University of California, San Francisco
Clinical Research Protocol
The TLC Study: Treatment with Lorcaserin for Cocaine Use

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Version Date:	7/22/2017
Investigational Product:	BELVIQ® XR (lorcaserin)
IND Number:	134951
Development Phase:	Phase II
Sponsor:	Glenn-Milo Santos, PhD, MPH University of California at San Francisco Department of Community Health Systems School of Nursing 2 Koret Way, N505 San Francisco, California 94143-0608
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Approval:

07-22-2017

PI or Sponsor Signature (Name and Title) *Date*

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PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: 17-21502

Protocol Title: **The TLC Study: Treatment with Lorcaserin for Cocaine Use**

Protocol Date: TBD

07-22-2017

Investigator Signature *Date*

Glenn-Milo Santos, Associate Professor

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LIST OF ABBREVIATIONS

ACASI	Audio Computer Assisted Survey Instrument
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BART	Balloon Analogue Risk Task – impulsivity test
BMI	Body Mass Index
BUN	blood urea nitrogen
CBC	Complete blood count
CBO	Community based organization
CCG	Community Consulting Group
CFR	Code of Federal Regulations
CRF	case report form
CPHR	Center for public health research
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
DSM-IV	Diagnostic and Statistical Manual for Mental disorders
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEE	generalized estimating equations
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	Human Immunodeficiency Virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MM	Medical Management counseling
MSM	Men who have sex with men
NIAAA	National Institute on Alcohol Abuse and Alcoholism
PrEP	pre-exposure prophylaxis
PI	Principal Investigator
SAE	serious adverse experience
SAMHSA	Substance Abuse and Mental Health Services Administration
SCID	Structural clinical interview for DSM disorders
SFDPH	San Francisco Department of Public Health
SMS	Text message
TLFB	Timeline follow-back

PROTOCOL SYNOPSIS

TITLE	The TLC Study: Treatment with Lorcaserin for Cocaine Use
SPONSOR	Glenn-Milo Santos
FUNDING ORGANIZATION	NIDA
NUMBER OF SITES	1
RATIONALE	Lorcaserin's mechanism of action as a potent 5-HT_{2C}R selective agonist may have inhibitory control on DA activity, which may decrease the positive rewarding effects of cocaine and lead to reductions in use, while 5-HT_{2C}R activation itself may lead to reductions in likelihood of relapse. There are no pharmacological agents available to reduce cocaine use disorder.
STUDY DESIGN	This study will enroll 45 actively using Men who have sex with men with cocaine use disorders in a placebo-controlled 12-week trial. Individuals will be randomly assigned (2:1) to receive 12 weeks of lorcaserin 20mg (n=30) or placebo (n=15) to be taken daily in this double-blind trial.
PRIMARY OBJECTIVE	To establish the feasibility, tolerability, acceptability and adherence of enrolling and retaining 45 adults with cocaine use disorders in a 12-week randomized, double-blind study of lorcaserin versus placebo.
SECONDARY OBJECTIVES	To evaluate the ***preliminary efficacy*** of lorcaserin versus placebo to reduce cocaine use and HIV-related sexual risk behaviors among MSM with cocaine use disorders, as determined by the proportion of cocaine-positivity from twice weekly urine samples and self-reported sexual behaviors.
NUMBER OF SUBJECTS	45
SUBJECT SELECTION CRITERIA	Inclusion Criteria: 1) Male gender; 2) self-reported anal intercourse with men in the prior six months while under the influence of cocaine; 3) cocaine use disorder by DSM-V SCID criteria; 4) current cocaine use confirmed by urinalysis and cocaine use at least 1 day in the past 30 days; 5) HIV-negative by rapid test or HIV-positive with medical record of HIV infection; 6) no current acute illnesses requiring prolonged medical care; 7) no chronic illnesses that are likely to progress clinically during trial; 8) able and willing to provide informed consent and adhere to visit schedule; 9) age 18–65 years; 10) baseline CBC, total protein, albumin, glucose, alkaline phosphatase, creatinine, BUN, and electrolytes without clinically significant abnormalities as determined by study clinician in conjunction with symptoms, physical exam, and medical history. Exclusion Criteria: 1) Any psychiatric condition (e.g., depression with suicidal ideation, schizophrenia) or medical condition that would preclude safe study participation; 2) HIV-positive test result at screening visit but previously unaware of HIV infection (i.e., newly diagnosed with HIV infection at screening; those with a medical record of HIV infection are

