disorder.

4. Is able to understand and provide written informed consent.

5. Has used cocaine on at least 1 day in the last 30 days prior to screening (based on SUR at first screening visit).

6. Has completed all psychological assessments and procedures during the screening period (up to 3 weeks).

7. Female subjects:

    a. Cannot be pregnant

    b. Cannot be lactating

    c. Must be unable to conceive (i.e., surgically sterilized, sterile, or post-menopausal defined as 1 year without bleeding or spotting) OR must agree to use an acceptable method of birth control (e.g., birth control pills, intrauterine device [IUD], or a double barrier method of birth control (condoms and spermicide together; or diaphragm, condom and spermicide together)

8. Has a total body weight of >50 kg (110 pounds) and a body mass index (BMI) of > 20 at screening.

9. Is, in the opinion of the study physician, in stable health as determined by pre-study physical examination, medical history, ECG, and laboratory evaluations and is likely to complete the study.

8.3 Exclusion Criteria

A subject who meets any of the following criteria may not be included in the study:

1. Use of lorcaserin HCl for any indication, including prior participation in this or any study of lorcaserin HCl, within the last 30 days prior to screening.

2. Has DSM-5 diagnosis of current substance use disorder, as verified by the SCID-5-RV, for any psychoactive substance other than cocaine, benzodiazepine, alcohol, nicotine, caffeine, or marijuana.

3. Has received methadone or buprenorphine maintenance treatment during the year prior to screening.

4. Has current alcohol use disorder that is judged to require medically supervised detoxification.

5. Fails to provide at least one urine sample that is benzoylecgonine (BE)-positive (>150 ng/mL) during the screening period.

6. Meets the DSM-5 criteria for schizophrenia, bipolar I and II disorder or any other psychotic disorder as verified by the SCID-5-RV. NOTE: Participants with other psychiatric conditions, such as MDD, GAD, Dysthymia, social phobia or specific phobia may be enrolled in the study if they are clinically stable, and if taking medications, dosages must be stable (no adjustment) in the past 3 months prior to screening.

7. Acute suicidality, as evidenced by answering "yes" for Question 4 or Question 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS), indicating active suicidal ideation with any intent to act, during the screening period. NOTE: these subjects will be referred to the appropriate medical provider.

8. History of suicidal behavior such that a determination of "yes" is made on the Suicidal Behavior section of the C-SSRS for "Actual Attempt", "Interrupted Attempt", or "Aborted Attempt."

9. Undergoing separate drug testing as a condition of probation or as mandated by a government agency (e.g., social services) or a court.

10. Has one or more positive on-site urine drug screen (UDS) test results for methamphetamine, amphetamine, methadone, buprenorphine, oxycodone, or other opiates during the screening period.

11. Is currently participating in or screening for potential participation in another clinical trial of an investigational (un-marketed) medication or has participated in any clinical trial of an investigational medication within 6 months prior to providing Informed Consent.

12. Has, in the opinion of the site study physician, any of the following:

    a. Clinically significant hepatic, renal, or gastrointestinal disorders that could alter absorption, metabolism, or excretion of the study drug.
    b. Significant heart disease (including report or documentation of myocardial infarction within one year prior to randomization), valvular heart disease, or symptomatic orthostatic hypotension.
    c. Any clinically significant ECG abnormality at screening, as determined by the study physician.
    d. History of cerebrovascular disease or stroke.
    e. A diagnosis of severe chronic obstructive pulmonary disease (COPD) and/or pulmonary hypertension.
    f. Uncontrolled and/or unstable metabolic and/or endocrine disorder.
    g. Any other medical or neurological disorder that would place the subject at greater risk or prejudice evaluation of the safety and efficacy of the study drug.
    h. Clinically significant laboratory values outside the normal range as determined by the study physician.
    i. History of serotonin syndrome or neuroleptic malignant syndrome.
    j. Impaired renal function as determined by estimated creatinine clearance (CrCl) <30 ml/min, calculated from the Cockcroft-Gault equation at screening. o Cockcroft-Gault equation: CrCl = (140-age) x body weight in kg/ serum creatinine (mg/dl) x 72 (x 0.85 for females)
    k. Impaired liver function as evidence by LFT (AST, ALT or total bilirubin) > 3 times of upper normal limit at screening.

l. Systolic Blood Pressure > 160 mmHg and/or Diastolic Blood Pressure >100 mmHg (confirmed after repeated measurement) at screening.

13. Has a serious or unstable medical or psychiatric condition or clinically significant new illness within the last 6 months prior to screening.

14. Has a known allergy to lorcaserin or sulfonamides.

15. Has a Beck Depression Inventory-II (BDI-II) score $\geq$ 20 at screening

16. Has Diabetes (all types).

17. Refuses to sign Verified Clinical Trials Authorization.

18. Is not, in the judgment of the site investigator (SI), expected to attend regular study visits or to complete the study protocol assessments as directed.

NOTE: If any medical conditions requiring treatment are uncovered during screening, the individual will be notified of the results and referred to appropriate treatment.

9 INVESTIGATIONAL PRODUCTS

9.1 Lorcaserin

The three drug products described below will match each other in color, shape and size of the hard gelatin capsules that will be used in this study.

The chemical name for lorcaserin hydrochloride (trade name Belviq®) is (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride hemihydrate (Belviq® Product Label, 2012). Each Belviq® tablet contains 10.4 mg of crystalline lorcaserin hydrochloride hemihydrate, equivalent to 10.0 mg anhydrous lorcaserin hydrochloride, and the following inactive ingredients: silicified microcrystalline cellulose; hydroxypropyl cellulose National Formulary (NF); croscarmellose sodium NF; colloidal silicon dioxide NF, polyvinyl alcohol United States Pharmacopeia (USP), polyethylene glycol NF, titanium dioxide USP, talc USP, FD&C Blue #2 aluminum lake, and magnesium stearate NF. Lorcaserin will be obtained by the research pharmacy from a commercial site. Each 10 mg lorcaserin tablet will be over-encapsulated in a size 0 light blue opaque hard gelatin capsule with a mixture of microcrystalline cellulose and magnesium stearate as filler by Murty Pharmaceuticals Inc. (Lexington, KY) under a contract with the National Institute on Drug Abuse.

9.2 Lorcaserin Placebo

Placebo capsules will be an identical match to the over-encapsulated lorcaserin capsule prepared by Murty Pharmaceuticals. Each placebo capsule will contain a filler that is a mixture of microcrystalline cellulose and magnesium stearate.

9.3 Acetazolamide (ACZM)

The 15 mg capsules will be manufactured using size 0 light blue opaque hard gelatin capsules by Murty Pharmaceuticals Inc. (Lexington, KY) under a contract with the National Institute on Drug Abuse. The acetazolamide (USP-NF) was procured from Spectrum Chemical (Catalog # A1266). Each acetazolamide

capsule will contain 15 mg acetazolamide and the following inactive ingredients: lactose monohydrate USP-NF (NF 310 Regular), sodium starch glycolate USP-NF (Type A), corn starch USP-NF, povidone USP (Kollidon 30), and magnesium stearate USP-NF.

9.4 Packaging and Labeling

The VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (CSPCRPCC) in Albuquerque, NM will serve as the research pharmacy for the current study.

Medication for week one (acetazolamide) will be provided to study sites in boxes containing 10 bottles. Each bottle will contain 14 capsules of 15 mg acetazolamide, sufficient study drug for one week. Each bottle will be labeled with the study number week, a bottle number, and dosing instructions.

Subject-specific treatment kits will contain 12 bottles with 20 capsules per bottle of 10 mg lorcaserin or matching placebo and two (2) emergency-dose bottles with 20 capsules per bottle of 10 mg lorcaserin or matching placebo, respectively. The emergency-dose bottles will be available in case a subject misplaces a bottle. Each bottle will contain sufficient study drug for one week plus extra doses to cover possible missed clinic visits. Each bottle within the treatment kit will be labeled with the study number, week number, treatment kit number, bottle number, and dosing instructions.

9.5 Drug Storage

Lorcaserin and ACZM will be stored at controlled room temperature (20°C – 25°C; 68°F – 77°F) with excursions permitted to 15C°- 30C°; 59F°- 86F° and protected from light in a secure location at each SI's facility. For further information, SI should refer to the product label.

9.6 Dispensing Record

A Receipt, Dispensing and Disposition/Returns to PCC log will be completed for each subject weekly. Accurate recording of all study drug dispensing will be made in the appropriate section of the log. On each weekly clinic visit starting with Study Day 8 (Week 2), subjects will be asked to return the bottle dispensed in the previous week with all unused drugs. Unused investigational product will be inventoried for discrepancies. Subjects who have not been taking their capsules regularly will be encouraged to do so in the future. At each and all clinic visits, self-reports of investigational product use since the last clinic visit will also be recorded.

9.7 Used/Unused Investigational Products

During the study, all investigational products not used by the subject must be returned to the clinic for assessment of subject compliance. At the end of the study, all unused drugs must be inventoried. If any investigational product is lost or damaged, its disposition should be documented on the dispensing log provided by the CSPCRPCC. Unused investigational products, including empty medication bottles, will be returned to the CSPCRPCC at the end of the study.

10 INTERVENTIONS

10.1 Study Drug

On Study Day 1, subjects will be given a child-proof, take-home bottle containing 14 "compliance marker capsules" containing a very low dose (15 mg) of acetazolamide. Subjects will be instructed to take one

capsule on the evening of Study Day 1 and two capsules per day, approximately 12 hours apart on Study Days 2-7.

On Study Day 8, subjects who progress to randomization will be assigned a subject-specific treatment kit, via the Interactive Web Response System (IWRS). Each subject's treatment kit is tied to one of two treatment groups, 10 mg lorcaserin or matching placebo, and contains enough study drug for the remaining 12 weeks of the Treatment Phase. At each weekly clinic visit during Study Weeks 2 to 13, subjects will be given a take-home bottle from their treatment kit containing 20 capsules and will be instructed to take one capsule two times a day, approximately 12 hours apart.

10.2 Counselor Guided Behavioral Therapy (Cocaine)

All subjects will be offered and encouraged to attend individual CBT in one-hour weekly sessions beginning at Week 1 and continuing until Week 13. The date and length of time for each CBT session will be recorded within the subject's CRFs. If a subject declines to participate in CBT, it will be recorded on the CRF and will not be considered to be a protocol violation.

The NIDA-published CBT treatment manual for cocaine dependence, "Cognitive Behavioral Therapy Approach: Treating Cocaine Addiction" will be implemented across all sites (Carroll, 1998). CBT regards coping skills training as the key component for avoiding drug use and preventing relapse. Skills training techniques include: (1) self-monitoring and functional analysis of situational factors associated with craving or drug use; (2) learning alternative non-drug responses for handling high risk situations; and (3) general lifestyle modifications (e.g., increasing pleasant drug-free events, anger management, interpersonal skills, and general problem solving).

10.3 Computer-Based Therapy (Alcohol)

A computer-based alcohol intervention will be viewed by all subjects on Study Day 1 and will be continued on an optional basis at the discretion of each subject. The alcohol intervention, "Quit to Quit", is an interactive set of modules based on an intervention developed by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) for use in medication trials (Devine *et al*., 2016).

11 STUDY PROCEDURES

Table 3, Schedule of Events, provides a detailed time table of study activities.

Table 3. Schedule of Events

Study Phase	Screen	Treatment Phase[a]													Early Term	Follow-Up	
Study Week	**-3 to -1[a]**	**1 (Study Day 1)[b]**	**2 (Study Day 8)**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**		**14**	**16**
Informed Consent	X																
Enrollment		X															
Randomization			X														
Demographics	X																
Medical History	X																
DSM-5 / (SCID-5-RV)	X																
Physical Exam	X														X		X
Vital Signs/Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X							X							X		X
C-SSRS (initial & since last visit)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BDI - II	X		X		X		X		X		X		X		X	X	
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Brief Subs. Craving Scale (BSCS)		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Drug Dispensing/Reconciliation		X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events	X	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood/Plasma																	
Plasma (lorcaserin)				X				X									
Plasma (acetazolamide)			X														
Blood Chemistries[c]	X							X							X		X
Hematology[d]	X							X							X		X
Urine																	
Urine Pregnancy Test	X	X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical Urinalysis[e]	X							X							X		X
Urine Toxicology Screen[f]	X[i]																
Urine Fentanyl	X[i]																
Urine Cotinine	X[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine BE		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Alcohol Test (EtG)	X[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Substance Use																	
Smoking & Alcohol History	X																
ASI –Lite		X												X	X		

Study Phase	Screen	Treatment Phase[a]													Early Term	Follow-Up	
Study Week	**-3 to -1[a]**	**1 (Study Day 1)[b]**	**2 (Study Day 8)**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**		**14**	**16**
SUR (initial & since last visit)	X	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AiView Data Collection (device)				X	X	X	X	X	X	X	X	X	X	X	X	X	
Behavioral Therapy																	
CBT (cocaine)		X	X	X	X	X	X	X	X	X	X	X	X	X			
Quit to Quit (alcohol intervention)		X	X[g]	X[g]					X[g]								

* Procedure that will be completed just prior to enrollment.

[a] Screening may take place during one or multiple visits within 21 days of providing Informed Consent.

[b] Treatment visits are scheduled to occur the same day of the week as much as possible.

[c] Blood chemistries include sodium, potassium, chloride, carbon dioxide, glucose, creatinine, calcium, alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), gamma-glutamyltranspeptidase (GGT), total bilirubin, alkaline phosphatase (ALP), blood urea nitrogen (BUN).

[d] Hematology includes complete blood count (CBC) with differentials and platelets.

[e] Urinalysis: Urine will be collected and analyzed for specific gravity, pH, blood, protein, glucose, ketones, leukocytes, and nitrite.

[f] The urine toxicology screen includes BE, marijuana, methamphetamines, amphetamines, ecstasy, phencyclidine, propoxyphene, benzodiazepines, barbiturates, tricyclic antidepressants, methadone, buprenorphine, oxycodone, and opiates.

[g] Subjects will be given the choice of viewing these optional modules of the alcohol intervention prior to randomization on Study Day 8 (Week 2). NOTE: Study Day 1 (Week 1) module is mandatory.

[h] Update at **every** clinic visit

i Repeat test at **every** screening visit (when applicable)

11.1 Subject Recruitment

Subjects will be recruited from a variety of sources which include but are not limited to: advertisements in local media, through local treatment providers, and by word of mouth. This study is also registered online at www.clinicaltrials.gov (NCT03007394). Recruitment advertisements must be approved by the site's Institutional Review Board (IRB) and by NIDA.

11.2 Screening (Study Days -21 to -1)

The purpose of screening is to establish the candidate's eligibility for study participation. The screening assessments required to determine eligibility are summarized in the **Table 3, Schedule of E.** At no time during the screening process will subjects be given information regarding exclusion criteria. When subjects are evaluated, questions should be asked in a way that the criteria are not discernable. If a subject meets inclusion/exclusion criteria for enrollment, s/he will be scheduled for the Study Day 1 visit.

The screening phase commences the day informed consent is signed and terminates when any of the following conditions have been met:

- The subject is determined to be ineligible for the study.
- The subject is enrolled in the single-blind run-in period (Study Day 1).
- 21 days have passed since the informed consent form (ICF) was signed and the subject has not been enrolled. No extensions beyond the prescribed 21 days for screening will be considered.

An electronic case report form (eCRF) indicating the primary reason each subject was deemed ineligible will be submitted for all screen failures.

Results from all screening assessments must be available and reviewed for verification of entry criteria prior to the enrollment visit (Day 1). Subjects who are found ineligible for the study will not be rescreened.

NOTE: The last day of screening cannot be the first day of enrollment

11.3 Scheduling of Study Day 1 Visit

As soon as possible after a subject has passed all screening assessments, s/he should be contacted to schedule both the Study Day 1 visit and the Study Day 8 visit. Subjects must be available on the same day of the week for two consecutive weeks to accommodate this scheduling because missing the Study Day 8 visit results in early termination from the study,. The Study Day 1 visit should be scheduled as soon as possible and no later than 21 days after signing the consent form.

11.4 Study Day 1 (Week 1) – Enrollment

At the time of arrival to the clinic on Study Day 1, a pregnancy test will be performed on every female subject. If the pregnancy test is positive, the subject's participation in the study will end and no other assessments will be done.

On Study Day 1, following enrollment, all other required assessments for Study Day 1(listed in Table 3) will be completed, including the subjects' participation in both the individual CBT session for cocaine dependence and the computer-based alcohol intervention, detailed in Sections 10.2 and 10.3, respectively.

11.5 Study Day 8 (Week 2) – Randomization

On Study Day 8, eligible subjects will be randomized using the Interactive Web Response System (IWRS). Although randomization occurs on Study Day 8, study staff must bear in mind that subjects are blinded to the change in study drug (from ACZM to lorcaserin or matched placebo) and should exercise appropriate caution in maintaining this blind. Subjects who fail to show up for their Study Day 8 visit or who are unable or unwilling to continue taking study drug for other reasons (*e.g.*, adverse events) will not be randomized.

Beginning on Study Day 8, all subjects will begin participating in a medication adherence monitoring procedure. Following randomization, subjects will be instructed on the use of a handheld device to log daily use of cocaine and alcohol and to record the daily administration of study drug. The devices are smartphones furnished by the sites and come pre-loaded with the medication monitoring AiView software. These devices are password protected and are programmed with limited functionality so that their use is restricted to study-specific tasks and activities completed by the subject. Use of the device grants subjects associated opportunities to earn rewards contingent upon appropriate performance of tasks. Rewards are described in Table 4, Subject Compensation. Other assessments are listed in **Table 3**, for Study Day 8 and are to be completed before the subject leaves the clinic.

11.6 Study Visits (Weeks 2 to 13)

Assessments to be performed at Study Visits during Weeks 2-13 are summarized in Table 3 and are further described in Section 12.

11.7 Follow-Up Visits (Weeks 14 and 16)

Subjects will attend two separate Follow-Up Visits in the clinic at Study Week 14 and Study Week 16. All assessments to be completed during the Initial and the Final Follow-Up Visits are detailed in **Table 3, Schedule of Events**. In addition to required assessments at the Week 14 Follow-Up Visit, a final record of medication adherence data will be collected along with medication bottles and the handheld devices used for medication monitoring .

11.8 Early Termination Visit – Prior to Dosing Completion

A subject's participation in the study will be terminated early if:

- The subject is unable to comply with the study protocol requirements
- The subject is incarcerated
- In the opinion of the SI, the continued participation would compromise the subjects' safety, the safety of others, or study integrity.

NOTE: Subjects terminated from the protocol secondary to a medical or psychiatric concern will be referred for appropriate treatment.

Terminated subjects will not be replaced.

If a subject discontinues prematurely, prior to dosing completion, regardless of the reason, the SI should be notified and the subject should return for the Early Termination Visit within 7 to 14 days of his/her last dose of study drug. All assessments required at the Early Termination Visit are outlined in **Table 3, Schedule of Events.** An Early Termination form documenting the reason for discontinuation is required for all subjects who discontinue prematurely. Once terminated, subjects may not re-enter the study.

Whenever a study subject stops coming to the clinic without notification, study staff will make a concerted effort to contact the subject (or the designated contact person if subject cannot be reached) to assure that s/he has no untoward effects from study participation. After three documented attempts, the research staff will cease to try to make further contact.

11.9 Situations Requiring Study Drug Discontinuation

A subject should no longer receive study drug if:

- The subject wishes to stop taking study drug or no longer wishes to participate in the study.
- The subject develops a medical illness, complication or side effects from study drug, and/or has an adverse experience which, in the opinion of the SI or physician, precludes safe continuation of the study drug.
- The subject fails to take study drug (for any reason) for 14 consecutive days.
- The female subject becomes pregnant (as evidenced by a positive pregnancy test) at any time during study.
- The subject has a BDI-II score of > 28 or scores > 0 on question # 9 (suicidal thoughts and wishes) will be referred to a mental health practitioner or primary care physician for further evaluation and follow-up.
- The subject has clinically significant abnormal laboratory findings and vital signs (after confirmatory repeat measurements) as deemed by the SI or physician, including but not limited to;
    - CrCl < 30 ml/min
    - LFT > 5 times UNL
    - Uncontrolled hypertension; SBP ≥ 180 mmHg and/or DBP ≥ 110 mmHg

If a subject loses substantial weight during the treatment period and, in the opinion of the site physician, he/she is approaching the lower limit of acceptable weight, the subject will be counselled for appropriate eating and nutrient intake, and the subject's weight will be followed closely during each subsequent visit. If the subject continues to lose weight so that, in the opinion of the site physician, it is unsafe to continue treatment, study medication will be discontinued.

If a subject expresses suicidal thoughts or exhibits acute psychosis or suicidal/homicidal behavior, the subject will be referred to a local treatment center, emergency department or be hospitalized as appropriate and study drug will be discontinued.

Subjects who are no longer receiving study drug will continue to be followed and will complete regularly scheduled assessments to provide as much data as possible. These subjects will be paid for each clinic visit but will not be rewarded for any additional bonus payments (including device-related rewards).

NOTE: Subjects who become pregnant during study participation will be immediately discontinued from the study drug. Subjects will be asked to sign a release of information form for study personnel to access medical records and information regarding the outcome of the pregnancy.

NOTE: In the event of uncontrolled hypertension, study drug should be withheld and the subject should be referred to a primary care physician for proper evaluation and treatment. The subject may resume his/her study drug (within 14 days) only after evaluation and reassessment by the site SI or physician for safe continuation. Study drug will be discontinued if an evaluation is not done, or not completed, within 14 days or if uncontrolled hypertension persists.

11.10 Early Study Termination

NIDA has the right to terminate this study at any time. Reasons for terminating the study may include, but shall not be limited to, the following:

- The incidence or severity of AEs indicates a potential health hazard to subjects.
- Subject enrollment is unsatisfactory.
- Data recording is inaccurate or incomplete.

NIDA will continue those subjects currently in treatment to completion if there is no compelling safety concern.

11.11 Preventing Study Drop-Outs

Subjects will be encouraged to come for treatment and evaluation sessions as described in this protocol. It will be emphasized to subjects during screening and throughout the study that even if they continue to use cocaine and/or have a relapse they should come to all scheduled appointments. Subjects will be discouraged from using cocaine, but there will be no penalty for using cocaine.

11.12 Subject Compensation

For the screening visit(s) and for up to 15 clinic visits during the treatment and follow-up periods, all subjects will receive $15 per visit as compensation for their time and inconvenience (up to $270 total). In addition, subjects will have the opportunity to earn additional compensation (totaling up to $635) as rewards for following specific protocol requirements. To promote regular clinic attendance and decrease the probability of missing data, subjects will receive a $20 reward in Week 6 if they have attended all of their scheduled visits for Weeks 3-6, they will receive a $30 reward in Week 10 if they have attended all of their scheduled visits for Weeks 7-10, and

they will receive a $40 reward in Week 14 if they have attended all of their scheduled visits on Weeks 11-14. They will receive a $5 reward on each visit from Week 1-14 if they provide complete self-report data on cocaine, alcohol, and cigarette use since their previous visit (data provided for each day), and they will receive a $5 reward on each visit from Weeks 2-14 if they bring their medication bottle with them.

Subjects are also eligible to earn rewards for remote documentation of medication adherence and for reporting of cocaine and alcohol use via the electronic handheld device (using AiView software). This is to promote appropriate use and return of the devices. Specifically, on each weekly visit during Weeks 3-14, subjects may receive up to two $15 rewards (up to $30 per visit) as follows: They will receive $15 if the number of capsules returned is within three capsules (over or under) of the number expected to be returned based on data transmitted by the device since their last visit and they will receive $15 if they have answered the device's questions about their cocaine and alcohol use each day since their last visit. Also, subjects will receive a $50 reward during the Week 16 (or Early Termination) visit if they have returned their device.

In summary, all subjects have the opportunity to receive up to $905 in compensation, as shown in **Table 4** below.

Table 4. Subject Compensation

SUBJECT COMPENSATION								
Scheduled Visit	Time and inconvenience (attended visit)	Bonus for attending four consecutive weekly visits (specified below)	Provide Complete Self-Report Data on Cocaine, Cigarette and Alcohol Use Since Last Visit	Bottle Returned	# Capsules Returned = # Expected ±3 (requires bottle return)	Provide Daily Report of Cocaine and Alcohol Use Since Last Visit via Device	Device Returned	***TOTAL***
Screening (1)	$15							$15
Screening (2)	$15							$15
Screening (3)	$15							$15
Week 1	$15		$5					$20
Week 2	$15		$5	$5				$25
Week 3	$15		$5	$5	$15	$15		$55
Week 4	$15		$5	$5	$15	$15		$55
Week 5	$15		$5	$5	$15	$15		$55
Week 6	$15	$20 (wks 3-6)	$5	$5	$15	$15		$75
Week 7	$15		$5	$5	$15	$15		$55
Week 8	$15		$5	$5	$15	$15		$55
Week 9	$15		$5	$5	$15	$15		$55
Week 10	$15	$30 (wks 7-10)	$5	$5	$15	$15		$85
Week 11	$15		$5	$5	$15	$15		$55
Week 12	$15		$5	$5	$15	$15		$55
Week 13	$15		$5	$5	$15	$15		$55
Week 14	$15	$40 (wks 11-14)	$5	$5	$15	$15		$95
Week 16	$15						$50	$65
TOTAL	$270	$90	$70	$65	$180	$180	$50	**$905**

11.13 Maintaining and Breaking Study Blind

Participating subjects, NIDA staff, the VA Protocol Chairperson, study personnel at each site, and individuals serving as adjudicators for inclusion criteria and study endpoints will be blinded to treatment assignment from the day of randomization (Study Day 8) forward. Subjects will be blinded to the change in study drug (from ACZM to lorcaserin or matched placebo) on Study Day 8, and appropriate caution will be exercised by site staff in conversations with subjects to maintain this blind.