	eligible); 3) any moderate to severe alcohol or substance use disorders (other than cocaine use disorders), according to DSM-V criteria; 4) known allergy or previous adverse reaction to lorcaserin; 5) current CD4 count < 200 cells/mm3 ;6) severe liver impairment (Child-Pugh score > 9); 7) severely impaired renal function (creatinine clearance £ 30 ml/min); 8) use of medications that affect the serotonergic neurotransmitter system (e.g., selective serotonin reuptake inhibitors (SSRIs), selective serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs)); 9) predisposition to priapism; 10) currently participating in another longitudinal intervention research study; 11) body mass index (BMI) ≥ 30 with desire to use weight management medication, *or* BMI > 40;12) BMI < 15; 13) anticipated use of agents that are associated with valvulopathy and/or pulmonary hypertension
TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	BELVIQ® XR (lorcaserin) 20mg., manufactured by: Arena Pharmaceuticals: Untere Brühlstrasse 4, 4800 Zofingen, Switzerland Product will be administered orally each day for 12 weeks length of time.
CONTROL PRODUCT, DOSE AND ROUTE OF ADMINISTRATION	Placebo, 20 mg. Product will be administered orally each day for 12 weeks length of time.
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Subjects will be on study for up to 12 weeks **Screening:** up to 4 weeks **Treatment:** 12 weeks The total duration of the study is expected to be 16 weeks or 4 months. 1 month for subject recruitment and 3 months for treatment phase.
CONCOMMITANT MEDICATIONS	**Allowed:** standard treatment **Prohibited:** Serotonin reuptake inhibitors (SSRIs), selective serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs)
EFFICACY EVALUATIONS	
PRIMARY ENDPOINT	In the overall sample of 45, proportions will be estimated with margins of sampling error (MSEs; i.e., half widths of 95% confidence intervals) of <=14.4 percentage points, and means with MSEs of 0.30 standard deviations, both typical for a small pilot study. While the study will only be powered to detect large between-group differences in process measures, it will provide warning of potential problems.
SECONDARY ENDPOINTS	We will also classify AEs as any AE that results in stopping study medication, specific common AEs (>2% in both groups), AEs for general

	organ system categories, and AEs potentially related to study drug. The probability of observing at least one AE with population incidence of 1, 2, and 5% in the active arm will be 26, 45, and 70% with 2:1 randomization, respectively.
SAFETY EVALUATIONS	Change in clinical safety labs from baseline to Week 12 Incidence of adverse events
PLANNED INTERIM ANALYSES	No planned interim analyses
STATISTICS **Primary Analysis Plan**	To establish the feasibility of enrolling and retaining 45 MSM with cocaine use disorders in a 12-week 2:1 randomized, double-blind study of lorcaserin versus placebo. We will calculate the following feasibility measures: 1) proportion of those eligible among those screened; 2) proportion enrolled among those eligible; and 3) study completion rate. Process measures (e.g., visit length, counseling session completion) and reactions to study procedures will also be collected and reported. Between-group differences will be assessed using Fisher's exact and Wilcoxon rank sum tests. We will also calculate Kaplan-Meier curves for time to dropout, by group, and test for differences using the log-rank test. Precision: In the overall sample of 45, proportions will be estimated with margins of sampling error (MSEs; i.e., half widths of 95% confidence intervals) of ≤14.4 percentage points, and means with MSEs of 0.30 standard deviations, both typical for a small pilot study. While the study will only be powered to detect large between-group differences in process measures, it will provide warning of potential problems. To explore the tolerability of lorcaserin versus placebo among MSM with cocaine use disorders, as determined by the number of adverse clinical events in the cocaine and placebo arms. We will compute the proportions of those experiencing adverse events, both overall and by type. Adverse clinical events, AEs and SAEs, and other binary safety outcomes will be presented as percent of participants that experience the safety outcome by treatment assignment. We will also classify AEs as any AE that results in stopping study medication, specific common AEs (>2% in both groups), AEs for general organ system categories, and AEs potentially related to study drug. The probability of observing at least one AE with population incidence of 1, 2, and 5% in the active arm will be 26, 45, and 70% with 2:1 randomization, respectively. To describe the acceptability and adherence for lorcaserin versus placebo MSM with cocaine use disorders. We will measure the acceptability of lorcaserin compared to placebo among participants through a qualitative interview and survey evaluations of the study procedures, study drug characteristics, and dosing schedule at the final visit. We will determine medication adherence via MEMs Cap data, pill count, and self-report from TLFB and SMS texts. Measures of interest will include percent of doses taken, patterns of adherence, and time to stopping medication. We will assess how these measures of adherence track with patterns of cocaine use as measured in TLFB and urinalysis. Concordance of the adherence measures will be examined using weighted Kappa and correlations.