Every study subject will be encouraged to carry a wallet card that identifies him or her as a subject in a clinical research study. The card will provide the emergency contact information for the SI, study physician and the study's research pharmacist. The card will also instruct the non-study physician rendering emergency care to provide information to the study site physician with regards to that care.

The study blind should not be broken except in a medical emergency, where knowledge of the study drug received is necessary for the medical management of the subject, or for a regulatory requirement. The SI should contact the CSPCRPCC Study Pharmacist and NIDA Medical Monitor to request an unblinding authorization.

If the blind is broken for an individual subject due to a medical emergency, the following information must be recorded in the subject's source documents: Date and time of unblinding together with the reason for the unblinding, and all associated AE information. The source documents should note that the subject's treatment assignment was unblinded and include the date of the unblinding to enable censoring of any data as appropriate.

Treatment assignment for all subjects within the study will remain blinded except as noted above and will not be revealed until all final clinical data have been entered into the database and all data queries have been resolved for all subjects, i.e., after the database is locked.

12 ASSESSMENT METHODS

Clinical assessments will be conducted according to the **Schedule of Events** (Table 3) and are briefly described as follows:

12.1 Subject Locator Form

A Subject Locator Form will be completed and will be kept securely at the clinical site, separate from the subject's study data. Data collected on the Subject Locator Form will be used to facilitate contact with the subject during the research and follow-up. Subjects will be asked to provide locator information including their residential street address and a working telephone number, and the contact information for a relative or friend who can reach the subject in emergencies.

12.2 Medical History

During screening, a medical history will be collected and reviewed by a clinical staff member with medical training to determine subject eligibility before enrollment.

12.3 Smoking and Alcohol History

The Smoking History Survey is a modified version of the Mayo Nicotine Dependence Center Patient Questionnaire (1991) and will be administered by a research assistant. The Smoking History Survey asks subjects the following: how many cigarettes per day they smoke and how many times they have attempted to quit (including methods). Information on other non-cigarette tobacco products is also noted. Subjects will also be asked about their alcohol consumption during the last 30 days: how many days did they have at least one drink; how many drinks did they usually have on the days they drank; and the largest number of drinks consumed on any one day during the 30-day period.

12.4 Psychiatric History

Structured Clinical Interview for DSM-5 – Research Version (SCID-5-RV) will be conducted by appropriately trained clinical staff. The SCID-5-RV will evaluate the subject's history or current diagnosis of the following categories of neuropsychiatric disorders: psychosis, bipolar illness, major depression, anorexia nervosa or bulimia, or presence of current anxiety disorder.

12.5 Demographics

Age, gender, race, ethnicity, years of education, usual employment pattern in the last 30 days, and marital status data will be collected on all consented subjects, whether or not they are randomized.

12.6 Addiction Severity Index-Lite (ASI-Lite)

The ASI-Lite is a multidimensional, semi-structured, clinician-administered interview. It is widely used in the substance abuse field and has good reliability and validity. It is designed to provide a comprehensive assessment of functioning in seven areas – medical, employment, alcohol use, drug use, legal, family/social relationships, and psychiatric symptoms. For each of the seven functional areas, the instrument produces composite scores, which are based on the respondent's answers to particular items.

12.7 Physical Exam

A physical exam of the head, eyes, ears, nose and throat, cardiovascular system, lungs, abdomen (liver/spleen), extremities, skin, brief neurological exam, musculoskeletal system and general appearance will be performed by a licensed study staff member with medical training. Subject's height will also be recorded on this form.

12.8 Vital Signs and Weight

Vital signs to be assessed include temperature, blood pressure (sitting after 3 minutes), pulse rate, and respiratory rate. Weight (in pounds) will also be measured. Body Mass Index (BMI) will be calculated at screening to verify inclusion criteria #8.

12.9 Pregnancy Test

An FDA-approved urine pregnancy test designed to measure β-human chorionic gonadotropin will be used. All female subjects will be tested regardless of their child-bearing capacity.

12.10 12-lead ECG

A 12-lead ECG will be performed on all subjects according to standard procedures. A licensed physician or a non-physician who is certified/accredited by the participating institution to read ECGs must read all ECGs. A board-certified cardiologist can be consulted, if needed.

12.11 Beck Depression Inventory-Second Edition (BDI-II)

The Beck Depression Inventory Second Edition (BDI-II) is a 21-item self-report instrument intended to assess the existence and severity of symptoms of depression. This assessment includes items intending to index symptoms of severe depression, which would require hospitalization. When presented with the BDI-II, the subject will be asked to consider each statement as it relates to the way they have felt for the past two weeks. Subsequent assessments of BDI-II during treatment will be compared to the subject's previous assessment in order to evaluate change (i.e. worsening.)

The subject will be asked to consider each statement as it relates to the way he/she has felt during the assessment period as described above. Each of the 21 items corresponding to a symptom of depression is summed to give a single score for the BDI-II. There is a four-point scale for each item ranging from 0 to 3. A total score of 0-13 is considered minimal depression range, 14-19 is mild, 20-28 is moderate, and 29-63 is severe.

During the treatment phase, the following action will be taken by the site investigator/team in response to BDI-II score:

- Score < 20: no action
- Score 20-28: consider further evaluation of possible clinical depression
  Score > 28: discontinue study drug and refer to mental health practitioner or to primary care physician for evaluation of clinical depression

12.12 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a 2-page form asking questions about suicidal ideation, intensity of ideation, and suicidal behavior developed by Posner and collaborators at the New York State Psychiatric Institute (Oquendo *et al.*, 2003). The "baseline/screening" version of the C-SSRS will be used to assess lifetime suicidality. The "since last visit" C-SSRS will be used to assess current suicidality. This scale is intended for use by trained administrators. The questions contained in the C-SSRS are suggested probes. Ultimately, the determination of the presence of suicidality depends on clinical judgment. Training is required before administering the C-SSRS through a 30-minute interactive slide presentation followed by a question-answer session through the Columbia University Medical Center. Those completing the training are certified to administer the C-SSRS, and must provide a valid training certificate for the study's regulatory files.

NOTE: If a subject expresses suicidal thoughts or exhibits acute psychosis or suicidal/homicidal behavior, the subject will be referred to a local treatment center, emergency department or be hospitalized as appropriate and study drug will be discontinued.

12.13 Blood Chemistries

Blood will be collected by the sites in serum separation evacuated venous blood collection tubes (e.g., Vacutainer®) and will be separated according to standard procedures and sent to a central clinical laboratory for testing (Q^2 Solutions, Valencia, CA). Quantitative analysis will be performed for the following analytes: sodium, potassium, chloride, carbon dioxide, glucose, creatinine, calcium, alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), gamma-glutamyltranspeptidase (GGT), total bilirubin, alkaline phosphatase (ALP), and blood urea nitrogen (BUN). Results will be made available to the clinical site staff upon completion of testing.

12.14 Hematology

Blood will be collected by the sites in evacuated venous blood collection tubes containing anticoagulant (e.g., Vacutainer®) for hematologic assessments and sent to a central clinical laboratory for testing (Q^2 Solutions, Valencia, CA). Complete blood counts (CBC) with differentials and platelet count will be performed. Quantitative analyses for hemoglobin, hematocrit, red blood cells, platelets, total white blood cells, neutrophils, lymphocytes, monocytes, eosinophils, and basophils will be performed. Results will be made available to the clinical site staff upon completion of testing.

12.15 Urinalysis

Urine will be collected using the collection kit provided by the central clinical laboratory (Q^2 Solutions, Valencia, CA) and analyzed for: specific gravity, pH, blood, protein, glucose, ketones, leukocytes, and nitrite. Results will be made available to the clinical site staff upon completion of testing.

12.16 Urine Drug Screen

Urine samples will be tested for cocaine and other drugs of abuse (as noted in **Table 3, Schedule of Events**) using a multi-panel on-site test device (Branan ToxCup® DT14) to identify individuals potentially using illicit drugs.

12.17 Urine Fentanyl

Urine samples will be collected and tested using an on-site one-step rapid fentanyl test stick to determine qualitative detection of fentanyl metabolite at 50 ng/mL cut-off concentration.

12.18 Urine Cotinine

Urine samples will be collected and tested using an on-site one-step rapid nicotine test stick to determine qualitative detection of cotinine levels at 200 ng/mL cut-off concentration.

12.19 EtG Urine Alcohol Test

Urine samples will be collected and tested using an on-site one-step rapid ethyl glucuronide (EtG) test stick to determine qualitative detection of alcohol levels at 500 ng/mL cut-off concentration and be used to evaluate the abstinence from the consumption of alcohol.

12.20 Urine BE Testing

Urine samples will be collected and sent to a central laboratory (Laboratory Corporation of America, Research Triangle Park, NC) to be analyzed for BE and creatinine using validated liquid chromatography-tandem mass spectrometry methods for analysis. The details of sample collection, labeling, storage, and shipment will be provided in a Study Operations Manual.

12.21 Blood Collections for Medication Adherence

As specified in **Table 3, Schedule of Events**, blood samples will be collected to determine the plasma concentrations of both acetazolamide (Study Day 8) and lorcaserin (Study Weeks 3 and 7) as a medication adherence marker. Each blood sample will be collected into a sodium heparin-containing Vacutainer® tube, and plasma will be separated according to standard procedures. Plasma concentrations of ACZM and lorcaserin will be determined at a central bioanalytical lab (XenoBiotic Laboratories, Inc., Plainsboro, NJ) using a validated liquid chromatography-tandem mass spectrometry method. The details of sample collection, labeling, storage, and shipment will be provided in a Study Operations Manual.

12.22 Cognitive Behavioral Therapy (CBT)

Attendance at the clinic for assessments and the behavioral counseling session will be recorded on an eCRF including the length of the session. The Behavioral Counseling eCRF will also record any additional behavioral methods the subject may have used on their own, *e.g.*, NA, AA, hypnosis, etc.

12.23 Alcohol Intervention: Quit to Quit

A computer-based alcohol intervention will be viewed by all subjects on Study Day 1 and will be continued on an optional basis at the discretion of each subject. The alcohol intervention, "Quit to Quit", will encourage abstinence from alcohol but it will be up to each subject to decide whether or not this will be one of their goals during the trial. Each subject's decision (yes or no) to continue viewing the alcohol intervention modules will serve as one of the stratification factors for randomization. The subject's case report forms will contain a record of all alcohol intervention modules viewed.

12.24 AiView Adherence Monitoring

Beginning on Study Day 8, subjects will participate in a medication adherence monitoring procedure, with associated opportunities to earn rewards that are contingent upon appropriate performance of tasks using a site-provided cell phone loaded with Health Insurance Portability and Accountability Act (HIPAA)-compliant AiView software (AiCure Technologies, New York, NY). AiView uses facial recognition and motion-sensing technology to confirm the ingestion of a study medication and transfers the resulting data (encrypted and blurred) to a secure central server in real time. The software will also be configured to remind patients of upcoming scheduled doses and record the previous day's cocaine and alcohol use.

12.25 Concomitant Medications

All medications taken by the subject within the 30 days prior to screening and during the screening period, up to and including the day of randomization, will be recorded. The reported medications will be reviewed and approved by the SI/study physician for possible interactions

with study drugs or an indication of a serious chronic or acute medical condition that would exclude the candidate from participation.

All medications taken by the subject during the Treatment Phase of the study through the Week 16 Follow-Up Visit will be recorded. Any medications taken during this time must be pre-approved by the SI/study physician whenever possible to avoid interactions with study drug.

NOTE: In general, participants who require any concomitant medications at the time of screening must have a stable medical condition and stable dosages for the 3 months prior to enrollment in the study. Subjects will be cautioned not to take concomitant medications, whether prescription, over-the-counter, herbal supplements, or health store products without first consulting with the SI or his/her designee. The NIDA Medical Monitor should be contacted if there are any questions.

12.25.1 Concomitant Medications Always Excluded

In general, concomitant medications that have been associated with serotonin syndrome and durgs that are metabolized by CYP 2D6 are not permitted under this protocol. The list below contains medications that are specifically not allowed at any time during the course of study participation. In addition, section 12.23.2 delineates a list of concomitant medications with limitations of use. Again, if in doubt, consult a physician assigned to the study or the NIDA Medical monitor.

Including but not limited to:

- Antispychotic Medications: haloperidol, thioridazine, aripiprazole, etc.
- All opioids: tramadol, oxycodone, hydrocodone, codeine, morphine, methadone, buprenorphine, etc.
- All beta-blockers: propranolol, metoprolol, etc.
- All Class I antiarrhythmic drug: flecainide, propafenone, mexiletine, etc.
- All monoamine oxidase inhibitors (MAOIs)
- Dexamphetamine, Lisdexamfetamine or Methamphetamine
- All tryptans, lithium, ondansetron, dolasetron, donepezil, metoclopramide, palanosetron, promethazine, safinamide, St. John's wort, tryptophan and any other dopaminergic or serotonergic drug that is not specifically listed as allowable in this protocol.
- Medications to treat erectile dysfunction (e.g. Viagra, Cialis, etc)

12.25.2 Allowable Concomitant Medications with Limitations

Subjects will be allowed to receive **no more than** one medication, included in the list below, at any given time during the course of study participation.

- Non-MAOI antidepressants: amitriptyline, atomoxetine, bupropion, clomipramine, desipramine, desvenlafaxine, duloxetine, fluoxetine, fluvoxamine, imipramine, levomilnacipran, minanserin, mirtazapine, paraoxetine, venlafaxine, vilazodone, and vortioxetine

- Dextromethorphan

12.26 Substance Use Report (SUR)

The SUR measures the subject's self-report of days of recent drug use. The use of cocaine, alcohol, nicotine, marijuana, methamphetamines, amphetamines, opiates, and benzodiazepines will be recorded on the SUR form. NOTE: Timeline Followback (TLFB) of cocaine and alcohol use will be obtained only for missing data beginning at Study Day 8 (data not captured by the AiView device).

12.27 Brief Substance Craving Scale (BSCS)

The BSCS is a self-administered assessment that asks the subject to rate his/her craving for cocaine. The BSCS used for this study is a modification of the State of Feelings and Cravings Questionnaire (Mezinskis et al., 2001). The composite BSCS severity score is a sum of three items: intensity, frequency, and length (each item ranges from 0 for no use to 4 for extreme use), ranging from 1 to 12. The higher the score, the more severe the cocaine craving is. However, members of study staff are not to offer interpretations of the questions.

12.28 Adverse Events

Adverse events will be assessed by medically trained study staff. If an adverse event requires medical attention, it will be reported to a study physician immediately. Adverse events will be assessed by asking the subject, "How have you been feeling since I saw you last?" **After current adverse events are assessed, the study physician must review with the subject and assess any adverse events unresolved from the previous visit.** After the adverse event assessment at each clinic visit, the type of adverse event, severity of each adverse event, and the relationship to the study drugs will be recorded on the Adverse Events eCRF, according to the procedures described in **Appendix I**. These categories are asking for the clinician's best judgment of the severity and relatedness of each adverse event.

As a precaution, all subjects will be closely monitored for treatment reports or signs of serotonin toxicity such as spontaneous clonus, inducible clonus with agitation or diaphoresis, ocular clonus with agitation or diaphoresis, tremor and hyperreflexia, hypertonia and hyperpyrexia with ocular or inducible clonus when adverse events are assessed during each weekly visit. The Hunter Serotonin Syndrome diagnostic criteria are noted in **Appendix I.**

NOTE: All follow-up Week 16 AEs will be recorded and followed to resolution, only if they are serious, or if the study physician assesses them to be clinically significant.

13 REGULATORY AND REPORTING REQUIREMENTS

13.1 Good Clinical Practices

This study will be conducted in accordance with the most current version of the International Conference on Harmonisation Guide for Good Clinical Practices (GCP).

13.2 FDA Form 1572

The SI agrees to sign and submit a Statement of Investigator (FDA Form 1572) to the sponsor prior to initiating this study.

13.3 IRB Approval

Prior to initiating the study, the SI will obtain written IRB approval to conduct the study. Should changes to the study protocol become necessary, the SI will submit protocol amendments in writing to the IRB for IRB approval prior to implementation. In addition, IRBs will approve all advertising materials used for subject recruitment and any educational materials given to the subject. Annual reports and progress reports will be submitted to the IRB annually or at a frequency requested by the IRB.

The SI will ensure that a duly constituted IRB at the study site that conforms to FDA regulations (21 CFR Part 56) will review the protocol and the volunteer informed consent form. The SI will follow IRB and FDA guidance regarding reporting of AEs. The SI will promptly report to the IRB all changes in research activity and all unanticipated problems involving risks to human subjects or others and will not make any changes in the protocol without IRB approval, except where necessary to eliminate immediate hazards to human subjects.

13.4 Informed Consent

The investigator, sub-investigators, study physician, or designated staff at each site will explain all aspects of the study in lay language and answer all of the candidate's questions regarding the study. If the candidate desires to participate in the study, s/he will be asked to sign and Informed Consent. No study procedure will be performed prior to signing Informed Consent. Candidates who refuse to participate or participants who withdraw from the study will be regarded without prejudice. All study subjects will be given a copy of the signed Informed Consent(s).

13.5 Use of Protected Health Information

At the time of informed consent, all potential candidates will be asked to sign a waiver authorizing the release and use of protected health information in this study. Clinical sites will employ a Protected Health Information Disclosure that details the health information that will be collected as part of this research and the agencies that may access that information during the study and after the study has been completed.

Health information gathered during this research study may be reviewed by representatives of NIDA, the Food & Drug Administration (FDA) and designated appointees for monitoring purposes. All data collected for this study will be sent to the VA CSP Coordinating Center (CSPCC) in Perry Point, MD for processing and analyses. Case report form data will be transmitted electronically to a secure server owned and operated by Medidata Solutions, Inc. The Medidata server is compliant with the Federal Information Security Management Act of 2002 (FISMA). Retrieval of data stored on the server is restricted to data management personnel at the VA CSPCC. De-identified data from third parties, such as clinical laboratory values or toxicology results, will be provided to the VA CSPCC electronically through NIDA's LiveLink server. Following retrieval of data, a database will be constructed and maintained locally at the VA CSPCC and all data contained within will be stored according to the HIPAA Privacy Rule.

13.6 Drug Accountability

Upon receipt, the SI/pharmacist is responsible for taking inventory of the study drug. A record of this inventory must be kept and usage must be documented. Any unused or expired study drug shall be returned to the VA CSPCRPCC by the sites, unless otherwise instructed.

13.7 Monitoring

13.7.1 Data and Safety Monitoring Board

Blinded safety data will be reviewed by the NIDA Data and Safety Monitoring Board that will convene on a quarterly basis during the conduct of this study, or earlier, if deemed necessary.

The DSMB will make a recommendation to the sponsor regarding whether to stop or continue the study. If the DSMB determines that the study should be stopped, all subjects will be immediately discontinued from receiving any investigational products and no new subjects will be consented or randomized.

In addition, NIDA has the right to discontinue the investigation at any time.

13.7.2 Medical Monitor

The NIDA medical monitor, Dr. Tanya Ramey, will be available for making recommendations to the SI on the severity of any SAEs, the relatedness to the study drug, and for determining if the SAE should be reported to the FDA in a 7- or 15-day expedited report or an annual report (**Appendix I**). The medical monitor will also be responsible for tracking and assessing trends in the adverse events reported.

13.7.3 Clinical Monitors

All SIs will allow representatives of the Sponsor to periodically review, at mutually convenient times during and after the study, all eCRFs and corresponding source documents for each subject. These monitoring visits provide the Sponsor with the opportunity to evaluate the progress of the study and to inform the Sponsor of potential problems at the study sites. The monitors will: ensure that submitted data are accurate and are in agreement with source documentation; verify that study drugs are properly stored and accounted for, verify that subjects' consent for study participation has been properly obtained and documented, confirm that subjects entered into the study meet inclusion and exclusion criteria, and assure that all essential documentation required by GCP guidelines are appropriately filed.

Clinical monitors will conduct a site initiation visit prior to the start of the study. At this visit, they will assure that proper study-related documentation exists, assist in training SIs and other site personnel in study procedures and GCP guidelines, confirm receipt of study supplies, and assure that acceptable facilities are available to conduct the study.

Routine monitoring visits by the Sponsor's representatives will be scheduled at appropriate intervals. At these visits, the monitors will verify that study procedures are being conducted according to the protocol guidelines. At the end of the study, they will advise on storage of study records and return of unused study drugs. All sites should anticipate visits by NIDA, the Sponsor, and the FDA.

13.8 Study or Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects.
- Subject enrollment is unsatisfactory.
- Data recording is inaccurate or incomplete.

The Sponsor will continue those subjects currently in treatment to completion, if there is no significant safety issue.

13.9 Retention of Records

Study documentation includes all eCRFs, workbooks, source documents, monitoring logs, appointment schedules, sponsor and SI correspondence, and regulatory documents (*e.g.*, signed protocol and amendments, IRB correspondence, approved consent form and signed informed consent forms, Statement of Investigator form, and clinical supplies receipt and distribution records).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Accordingly, source documents include, but are not limited to, laboratory reports, ECG tracings, X-rays, radiologist reports, subject diaries, biopsy reports, ultrasound photographs, subject progress notes, hospital charts or pharmacy records and any other similar reports or records of any procedure performed in accordance with the protocol. Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original document. Clinical records for all subjects studied including history and physical findings, laboratory data, and results of consultations are to be maintained by the SI in a secure storage facility.

Government agency regulations and directives require that the SI must retain all study documentation pertaining to the conduct of a clinical trial. These documents must be kept for a minimum of two years after discontinuation of the IND or two years after the approval of a new drug application (NDA) and finalization of all marketing strategies. In all instances you must get permission from NIDA prior to disposition of any study documentation and materials.

13.10 Adverse Events Reporting

In accordance with FDA reporting requirements, all AEs occurring during the course of the clinical trial will be collected, documented, and reported by the SI or sub-investigator according to the specific instructions detailed in this section of the protocol and **Appendix I**. The occurrence of AEs will be assessed at each study visit beginning on the day the Informed Consent is signed through the Follow-up Visit at Week 16.

An AE is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial, whether or not the event is considered investigational product-related or clinically significant. For this study, AEs will include events reported by the subject, as well as

clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant clinical laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. Stable chronic conditions, such as arthritis, which are present prior to clinical trial entry and do not worsen are not considered AEs. All AEs must be recorded on the AE CRF. The AE CRF is also used to record follow-up information for unresolved events reported on previous visits.

Each week, a study physician must review all new AEs reported the previous week and any events that were reported as continuing. All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed by SIs until satisfactory resolution.

13.10.1 Pregnancy

A subject's reported pregnancy at any time during study participation starting after the first dose of study drug through the final study visit is considered an AE and must be reported to NIDA in accordance with the reporting requirements described in **Appendix I**. Subjects who become pregnant will be discontinued from the study drug and will be referred for appropriate treatment as necessary. Subjects will be asked to sign a release of information form for study personnel to access medical records to obtain information regarding the outcome of the pregnancy.

13.11 Serious Adverse Events

Each AE or reaction will be classified by the SI as serious or non-serious. Based on the seriousness of the adverse event or reaction, appropriate reporting procedures will be followed. The "*International Conference on Harmonisation (ICH) Guideline for Industry: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH-E2A March 1995*," as implemented by the U.S. Food and Drug Administration defines serious adverse event (SAE) or reaction as any untoward medical occurrence that at any dose:

- results in death;
- is life-threatening; *(NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.)*
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity; or
- is a congenital anomaly/birth defect.

In addition, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug reaction, when based on appropriate medical judgment that may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. An unexpected event is one that is not described with respect to nature, severity, or frequency in the current Investigator's Brochure or product package insert.

Reporting of AEs and SAEs is described in **Appendix I**. There can be serious consequences including criminal and/or civil penalties for Sponsors who fail to comply with FDA regulations governing the reporting of SAEs to FDA. The SIs in this study have the responsibility of promptly reporting all SAEs to NIDA in order that NIDA, as the IND Sponsor, can comply with these regulations.

If a study subject withdraws from the study or if a SI decides to discontinue the subject from the study because of a SAE, the subject must have appropriate follow-up medical monitoring. If the subject is hospitalized, medical monitoring will consist of not less than daily evaluation by physical examination, vital signs, laboratory evaluations, and if applicable, ECG monitoring for significant treatment-emergent abnormalities. Monitoring will continue until the problem prompting hospitalization has resolved or stabilized with no further change expected or is discovered to be clearly unrelated to use of investigational products or progresses to death.