Rationale for Number of Subjects	In the overall sample of 45, proportions will be estimated with margins of sampling error (MSEs; i.e., half widths of 95% confidence intervals) of ≤14.4 percentage points, and means with MSEs of 0.30 standard deviations, both typical for a small pilot study. While the study will only be powered to detect large between-group differences in process measures, it will provide warning of potential problems.

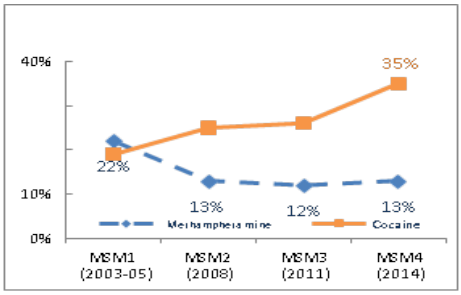
1. BACKGROUND

Lorcaserin, a novel selective serotonin (5-HT) receptor agonist, is a promising agent to treat cocaine use disorders. Cocaine use increases dopamine (DA) levels, the neurochemical responsible for the reinforcing effects of the drug, and there is compelling data suggesting that the DA system's activity is modulated by the central 5-HT systems.[69-71]

In particular, the 5-HT_{2C} receptor (5-HT_{2C}R) has been identified as the primary 5-HT receptor subtype that inhibits the DA system's activity.[71] 5-HT_{2C}R agonists have reduced dopamine release in the nucleus accumbens (NAcc) and frontal neurocortex.69,71 Conversely, increased DA release in the NAcc result from the blockade of 5-HT_{2C}R.[72]

OVERVIEW OF CLINICAL STUDIES

Cocaine use in the US is an *unrelenting public health problem* with serious negative medical, societal, and economic impacts.[1-3] The US is the world's largest consumer of cocaine, accounting for nearly 36% of the total global consumption.[4,5] In both powder and rock (i.e., "crack") form, cocaine is an addictive psychostimulant; it is estimated that up to one in six cocaine users may develop dependence/moderate-to-severe use disorders.[2,6,7] Cocaine is the leading cause of illicit substance–related emergency department visits in the US[3] and it is associated with direct cardiac toxicity, myocardial infarctions and, sudden cardiac death.[9-13] **Cocaine use is a** significant decrease (test for trend p<0.001)[17,18] in methamphetamine use among San Francisco MSM (from 22% to 13%). San Francisco community-based surveys observed similar trends: cocaine use among MSM increased from 9.6% in 2009 to 20.4% in 2013.[19,20] Of the estimated 19,657 illicit psychostimulant- using MSM in San Francisco, 81.3% are cocaine users.[16] **MSM remain disproportionately impacted by HIV**—despite sizable efforts to stem the epidemic in this group—accounting for 61% and 90% of new infections in the US and San Francisco, respectively.[21-24] It is imperative to develop more evidence-based HIV interventions for MSM; the National HIV/AIDS Strategy specifically calls for additional interventions for this population.[25] **Cocaine use is associated with HIV-related sexual risk behaviors in MSM.** In NHBS, 54% of cocaine users reported having sex while under the influence of cocaine.[14] The acute pharmacological effects of cocaine (e.g., altered cognition, impairment of judgment, and increased sexual desire and confidence) have been attributed to the association between cocaine use and sexual risk behaviors.[26-30] Moreover, a myriad of psychosocial factors (e.g., cognitive escape, impulsivity, and expectancies) are thought to account for the link between cocaine use and sexual risks.[31-34] Furthermore, the bar, club, and circuit-party (weekend-long dance events) settings frequented by MSM are environments conducive to both cocaine use and meeting multiple sex partners.[35-37] Indeed, cocaine use is independently associated with unprotected anal intercourse, multiple partners, increased duration of sex, anonymous partners, sex in a public sex venue, and exchanging money or drugs for sex.[38-43] In the Project ECHO study, a large San Francisco study of substance-using MSM conducted by the proposed research team, *increased frequency of cocaine use* was associated with greater HIV-related sexual risk; those who reported episodic use (less than weekly) and those with weekly or greater cocaine use had 1.86- and 3.13-fold greater odds of HIV serodiscordant unprotected anal intercourse,