13.12 Subject Confidentiality

To maintain subject confidentiality, all laboratory specimens, eCRFs, and reports will be identified by an alpha-numeric code. Clinical records will be stored separately from research records in a secure location. Subject information will not be released without the subject's written permission, except as necessary for monitoring by the FDA, the VA CSP, and Sponsor authorized monitors. Release of personal health information will be in accordance with current Standards for Privacy of Individually Identifiable Health Information (45 CFR parts 160 and 164) of the Health Insurance Portability and Accountability Act (HIPAA).

Particular attention is drawn to the regulations promulgated by the FDA under the Freedom of Information Act providing, in part, that proprietary information furnished to SIs and IRBs will be kept confidential by the FDA only if maintained in confidence by the SI and IRB.

By participating in this protocol the SI affirms to NIDA that information furnished to the SI by NIDA will be maintained in confidence and such information will be divulged to the IRB, Ethical Review Committee or similar expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees.

By participating in this protocol the SI agrees that within local regulatory restrictions and ethical considerations, NIDA or any regulatory agency may consult and/or copy study documents in order to verify eCRF data.

The procedure for applying for a certificate of confidentiality is provided in **Appendix II**.

14 STATISTICAL ANALYSIS

Descriptive statistics will be used to present study data. Continuous variables will be presented as number of observations (n), mean, standard deviation (SD), median, minimum and maximum values. Categorical variables will be presented as counts and percentages. All data will be presented separately by treatment group. Summaries of the safety data will be presented for the Safety Population and the Evaluable Population. All data will be presented in listings.

14.1 Predictive Enrichment Strategy and Sample Size

A predictive enrichment strategy based on pre-randomization data (collected during screening and the one-week, single-blind run-in period) will be used to define a subpopulation of study participants who are likely to be medication adherent after randomization and likely to exhibit a low placebo response rate. Data from only this subpopulation, termed the "prequalified for primary efficacy endpoint" (PPEE) population, will be utilized for the primary efficacy endpoint. Predictive enrichment strategies have been endorsed by the FDA (US Department of Health and Human Services Food and Drug Administration. Guidance for industry enrichment strategies for clinical trials to support approval of human drugs and biological products, December, 2012) and their use has been suggested as a means to address the overlapping issues of medication nonadherence, "professional subjects" and increasing placebo response rates (McCann *et al.*, 2015).

While 272 subjects will be enrolled in the current study, it is estimated that 180 subjects (approximately 90 subjects per group) will meet criteria for inclusion in the PPEE population. Assuming 6% and 20% success rates (for achieving abstinence from cocaine) during placebo and lorcaserin treatment, respectively, 90 subjects per group in the PPEE population would yield 80% power (Pearson's Chi-square test for two proportions; two-sided comparison, alpha = 0.05). The assumption of 6% success in the placebo group is based on results from similar cocaine medication trials conducted by NIDA in the past, using the same definition of "success" (placebo group success rates have ranged from 0 to 9%). The goal of 20% success in the lorcaserin group would constitute slightly more than a three-fold increase in success compared to the expected placebo success rate. Such efficacy would be clinically meaningful. No medications are currently approved for the treatment of cocaine use disorder, but a 3-fold increase in quit rate (vs. placebo) would constitute greater efficacy than has been observed for FDA-approved smoking cessation medications. A recent meta-analysis of randomized, placebo-controlled smoking cessation trials (Eisenberg *et al.,* 2008) revealed that placebo and bupropion quit rates were 11% and 20%, respectively (16 trials), placebo and nicotine gum quit rates were 14% and 19%, respectively (22 trials), placebo and nicotine patch quit rates were 7.5% and 13%, respectively (30 trials), and placebo and varenicline quit rates were 15% and 26%, respectively (13 trials). For the current study, multiple factors were considered in estimating that 180 of the 272 enrolled subjects will qualify for inclusion in the PPEE population. Further explanation requires an understanding of enrichment strategy details.

For a subject to be included in the PPEE population, two criteria must be met. First, the plasma sample collected prior to randomization on Study Day 8 must yield an acetazolamide concentration of at least 15 ng/mL. Based on a prior NIDA PK study (unpublished), plasma acetazolamide concentrations can be expected to stay above 15 ng/mL for 48 hours after a single 15 mg oral dose in approximately 99.9% of subjects (the lower boundary of the 99.9% CI for plasma samples collected 48 hours post-dose was 15.2 ng/mL). As subjects are supposed to take 15 mg acetazolamide capsules twice daily during the single-blind run-in period (with the last dose on the morning of Study Day 8), they would have to miss at least three or more consecutive doses at the end of the run-in period for their plasma concentrations to fall below 15 ng/mL during the clinic visit on Study Day 8. When such extreme nonadherence occurs during the first week of a trial, it brings into question the motivation of the subject. Such a subject may not be interested in receiving treatment and may have falsely claimed to be "treatment seeking" to gain

study enrollment. Unfortunately, deception to gain enrollment has been well-documented in repeat clinical trial participants (Devine *et al.*, 2013; Shiovitz *et al.*, 2013). In a prior NIDA trial that evaluated modafinil in the treatment of methamphetamine dependence (Anderson *et al.,* 2012), 10% of subjects in the active treatment groups never had any detectable modafinil in their urine samples from week 1 through the end of the 12-week trial. Based on this experience, it is estimated that that approximately 10% of subjects who enroll in the current study will fail to meet the 15 ng/mL acetazolamide cutoff level and will therefore not qualify for the PPEE population.

The second criterion for inclusion in the PPEE population is focused on cocaine use self-report data collected during the first day of screening. To be included in the PPEE population, subjects must report using cocaine on at least 8 days during the 30 days immediately prior to screening. Subjects reporting 1 to 7 days of cocaine use will still be enrolled, and their data will be evaluated for exploratory efficacy endpoints, but they will not qualify for the PPEE population. In an unpublished evaluation of recent NIDA-sponsored cocaine medication trials, higher placebo success rates were observed for subjects reporting <8/30 days of cocaine use immediately prior to screening. For example, in a trial evaluating nepicastat vs. cocaine dependence (manuscript in preparation), 18% of placebo subjects reporting <8/30 days of cocaine use prior to screening were successful in achieving 3 weeks of abstinence at the end of the study, whereas only 6% of placebo subjects reporting >7/30 days of cocaine use prior to screening were able to achieve this same duration of abstinence. In the nepicastat trial, 22% of enrolled subjects reported <8/30 days of cocaine use. Based on this experience, we estimate that approximately 22% of subjects who enroll in the current trial will report <8/30 days of cocaine use prior to screening and, therefore, will not qualify for the PPEE population.

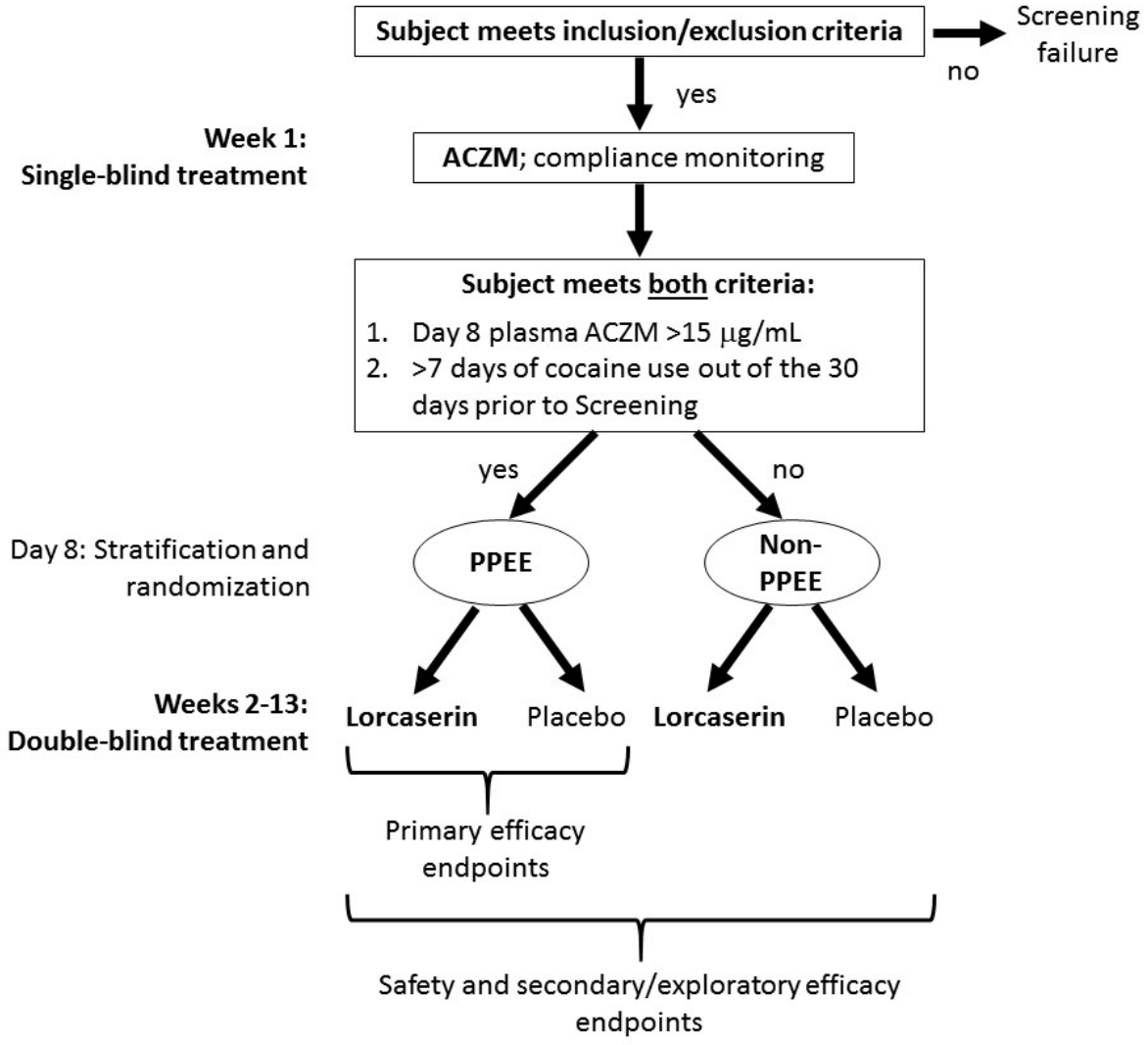
In addition to subjects failing to meet the two criteria mentioned above, it is anticipated on the basis of past experience that approximately 5% of subjects who are enrolled in the current study will drop out prior to randomization on Study Day 8 (a 5% dropout rate was seen during the first week of the NIDA nepicastat trial).

With the above factors in mind, the estimated size of the PPEE population can be addressed. If 272 subjects are enrolled and 22% (60) report <8/30 days cocaine use (excluding them from the PPEE population), 212 subjects remain eligible. If approximately 10% (22) of the remaining 212 subjects fail to qualify for the PPEE population based on nonadherence during the run-in period (Study Day 8 plasma acetazolamide <15 ng/mL), 190 subjects remain eligible. If approximately 5% (10) of the remaining 190 subjects drop out prior to Study Day 8, 180 subjects will qualify for the PPEE population.

While the enrichment strategy adds complexity to the process of data analysis, it does not substantively complicate clinical site procedures. Subjects will be classified as “PPEE” or “Non-PPEE” during data analysis, and clinical site staff will not be aware of key data (acetazolamide plasma concentrations) required for the classification.

Figure 3 schematically depicts this predictive enrichment strategy for the purposes of endpoint analysis.

Figure 3. Enrichment Strategy Study Design



14.2 Definitions of Study Populations

1) The "Intent-to-Treat (ITT) Population" – All subjects who may have taken at least one dose of lorcaserin or placebo after randomization on Study Day 8. This includes all subjects who receive at least one bottle of study drug (lorcaserin or placebo) after randomization on Study Day 8, with the exception of any subjects who return the full bottle before leaving the clinic on Study Day 8 (this may occur, for example, if a subject changes his/her mind about continuing in the study).

2) The "PPEE Population" – The subset of the ITT Population who prequalify for the primary efficacy endpoint by meeting the specified PPEE criteria prior to randomization.

3) The "Non-PPEE Population" – The subset of the ITT Population who fail to meet the specified PPEE criteria and, therefore, do not prequalify for the primary efficacy endpoint.

4) The "Non-Drinker Population" – The subset of the ITT Population who are non-drinkers, as evidenced by 100% negative results for the presence of EtG in urine from the beginning of screening through the urine test on Study Day 8, prior to randomization and 2) consistent self-report of no alcohol use throughout this same period of time, as well as the 30 days prior to screening.

5) The "Attempting Alcohol Abstinence (AAA) Population" – The subset of the ITT Population who: 1) fail to meet criteria for the "Non-Drinker Population" and 2) commit to quitting drinking during the study, as evidenced by viewing the optional Quit to Quit module on Study Day 8 prior to randomization.

6) The "Baseline Low Use/Adherent Population" – The subset of the non-PPEE Population who failed to qualify for the primary efficacy endpoint only because they reported <8 days of cocaine use during the 30 days prior to screening (plasma acetazolamide level on Study Day 8 was ≥15 ng/mL).

7) The "Baseline Adherent Population" – The combination of the PPEE Population and the Baseline Low Use/Adherent Population (all subjects with Study Day 8 plasma acetazolamide levels ≥15 ng/mL).

8) The Baseline Non-Adherent Population – The subset of the ITT Population who are not part of the Baseline Adherent Population (all subjects with Study Day 8 plasma acetazolamide levels <15 ng/mL).

9) The "Acetazolamide Safety Population" – All subjects who participate in the 1-week, single-blind run-in period. Note: Treatment-emergent AEs recorded during this period will be assessed in relationship to acetazolamide.

10) The "Lorcaserin/Placebo Safety Population" – The same group of subjects defined above for the ITT Population. Note: Treatment-emergent AEs recorded in this group after randomization will be assessed in relationship to lorcaserin/placebo.

14.3 Outcome Measures

14.3.1 Primary Efficacy Outcome Measures

The primary endpoint is the proportion of subjects successfully achieving abstinence from cocaine during the last three weeks of treatment (Study Weeks 11-13) in the PPEE population. Comparison of this proportion in subjects receiving lorcaserin vs. placebo will constitute the primary endpoint analysis.

A subject will be regarded as a treatment success (abstinent from cocaine during the last three weeks of treatment) if:

- There are self-report data indicating no cocaine use on each day of the 3-week period;
- There is at least one benzoylecgonine (BE) assay result for a urine sample collected within the 3-week period; and

- BE assay results are negative (BE <150 ng/mL) for all urine samples collected during the 3-week period.

Subjects not meeting these three criteria (including dropouts) will be regarded as treatment failures.

14.3.2 Secondary Efficacy Outcome Measures

The secondary endpoint is the proportion of subjects successfully achieving abstinence from cocaine during the last three weeks of treatment (Study Weeks 11-13) in the subset of the PPEE population who are also part of the Non-Drinker Population or the AAA Population. Comparison of this proportion in subjects receiving lorcaserin vs. placebo will constitute the secondary endpoint analysis. Abstinence will be defined as described for the primary endpoint.

14.3.3 Exploratory Outcome Measures

a) The proportion of subjects successfully achieving abstinence from cocaine during the last three weeks of treatment (Study Weeks 11-13) in the ITT population. Comparison of this proportion in subjects receiving lorcaserin vs. placebo will constitute the analysis. Abstinence will be defined as described for the primary endpoint. (Note: what the primary endpoint would have been if there were no enrichment strategy)

b) The proportion of subjects successfully achieving abstinence from cocaine during the last three weeks of treatment (Study Weeks 11-13) in the subset of the ITT population who are also part of the Non-Drinker population or the AAA Population. Comparison of this proportion in subjects receiving lorcaserin vs. placebo will constitute the analysis. Abstinence will be defined as described for the primary endpoint. (Note: what the secondary endpoint would have been if there were no enrichment strategy)

c) The proportion of subjects successfully achieving abstinence from cocaine during the last three weeks of treatment (Study Weeks 11-13) in the non-PPEE population. Comparison of this proportion in subjects receiving lorcaserin vs. placebo will constitute the analysis. Abstinence will be defined as described for the primary endpoint.

d) The proportion of subjects successfully achieving abstinence from cocaine during the last three weeks of treatment (Study Weeks 11-13) in the subset of the non-PPEE population who are also part of the Non-Drinker population or the AAA Population. Comparison of this proportion in subjects receiving lorcaserin vs. placebo will constitute the analysis. Abstinence will be defined as described for the primary endpoint.

e) The proportion of subjects successfully achieving abstinence from cocaine during the last three weeks of treatment (Study Weeks 11-13) in the Baseline Low Use/Adherent Population. Comparison of this proportion in subjects receiving lorcaserin vs. placebo will constitute the analysis. Abstinence will be defined as described for the primary endpoint. (Note: similar to primary endpoint but in subjects excluded from the PPEE population only because of low baseline cocaine use)

f) The proportion of subjects successfully achieving abstinence from cocaine during the last three weeks of treatment (Study Weeks 11-13) in the subset of the Baseline Low Use/Adherent Population who are also part of the Non-Drinker population or the AAA Population. Comparison

of this proportion in subjects receiving lorcaserin vs. placebo will constitute the analysis. Abstinence will be defined as described for the primary endpoint. (Note: similar to secondary endpoint but in subjects excluded from the PPEE population only because of low baseline cocaine use)

g) The proportion of subjects successfully achieving abstinence from cocaine during the last three weeks of treatment (Study Weeks 11-13) in the Baseline Adherent Population. Comparison of this proportion in subjects receiving lorcaserin vs. placebo will constitute the analysis. Abstinence will be defined as described for the primary endpoint. (Note: what the primary endpoint would have been if low baseline cocaine use had not excluded subjects from the PPEE Population)

h) The proportion of subjects successfully achieving abstinence from cocaine during the last three weeks of treatment (Study Weeks 11-13) in the subset of the Baseline Adherent Population who are also part of the Non-Drinker population or the AAA Population. Comparison of this proportion in subjects receiving lorcaserin vs. placebo will constitute the analysis. Abstinence will be defined as described for the primary endpoint. (Note: what the secondary endpoint would have been if low baseline cocaine use had not excluded subjects from the PPEE Population)

i) The proportion of subjects successfully achieving abstinence from cocaine during the last three weeks of treatment (Study Weeks 11-13) in the subset of the AiView Users Population who are also part of the PPEE Population. Comparison of this proportion in subjects receiving lorcaserin vs. placebo will constitute the analysis. Abstinence will be defined as described for the primary endpoint.

j) The proportion of subjects successfully achieving abstinence from cocaine during the last three weeks of treatment (Study Weeks 11-13) in the subset of the AiView Non-Users Population who are also part of the PPEE Population. Comparison of this proportion in subjects receiving lorcaserin vs. placebo will constitute the analysis. Abstinence will be defined as described for the primary endpoint.

k) The proportion of subjects successfully achieving abstinence from alcohol during the last three weeks of treatment (Study Weeks 11-13) in the subset of the AAA Population who are also in the Baseline Adherent Population and who received a diagnosis of Alcohol Use Disorder (AUD) during screening. Comparison of this proportion in subjects receiving lorcaserin vs. placebo will constitute the analysis. A subject will be regarded as abstinent from alcohol during the last three weeks of treatment if:

- There are self-report data indicating no alcohol use on each day of the 3-week period;
- There is at least one ethyl glucuronide (EtG) assay result for a urine sample collected within the 3-week period; and
- EtG assay results are negative (EtG < 500 ng/mL) for all urine samples collected during the 3-week period.

Subjects not meeting these three criteria (including dropouts) will be regarded as having failed to achieve abstinence from alcohol.

l) The proportion of subjects successfully achieving abstinence from alcohol during the last three weeks of treatment (Study Weeks 11-13) in the subset of the AAA Population who are also in the Baseline Adherent Population. Comparison of this proportion in subjects receiving lorcaserin vs. placebo will constitute the analysis. Abstinence from alcohol will be defined as described above. (Note: attempting alcohol abstinence and good baseline adherence +/- AUD)

m) The proportion of subjects successfully achieving abstinence from alcohol during the last three weeks of treatment (Study Weeks 11-13) in the subset of the AAA Population who received a diagnosis of AUD during screening. Comparison of this proportion in subjects receiving lorcaserin vs. placebo will constitute the analysis. Abstinence from alcohol will be defined as described above. (Note: attempting alcohol abstinence with AUD +/- good baseline adherence)

n) The proportion of subjects successfully achieving abstinence from alcohol during the last three weeks of treatment (Study Weeks 11-13) in the subset of the ITT Population who received a diagnosis of AUD during screening. Comparison of this proportion in subjects receiving lorcaserin vs. placebo will constitute the analysis. Abstinence from alcohol will be defined as described above. (Note: includes all subjects with AUD whether or not trying to abstain from alcohol)

o) The proportion of subjects successfully achieving abstinence from alcohol during the last three weeks of treatment (Study Weeks 11-13) in the ITT Population. Comparison of this proportion in subjects receiving lorcaserin vs. placebo will constitute the analysis. Abstinence from alcohol will be defined as described above.

p) The proportion of subjects in the ITT Population reporting no alcohol use for each day of the last three weeks of treatment (Study Weeks 11-13). Comparison of this proportion in subjects receiving lorcaserin vs. placebo will constitute the analysis. (Note: comparison with results for the endpoint described immediately above will provide an indication of the extent to which subjects under-reported their alcohol use and falsely claimed alcohol abstinence at the end of the study)

q) The proportion of subjects successfully achieving abstinence from cocaine during the last three weeks of treatment (Study Weeks 11-13) in the subset of the PPEE Population who completed the Treatment Phase (remaining through the end of Study Week 13) and were abstinent from alcohol during the last three weeks of treatment. Comparison of this proportion in subjects receiving lorcaserin vs. placebo will constitute the analysis. Abstinence from cocaine will be defined as described for the primary endpoint, and abstinence from alcohol will be defined as described above.

r) The proportion of subjects successfully achieving abstinence from cocaine during the last three weeks of treatment (Study Weeks 11-13) in the) in the subset of the PPEE Population who completed the Treatment Phase (remaining through the end of Study Week 13) and were NOT abstinent from alcohol during the last three weeks of treatment. Comparison of this proportion in subjects receiving lorcaserin vs. placebo will constitute the analysis. Abstinence from cocaine will be defined as described for the primary endpoint, and abstinence from alcohol will be defined as described above.

s) The proportion of subjects successfully achieving abstinence from cocaine during the last six weeks of treatment (Study Weeks 8-13) in the PPEE population. Comparison of this proportion in subjects receiving lorcaserin vs. placebo will constitute the primary endpoint analysis.

A subject will be regarded as a treatment success (abstinent from cocaine during the last six weeks of treatment) if:

- There are self-report data indicating no cocaine use on each day of the 6-week period;
- There is at least one benzoylecgonine (BE) assay result for a urine sample collected within the 6-week period; and
- BE assay results are negative (BE < 150 ng/mL) for all urine samples collected during the 6-week period.

Subjects not meeting these three criteria (including dropouts) will be regarded as treatment failures.

t) The proportion of subjects successfully achieving abstinence from alcohol during the last six weeks of treatment (Study Weeks 8-13) in the subset of the AAA Population who are also in the Baseline Adherent Population and who received a diagnosis of Alcohol Use Disorder (AUD) during screening. Comparison of this proportion in subjects receiving lorcaserin vs. placebo will constitute the analysis. A subject will be regarded as abstinent from alcohol during the last six weeks of treatment if:

- There are self-report data indicating no alcohol use on each day of the 6-week period;
- There is at least one ethyl glucuronide (EtG) assay result for a urine sample collected within the 6-week period; and
- EtG assay results are negative (EtG < 500 ng/mL) for all urine samples collected during the 6-week period.

Subjects not meeting these three criteria (including dropouts) will be regarded as having failed to achieve abstinence from alcohol.

u) The proportion of subjects in the [subset of the Baseline Adherent Population with at least one lorcaserin plasma assay result] whose lorcaserin plasma levels were in the expected range for all assay results (expected range to be specified in Statistical Analysis Plan).

v) The proportion of subjects in the [subset of the Baseline Non-Adherent Population with at least one lorcaserin plasma assay result] whose lorcaserin plasma levels were in the expected range for all assay results (expected range to be specified in Statistical Analysis Plan).

w) The proportion of subjects in the [subset of the PPEE Population with at least one lorcaserin plasma assay result] whose lorcaserin plasma levels were in the expected range for all assay results (expected range to be specified in Statistical Analysis Plan).

x) The proportion of subjects in the [subset of the Non-PPEE Population with at least one lorcaserin plasma assay result] whose lorcaserin plasma levels were in the expected range for all assay results (expected range to be specified in Statistical Analysis Plan).

y) Self-reported cigarette consumption in the subset of the Baseline Adherent Population who report smoking during the screening period. The outcome will be compared in subjects receiving lorcaserin vs. placebo. Further details of the analysis will be included in the Statistical Analysis Plan.

z) The relationship between Study Day 8 plasma acetazolamide levels and observed study drug adherence after randomization will be explored. Details of the analysis will be included in the Statistical Analysis Plan.

aa) Descriptive breakdown of the PPEE and Non-PPEE populations by severity of cocaine use disorder (the proportion of subjects in each population with diagnosed severity of mild, moderate and severe).

bb) Change in ASI-Lite score (placebo vs. lorcaserin) for the subgroup of the PPEE population who have values from both Day 1 and Week 13 visits.

cc) Change in BSCS score (placebo vs. lorcaserin) from baseline through week 13 for the subgroup of the PPEE population who remain in treatment through at least the week 3 visit (first visit after lorcaserin dosing with BSCS assessment). For this analysis, baseline = average of BSCS results from Week 1 (Day 1) and Week 2 (Day 8) visits for each subject.