respectively, compared to non-users.[44] This dose-dependent relationship is consistent with findings from a probability sample of HIV-negative MSM; those with cocaine dependence were more likely to have high-risk sexual behaviors than their non-dependent counterparts.[41]

Cocaine use has been significantly associated with new HIV infections.[45-47] In the EXPLORE longitudinal study of 4,295 HIV-negative MSM from six cities, cocaine use was associated with a 2.24-fold greater hazard for HIV seroconversion.[46] Similarly, in the Multicenter AIDS Cohort Study, use of cocaine or other stimulants, alone or in combination with other drugs, was attributed to 37.3% of the new HIV infections in the study.[45] In a probability sample of San Francisco MSM, cocaine and other stimulant use was also 2.5-fold more common among MSM living with HIV.[48] Among HIV-positive individuals, cocaine use was associated with poor adherence to antiretroviral treatment (ART), HIV disease progression, lower CD4 count, and higher mortality.[49-52] Weekly cocaine use was associated with higher HIV viral load, even after controlling for ART adherence,[53] and in *in vitro* studies, cocaine enhanced HIV viral replication.[54,55] Poor ART adherence and higher HIV viral load among cocaine users may potentiate greater risk of HIV transmission.[56]

Innovative treatments for cocaine use disorders are needed for MSM.[57] Because cocaine use is common among MSM and is associated with high-risk sexual behavior and HIV infection, interventions that can reduce cocaine use are likely to have an impact on reducing the transmission of HIV.[28] Current prevention approaches to cocaine use for MSM are therapy and substance use treatment programs. However, most substance-using MSM do not access drug treatment, reinforcing the need to develop interventions outside of treatment settings.[44,58,59] Furthermore, while some behavioral interventions for substance-using MSM report reductions in both substance use and HIV risk behaviors,[60,61] behavioral interventions alone have limited efficacy and may benefit from adjuvant pharmacologic agents.[57,62] However, **there are no FDA-approved medications for cocaine use disorders, which severely limits treatment options.**[63,64] Pharmacologic approaches have been successful in treating nicotine, alcohol, and heroin dependence.[65-67] **Despite the link between cocaine use and HIV risk, the use of pharmacologic interventions to reduce cocaine-related sexual risk among MSM remains underexplored.** The absence of published studies on efficacious interventions to reduce cocaine- related sexual risk behaviors among MSM who have no desire to abstain from cocaine ***presents a major gap in the field of substance use research and HIV prevention.*** Pharmacotherapy for methamphetamine dependence in MSM has shown that reductions in substance use can result in parallel reductions in methamphetamine-related sexual risk behaviors among MSM not seeking treatment.[68] Pharmacotherapy for cocaine use may lead to an analogous parallel reduction in cocaine-related sexual risks.

Lorcaserin, a novel selective serotonin (5-HT) receptor agonist, is a promising agent to treat cocaine use disorders. Cocaine use increases dopamine (DA) levels, the neurochemical responsible for the reinforcing effects of the drug, and there is compelling data suggesting that the DA system's activity is modulated by the central 5-HT systems.[69-71] In particular, the 5-HT_{2C} receptor (5-HT_{2C}R) has been identified as the primary 5-HT receptor subtype that inhibits the DA system's activity.[71] 5-HT_{2C}R agonists have reduced dopamine release in the nucleus accumbens (NAcc) and frontal neurocortex.[69,71] Conversely, increased DA release in the NAcc result from the blockade of 5-HT_{2C}R.[72] Furthermore,