14.4 Safety Evaluations

During the course of the study, safety data will be collected for all subjects who have entered screening. For the Combined PPEE/Non-PPEE Population, data will be summarized by treatment group (and by visit, when applicable).

The incidence and severity of treatment-emergent AEs will be summarized by treatment group. The results of clinical laboratory tests; 12-lead ECGs; physical examinations; suicidality evaluations (C-SSRS), body weight and vital sign measurements will be summarized with descriptive statistics, by treatment group, for all time-points at which these variables are collected. Individual patient data for vital signs, ECG results, and laboratory test results will be assessed for potentially clinically significant values according to predetermined criteria. Any potentially clinically significant values identified will be summarized by treatment group.

For parameters measured during screening, the safety variables of interest are the changes from baseline. Data collected after subjects receive the first dose of acetazolamide but before randomization to lorcaserin will be summarized and compared with data collected during screening. Adverse events will also be summarized for subjects who do not progress beyond screening.

15 DATA MANAGEMENT AND ELECTRONIC CASE REPORT FORMS (ECRFS)

Data management activities and statistical analytical support will be coordinated through the CSPCC at the VA in Perry Point, MD.

15.1 Data Collection

Site Investigators are responsible for maintaining accurate, complete and up-to-date records for each subject. This includes all source documentation related to the study, such as progress notes, films, ECG tracings, computer discs or tapes. After initial data entry onto source documents, site staff will make subsequent data entries onto electronic case report forms (eCRFs) within the study's electronic data capture (eDC) system. The eDC system will contain a record for every subject who provides consent to participate in the study. Data entry will be guided through nested folders that are accessible sequentially, usually upon completion of required procedures. For example, site personnel may only access enrollment forms once screening data have been entered.

The eDC system utilized for this study is furnished by Medidata Solutions, Inc. The eDC system will be accessible only by site personnel who have received the required training. Further, permissions to add, modify or view data will be customized based on individual site personnel's roles within the study. Permissions will be set and maintained by the CSPCC, the data coordinating center for the study. The CSPCC will revoke permissions for any staff member who fails to maintain required training, including human subjects protection and good clinical practices (GCP) training.

15.2 Data Editing and Control

Data submitted via the eDC system will undergo a series of automated and manual quality checks and reviews. Incomplete, inconsistent or inaccurate data will generate requests for clarification that will require response(s) from site personnel. Details of the number of subjects entered into the system and the quality and quantity of the data submitted will be available by site to end users upon log in. These data will also be made available to representatives of the NIDA DTMC on a monthly basis, or as needed to chart the study's progress or individual sites' performance.

Site investigators agree to routine data audits by the staff of the Department of Veterans Affairs Cooperative Studies Program (VA CSP) monitoring unit, as well as by NIDA. VA CSP monitors will routinely visit each site to assure that data submitted on the appropriate forms are in agreement with source documents at the sites. They will also verify that study drugs have been properly stored and accounted for, subject informed consent for study participation has been obtained and documented in the subject's progress notes, all essential documents required by GCP regulations are on file, and sites are conducting the study according to the research protocol. Any inconsistencies will be resolved, and any changes to the data forms will be made using established CSPCC procedures. Further, monitors will be granted access to view and query data remotely within the eDC system in preparation for their routine visits.

15.3 Data Entry, Processing and Analyses

Data from eCRFs will be transmitted into a database at the CSPCC. When the study is completed and all data have been entered into the clinical database, and the database has been checked by Quality Assurance and locked, statistical analysis of the data will be performed by the CSPCC statisticians in accordance with the Statistical Analysis Plan (SAP) of this protocol. Periodically, during the investigation, CSPCC will also prepare summary reports of the data so that progress of the study can be monitored by NIDA and the DSMB. De-identified datasets will also be submitted to the NIDA DTMC central data repository.

16 PUBLICATION OF THE STUDY RESULTS

NIDA and the investigative group agree that data will be made available to individual SIs to encourage other publications, either by a group or by an individual SI provided that: manuscripts based on the use of lorcaserin for cocaine use disorder may not be submitted for publication until the main findings of the study have been published. Review of manuscripts resulting from this study or from data generated during this study must occur according to the NIDA DTMC Publications Policy prior to submission for publication. Authorship shall be consistent with NIDA and DTMC policies.

17 SIGNATURES

NIDA/VA REPRESENTATIVES

Typed Name	Signature	Date
Dave McCann, Ph.D. National Institute on Drug Abuse	_____	_____
Shwe Gyaw, M.D. National Institute on Drug Abuse	_____	_____
TBD VA Protocol Chairperson	_____	_____
Kousick Biswas, Ph.D. VA Cooperative Studies Program	_____	_____

SITE INVESTIGATOR(S)

I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol; deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment with the IRB approval. I also agree to report all information or data in accordance with the protocol, and in particular I agree to report any serious adverse experiences as defined in Section 13.10 of this protocol.

Typed Name	Signature	Date
_____ Principal Investigator	_____	_____

18 REFERENCES

Acetazolamide Tablets USP. Product Label. Taro Pharmaceuticals U.S.A., Inc.; October 2015. Available at http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=abeb13eb-66a5-4030-9bc2-5981acd196b9

Amato L, Minozzi S, Pani PP, Solimini R, Vecchi S, Zuccaro P, Davoli M. Dopamine agonists for the treatment of cocaine dependence (Review). *The Cochrane Collaboration*. 2011; Published by John Wiley & Sons, Ltd.

Anderson AL, Li SH, Biswas K, McSherry F, Holmes T, *et al.* Modafinil for the treatment of methamphetamine dependence. *Drug Alcohol Depend*. 2012; 120:135-141.

Belviq® (lorcaserin hydrochloride) tablets. Product Label. Eisai Inc.; June 2012. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022529lbl.pdf

Buydens-Branchey L, Branchey M, Hudson J, Rothman M, Fergeson P, McKernin C. Effect of fenfluramine challenge on cocaine craving in addicted male users. *Am J Addict*. 1998; 7:142-155.

Carroll KM. *A Cognitive-Behavioral Approach: Treating Cocaine Addiction. Therapy Manuals for Drug Abuse: Manual 1*. NIH Publication Number: 98-4308. Rockville, MD: National Institute on Drug Abuse; 1998.

Castells X, Casas M, Pérez-Mañá C, Roncero C, Vidal X, Capellà D. Efficacy of psychostimulant drugs for cocaine dependence. *Cochrane Database Syst Rev.* 2010; CD007380.

Collins GT, Gerak LR, Javors MA, France CP. Lorcaserin reduces the discriminative stimulus and reinforcing effects of cocaine in rhesus monkeys. *J Pharmacol Exp Ther*. 2016; 356:85-95.

Connolly HM, Crary JL, McGoon MD, Hensrud DD, Edwards BS, Edwards WD, Schaff HV. Valvular heart disease associated with fenfluramine-phentermine. *N Engl J Med*. 1997; 337:581-588.

Devine EG, Ryan ML, Falk DE, Fertig JB, Litten, RZ. An exploratory evaluation of *Take Control*: A novel computer-delivered behavioral platform for placebo-controlled pharmacotherapy trials for alcohol use disorder. *Contemp Clin Trials*. 2016; 50:178-185.

Devine EG, Waters ME, Putnam M, Surprise C, O'Malley K, *et al.* Concealment and fabrication by experienced research subjects. *Clin Trials*. 2013; 10:935-948.

Di Matteo V, Di Giovanni G, Di Mascio M, Esposito E. SB 242084, a selective serotonin2C receptor antagonist, increases dopaminergic transmission in the mesolimbic system. *Neuropharm*. 1999; 38:1195-1205.

Eisai Inc., and Arena Pharmaceuticals Inc. Press Release. Eisai and Arena Pharmaceuticals report results of an investigational phase 2 trial of lorcaserin HCl as an aid for smoking cessation. November 3, 2014. Available at

http://files.shareholder.com/downloads/ARNA/2641484823x0x790638/D8F6EDCD-1B75-4DCD-A98F-FF410D84B7AB/ARNA_News_2014_11_3_General.pdf

Eisenberg MJ, Filion KB, Yavin D, Bélisle P, Mottillo S, *et al*. Pharmacotherapies for smoking cessation: a meta-analysis of randomized controlled trials. *CMAJ*. 2008; 179: 135-144.

FDA Guidance for Industry: Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products. U.S. Department of Health and Human Services, Food and Drug Administration. Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Devices and Radiological Health (CDRH). December 2012.

Fletcher PJ, Rizos Z, Sinyard J, Tampakeras M, Higgins GA. The 5-HT_{2C} receptor agonist Ro60-0175 reduces cocaine self-administration and reinstatement induced by the stressor yohimbine, and contextual cues. *Neuropsychopharmacology*. 2008; 33:1402-1412.

Fletcher PJ, Chintoh AF, Sinyard J, Higgins GA. Injection of the 5-HT2C receptor agonist Ro60-0175 into the ventral tegmental area reduces cocaine-induced locomotor activity and cocaine self-administration. *Neuropsychopharmacology*. 2004; 29:308-318.

Hampson AJ, Babalonis S, Lofwall MR, Nuzzo PA, Krieter P, Walsh SL. A pharmacokinetic study examining acetazolamide as a novel adherence marker for clinical trials. *J Clin Psychopharmacol.* 2016; 36:324-332.

Harvey-Lewis C, Li X, Higging GA, Fletcher PJ. The 5-HT2C receptor agonist lorcaserin reduces cocaine self-administration, reinstatement of cocaine-seeking and cocaine induced locomotor activity. *Neuropharmacology*. 2016; 101:237-245.

Higgins GA, Silenieks LB, Rossmann A, Rizos Z, Noble K, Soko AD, Fletcher PJ. The 5-HT2C receptor agonist lorcaserin reduces nicotine self-administration, discrimination, and reinstatement: relationship to feeding behavior and impulse control. *Neuropsychopharmacology*. 2012; 37:1177-1191.

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

Litten RZ, Ryan ML, Fertig JB, Falk DE, Johnson BA, *et al.* A double-blind, placebo-controlled trial assessing the efficacy of varenicline tartrate for alcohol dependence. *J Addict Med*. 2013; 7:277-286.

Lorcaserin Clinical Pharmacology and Biopharmaceutics Review(s). Arena Pharmaceuticals Inc. 2012. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/022529Orig1s000ClinPharmR.pdf

McCann DJ, Petry NM, Bresell A, Isacsson E, Wilson E, Alexander RC. Medication nonadherence, "professional subjects," and apparent placebo responders: Overlapping challenges for medications development. *J Clin Psychopharmacol*. 2015; 35:566-573.

Mezinskis JP, Honos-Webb L, Kropp F, Somoza E. The measurement of craving. J Addict Dis. 2001; 20(3):67-85.

Negus SS, Mello NK, Blough BE, Baumann MH, Rothman RB. Monoamine releasers with varying selectivity for dopamine/norepinephrine versus serotonin release as candidate "agonist" medications for cocaine dependence: studies in assays of cocaine discrimination and cocaine self-administration in rhesus monkeys. *J Pharmacol Exp Ther*. 2007; 320:627-36.

Nguyen CT, Zhou S, Shanahan W, Fain R. Lorcaserin in Obese and Overweight Patients Taking Prohibited Serotonergic Agents: A Retrospective Analysis. *Clinical Therapeutics*. 2016; 38:1498-1509.

Oquendo MA, Halberstam B, Mann JJ. Risk factors for suicidal behavior: The utility and limitations of research instruments. In: First MB, ed. *Standardized Evaluation in Clinical Practice*. Washington, DC: American Psychiatric Publishing; 2003: 103-130.

Rezvani AH, Cauley MC, Levin ED. Lorcaserin, a selective 5-HT2C receptor agonist, decreases alcohol intake in female alcohol preferring rats. *Pharmacol Biochem Behav*. 2014; 125:8-14.

Roth BL. Drugs and valvular heart disease. *New Engl J Med*. 2007; 356:6-9.

Shanahan, WR; Rose, JE; Glicklich, A; Stubbe S; Sanchez-Kam , M. Lorcaserin for smoking cessation and associated weight gain: A randomized 12-week clinical trial. *Nicotine Tob Res. 2016;* ntw301. doi: 10.1093/ntr/ntw301

Shiovitz TM, Wilcox CS, Gevorgyan L, Shawkat A. CNS sites cooperate to detect duplicate subjects with a clinical trial subject registry. *Innov Clin Neurosci*. 2013; 10:17-21

Somoza EC, Winship D, Gorodetzky CW, Lewis D, Ciraulo DA, *et al.* A multisite, double-blind, placebo-controlled clinical trial to evaluate the safety and efficacy of vigabatrin for treating cocaine dependence. *JAMA Psychiatry*. 2013; 70:630-647.

Thomsen WJ, Grottick AJ, Menzaghi F, Reyes-Saldana HH, Espitia S, Yuskin D, Whelan K, Martin M, Morgan M, Chen WW, Al-Shamma HH, Smith B, Chalmers D, Behan D. Lorcaserin, a novel selective human 5-hydroxytryptamine2C agonist: in vitro and in vivo pharmacological characterization. *J Pharmacol Exp Ther*. 2008; 325:577-587.

Usmani KA, Chen WG, Sadeque AJ. Identification of human cytochrome P450 and flavin-containing monooxygenase enzymes involved in the metabolism of lorcaserin, a novel selective human 5-hydroxytryptamine 2C agonist. *Drug Metab Dispos*. 2012; 40:761-771.

APPENDIX I: *Instructions for Evaluating and Reporting Adverse Events and Serious Adverse Events*

A. GENERAL INSTRUCTIONS

1. Adverse Events (AEs) will be assessed and reviewed at each clinic visit by a medically trained study staff member.

2. Record AEs beginning on the day of informed consent.

3. Report the severity of the event following the guidance in Section B below.

4. Report the relatedness of the event to the study drug administration according to the guidance in Section C.

B. DEFINITIONS

B-1. Adverse Event (AE)

An adverse event is any undesirable experience associated with the use of a medical product in a patient.

B-2. Serious Adverse Event (SAE)

A 'serious' AE is defined as any untoward medical occurrence that:

- Results in death
- Is life-threatening - The patient was at substantial risk of dying at the time of the adverse event, or use or continued use of the device or other medical product might have resulted in the death of the patient
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Required intervention to prevent permanent impairment or damage (Devices)
- Is an important medical event - The event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes.

B-3. Severity of Events

Mild: Awareness of symptom, but easily tolerated.

Moderate: Discomfort enough to cause interference with usual activity.

Severe: Incapacitating with inability to work or do usual activity.

B-4. Unexpected Adverse Event

An adverse event is considered "unexpected" if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed; or, if the Investigator's Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended).

C. DEFINITIONS – RELATEDNESS OF EVENTS

The study physician is responsible for defining, in his/her best judgment, the relationship of the AE/SAE to the study drug. The degree of certainty for which the AE/SAE is attributed to the study drug or alternative causes (e.g., natural history of the underlying disease, concomitant therapies, etc.) should be determined by how well the experience can be understood in terms of one or more of the following:

- ***Exposure:*** Is there evidence that the subject was actually exposed to the drug/compliance marker?

- ***Timing of the study drug:*** Did the AE/SAE follow in a reasonable temporal sequence from administration of the drug test?

- ***Consistency with study drug profile:*** Known pharmacology and toxicology of the study drug in animals and man; reaction of similar nature having been previously described with the study drug.

- ***Alternative explanations*** for the adverse event such as concomitant medications, concurrent illness, non-medicinal therapies, diagnostic tests, procedures or other confounding findings.

- ***Response to discontinuation*** of the study drug.

Terms and definitions to be used in assessing the study drug relationship to the AE/SAE are:

- *Definitely Related*: The adverse event is clearly related to the investigational agent/procedure – i.e., an event that follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the suspected intervention, that is confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by the known characteristics of the subject's clinical state.
- *Possibly Related:* An adverse event that follows a reasonable temporal sequence from administration of the study intervention follows a known or expected response pattern to the suspected intervention, but that could readily have been produced by a number of other factors.
- *Not Related:* The adverse event is clearly not related to the investigational agent/procedure – i.e., another cause of the event is most plausible; and/or a clinically

plausible temporal sequence is inconsistent with the onset of the event and the study intervention and/or a causal relationship is considered biologically implausible.

D. SPECIFIC INSTRUCTIONS – LABORATORY/ECG ADVERSE EVENT

A laboratory or ECG AE is any clinically significant worsening in a test variable that occurs during the course of the study, whether or not considered to be attributable to the study drug. For each such change, provide the information requested on date of test, severity, likelihood of a relationship to study drug, change in study drug dosage due to the AE, and treatment required.

All laboratory AEs should be specified as an increased or decreased test result (e.g., "increased glucose", "decreased potassium") or as a term that implies an abnormality (e.g., hypercalcemia, azotemia, hypokalemia, or bradycardia). Any abnormal laboratory value that is considered not clinically significant will be recorded as such on the clinical laboratory report along with a comment providing justification for that determination.

E. SPECIFIC INSTRUCTIONS – PREGNANCY

1. Record results of pregnancy test on subject's source documentation and enter the results on the electronic case report form (eCRF).
2. Document the pregnancy as an adverse event in the subject's source documentation and enter the adverse event on the electronic case report form (eCRF).
3. Primary responsibility will be to follow the pregnancy through until its completion. There are several possible outcomes:
    a. The mother chooses to have an abortion. In that case NIDA will report to FDA that the pregnancy was intentionally terminated by the mother and that there is no further follow-up required. NIDA will also include this in the final clinical study report.
    b. The mother experiences a spontaneous abortion. In that case NIDA will report to FDA that the pregnancy resulted in a spontaneous abortion and it will be recorded as an SAE and at least possibly related. At that point there is no further follow-up required. NIDA will also include this in the final clinical study report and in the SAE listings.
    c. The baby goes to term and is born healthy. In that case NIDA will report to FDA that the birth was without issue and that there is no further follow-up required. NIDA will obtain the hospital record of the birth, if possible, and also include it in the final clinical study report.
    d. The baby goes to term and is born with a congenital anomaly. In that case NIDA will report to FDA that the pregnancy resulted in a congenital anomaly and it will be recorded as an SAE and at least possibly related. At that point there may be further follow-up required depending upon what the anomaly was. NIDA will obtain the hospital record of the birth, if possible, and also include it in the final clinical study report and in the SAE listings.
4. NIDA will submit an Information Amendment to the IND reporting any pregnancy and follow-up thereafter.

F. THE HUNTER SEROTONIN SYNDROME (DIAGNOSTIC CRITERIA)

Subjects that meet one of the following conditions to be considered for serotonin syndrome:

- Spontaneous clonus
- Inducible clonus PLUS agitation or diaphoresis
- Ocular clonus PLUS agitation or diaphoresis
- Tremor PLUS hyperreflexia
- Hypertonia PLUS temperature above 38ºC PLUS ocular clonus or inducible clonus

G. SERIOUS ADVERSE EVENT AND UNEXPECTED ADVERSE EVENT REPORTING

24 hour Reporting Requirements

Any SAEs due to any cause, that occur during the course of this investigation, whether or not related to the investigational agent, must be reported to the Study Medical Monitor and the NIDA Project Manager within 24-hours by phone or email with receipt confirmation to these two individuals is required:

NIDA Medical Monitor: Tanya Ramey, M.D., Ph.D. Tel: 301-827-5944, email: tanya.ramey@nih.gov

NIDA Project Manager: Liza Zeinert, M.A., Tel: 301-443-1138, email: liza.zeinert@nih.gov

The following information must be provided with the initial report of an SAE or unexpected AE:

- Name of person reporting the SAE/unexpected AE
- Subject's ID number & ALPHA Code
- Name of the SI and institution
- Date the subject signed informed consent
- Date of first dose of study drug
- Description of the SAE/unexpected AE
- Date and time of onset
- Date/time of administration of last dose of study drug prior to the SAE/unexpected AE
- Severity of the SAE/unexpected AE
- SI's assessment of the relationship of the SAE/unexpected AE to study drug (related, possibly related, probably related, unlikely related, not related)
- Any action taken with the study drug, alteration to protocol defined schedule, diagnostics, and treatments secondary to the SAE/unexpected AE.

3-day Supporting Documentation Requirements

Documentation for all SAEs/unexpected AEs must be received by the NIDA Medical Monitor and the NIDA Project Manager within 3 days of reporting the event. Required documents that

must be submitted include the following:

- SAE CRF

Additional documentation may include:

- Copies of source documents pertinent to the event (lab reports, ECG tracings, medical chart notes, etc.)
- Any other relevant information necessary to facilitate the SI's judgment regarding the SAE's relatedness to the severity OR by request of the Medical Monitor/Alternate

These documents may be submitted by facsimile, as email attachments, or via overnight courier. Any personally identifiable information (i.e., names, birthdates, etc.) should be removed/obscured before sending. Subject ID and ALPHA-NUMERIC code are allowable.

Follow-Up of All Adverse Events/Serious Adverse Events

All adverse medical events must be followed until they are resolved, or until all attempts to determine the resolution of the AE/SAE are exhausted. This may require an extended hospitalization period or a change in status from outpatient to inpatient. All treatments, outcomes and information regarding whether or not the subject was referred to their Primary Care Provider for additional follow-up must be recorded in the source document. All serious and unexpected adverse events occurring at any time (up to and including the Week 16 visit) must be reported. All follow-up Week 16 AEs will be recorded and followed to resolution, only if they are serious, or if the study physician assesses them to be clinically significant.

The SI is required to provide the Medical Monitor and the NIDA Project Manager with all relevant follow-up information necessary to facilitate a thorough understanding of the event and judgment regarding the relationship to the study drug.

Reporting to the FDA

The IND sponsor is required to report SAEs to the FDA:

- in 7 days if the SAE is unexpected (or, if expected, unusually serious or rarely seen), life-threatening or lethal, and at least possibly related to the study drug, with a follow-up written report in 8 days;

- in 15 days if the SAE is unexpected (or, if expected, unusually serious or rarely seen), but not immediately life-threatening; and

- in an annual report in all other cases.

APPENDIX II: *Procedure for Applying for a Certificate of Confidentiality*

The only people who will know the identity of the subjects are members of the research team and, if appropriate the physicians and nurses. No information about the subjects, or provided by the subjects during the research, will be disclosed to others without the subjects' written permission, except:

- if necessary to protect subjects' rights or welfare

When the results of the research are published or discussed in conferences, no information will be included that would reveal subjects' identity. Authorized representatives of the FDA and NIDA study monitors may need to review records of individual subjects. As a result, they may know subjects' names, but they are bound by rules of confidentiality not to reveal their identity to others. The results of this study including laboratory results and clinical information collected during this study will be submitted to the FDA and may be used for research purposes. The results of this study may be published but will not personally identify any subjects. All records will be kept in locked storage locations that will be accessible only to authorized study personnel.

NIDA will apply for a Certificate of Confidentiality for all participating sites.

This Certificate of Confidentiality helps researchers protect the privacy of subjects in health research projects against compulsory legal demands (e.g., court orders and subpoenas) that seek the names or other identifying characteristics of research subjects. The certificate was developed to protect against the involuntary release of personally identified research information of a sensitive nature sought through any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. This authority was granted under the Comprehensive Drug Abuse Prevention and Control Act of 1970, Public Law No. 91-513, Section 3(a).

This certificate is necessary for SIs to avoid being required to involuntarily disclose personally identifiable research information about individual study subjects. Under this statute:

"The Secretary [of the Department of Health and Human Services] may authorize persons engaged in biomedical, behavioral, clinical, or other research (including research on mental health, and on the use and effect of alcohol and other psychoactive drugs) to protect the privacy of individuals who are the p subject of such research by withholding from all persons not connected with the conduct of such research the names or other identifying characteristics of such individuals. Persons so authorized to protect the privacy of such individuals may not be compelled in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings to identify such individuals" (Public Health Service Act 301 (d), 42 U. S. C. 241 (d), as amended by Public Law No. 100-607, Section 163 (November 4, 1988))."

Accordingly, this special privacy protection can be granted only to research (i.e., a systematic investigation, designed to develop or contribute to generalizable knowledge). It is granted only when the research is of a sensitive nature where the protection is judged necessary to achieve the research objectives.

The study subjects should be informed that a Certificate is in effect, and be given a fair and clear explanation of the protection it affords, including the limitations and exceptions. This information will be included in the informed consent. Please see below some suggested wording: "We have received a Certificate of Confidentiality from the National Institute on Drug Abuse, which will help us protect your privacy. The Certificate protects against the involuntary release of information about your participation in this study. The researchers involved in this project cannot be forced to disclose your identity or your participation in this study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, you or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if you or your guardian requests disclosure of your participation, the researchers will provide research data. The Certificate does not protect against that voluntary disclosure.

Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or a Food and Drug Administration request under the Food, Drug and Cosmetics Act."