genetic variations in the 5-HT_{2C}R and its functional status have been associated with vulnerability to cocaine cue reactivity—a strong predictor of relapse—and relapse- like behaviors in cocaine dependent rodents and humans.[73,74] *These data lend support to the use of agents that selectively activate the 5-HT_{2C}R.* **We postulate that lorcaserin's mechanism of action as a potent 5-HT_{2C}R selective agonist will have inhibitory control on DA activity, which may decrease the positive rewarding effects of cocaine and lead to reductions in use, while 5-HT_{2C}R activation itself may lead to reductions in likelihood of relapse.**

Preclinical data support the potential of lorcaserin in reducing cocaine use.[70,75-85] Lorcaserin is 18- and 120-fold more selective toward the 5-HT_{2C}R compared to 5-HT_{2A} and 5-HT_{2B} receptors, respectively.[86] 5-HT_{2C}R selective agonists, including lorcaserin, have been associated with reductions in cocaine self-administration in mice[87,88] and non-human primates.[84,89] Consistent reductions in cue- and cocaine-primed drug seeking have resulted from use of 5-HT_{2C}R selective agonists.[79,87,90,91] Furthermore, 5-HT_{2C}R selective agonists have attenuated acute cocaine-induced activity and the development of long-term cocaine-induced locomotor sensitization.[78] Reinstatement studies to model the relapse processes have also found that 5-HT_{2C}R selective agonists reduced cocaine seeking behavior, again in both rodents[79,87,91-94] and primates.[84]

Data from other preclinical and clinical studies also support lorcaserin's potential to treat drug disorders. For example, lorcaserin has been shown to reduce nicotine self-administration, [95] as well as nicotine discrimination, and cue-induced reinstatement of nicotine seeking.[96] Currently, another team is evaluating lorcaserin in a placebo-controlled Phase 2, 12-week trial on smoking cessation (ClinicalTrials.gov #: NCT02044874).

2. STUDY RATIONALE

2.1 Study Overview:

This study will represent the ***first*** Phase 2 randomized outpatient clinical trial to evaluate the potential of lorcaserin to reduce cocaine use among actively using participants with cocaine use disorders. Although there is an ongoing human laboratory study of lorcaserin's effects on craving and intravenous cocaine self-administration during overnight confinements at a medical center (ClinicalTrials.gov #: NCT02680288), our proposed study will provide distinct yet complementary data on the viability of lorcaserin to reduce cocaine. Our study is unique because it involves the outpatient treatment and evaluation of lorcaserin to reduce cocaine use and cocaine- associated sexual risk behaviors among men who have sex with men ***over a 12-week follow-up period***. Hence, data from this pilot can inform the sample size required for a larger clinical efficacy trial of lorcaserin for outpatient treatment of cocaine use. Additionally, this study will determine if lorcaserin is a feasible, tolerable, and acceptable option for cocaine outpatient treatment.

2.2 Risk / Benefit Assessment

Lorcaserin is an FDA-approved medication that is well-tolerated with relatively few adverse events (AEs).[103] Three Phase 3 trials (cumulative N=7789) that evaluated lorcaserin's treatment effect on obesity have established its safety among patients with and without diabetes.[104-107] The most

common reported side effects for lorcaserin include headaches, dizziness, fatigue, nausea, dry mouth, and constipation.[104-107] In these trials, 8.6% of individuals given lorcaserin discontinued treatment as a result of AEs, compared to 6.7% individuals given placebo.[104-107] Aside from pregnancy, there are no contraindications for lorcaserin.[104] Nevertheless, the safety and tolerability of lorcaserin among active cocaine users is unknown. **Lorcaserin has a low potential for abuse.**[108] The frequency of AEs associated with lorcaserin increases when taken above the therapeutic dose, which may limit abuse potential.[104,108] A double-blind randomized crossover study to test abuse liability found that lorcaserin was similar to placebo with respect to subjective liking, overall liking, and ratings on desire to take the drug again.[108] Exceeding the recommended lorcaserin dose levels (10 mg, twice daily) were associated with higher levels of known unpleasant side effects and subjective dislike, compared to placebo.[108] Thus, lorcaserin dose escalation would result in primarily negative subjective effects; these self-regulating properties will likely limit the medication's abuse liability.[70,10]

3. STUDY OBJECTIVES

3.1 Primary Objective

The primary objective is to evaluate the feasibility, tolerability, acceptability and adherence of lorcaserin versus placebo (2:1) to reduce cocaine use disorder among 45 MSM cocaine users over 12 week treatment period.

3.2 Secondary Objectives

To evaluate the ***preliminary efficacy*** of lorcaserin versus placebo to reduce cocaine use and

HIV-related sexual risk behaviors among MSM with cocaine use disorders, as determined by the proportion of cocaine-positivity from twice weekly urine samples and self-reported sexual behaviors over a 12 week treatment period.

4. STUDY DESIGN

4.1 Study Overview

The goal of the TLC Study is to evaluate the *feasibility, tolerability, acceptability* and *adherence* for lorcaserin among actively using, MSM with cocaine use disorders in a placebo-controlled 12-week trial. In a double-blind trial, 45 individuals will be randomly assigned (2:1) to receive 12 weeks of lorcaserin 20mg (n=30) or placebo (n=15), to be taken once a day.

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

The following treatment regimens will be used:

- Experimental treatment: BELVIQ® XR (lorcaserin). 20 mg.
- Placebo or Comparator – Placebo, 20 mg.

Total duration of subject participation will be twelve weeks. Total duration of the study is expected to be 16 weeks.

5. CRITERIA FOR EVALUATION

5.1 Primary Efficacy Endpoint

For the primary efficacy endpoint, we conservatively estimate that the sample will provide 80% power to detect reductions of 29 percentage points in the rate of cocaine urine positivity. The time course for which this endpoint will be assessed will be from baseline to 12 week end of treatment. We will also evaluate between-group differences on changes in: 1) any cocaine positive samples, defined as having a positive urine or sweat patch sample, over follow-up; 2) any cocaine positive samples or self-report of cocaine use in text messages; and 3) cocaine positivity from sweat samples only.

5.2 Secondary Efficacy Endpoints

For the secondary efficacy endpoint, to evaluate treatment effects on cocaine-associated sexual risk behaviors, GEE Poisson, binomial, and negative binomial models will be used to assess treatment effects on HIV sexual risk behaviors including high-risk sexual behaviors while under the influence of cocaine.

5.3 Safety Evaluation:

- Change in clinical laboratory findings
- Incidence of adverse events

6. SUBJECT SELECTION

6.1 Study Population

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

6.2 Inclusion Criteria

1) Male gender;
2) self-reported anal intercourse with men in the prior six months while under the influence of cocaine;
3) cocaine use disorder by DSM-V SCID criteria;
4) current cocaine use confirmed by urinalysis and cocaine use at least 1 day in the past 30 days;
5) HIV-negative by rapid test or HIV-positive with medical record of HIV infection;
6) no current acute illnesses requiring prolonged medical care;
7) no chronic illnesses that are likely to progress clinically during trial;
8) able and willing to provide informed consent and adhere to visit schedule;
9) age 18–65 years;
10) Baseline CBC, total protein, albumin, glucose, alkaline phosphatase, creatinine, BUN, and electrolytes without clinically significant abnormalities as determined by study clinician in conjunction with symptoms, physical exam, and medical history.
11) Written informed consent (and assent when applicable) obtained from subject or subject's legal representative and ability for subject to comply with the requirements of the study.

6.3 Exclusion Criteria

1) Any psychiatric condition (e.g., depression with suicidal ideation, schizophrenia) or medical condition that would preclude safe study participation;

2) HIV-positive test result at screening visit but previously unaware of HIV infection (i.e., newly diagnosed with HIV infection at screening; those with a medical record of HIV infection are eligible);

3) any moderate to severe alcohol or substance use disorders (other than cocaine use disorders), according to DSM-V criteria;

4) known allergy or previous adverse reaction to lorcaserin;

5) current CD4 count < 200 cells/mm3 ;

6) severe liver impairment (Child-Pugh score > 9);

7) severely impaired renal function (creatinine clearance £ 30 ml/min);

8) use of medications that affect the serotonergic neurotransmitter system (e.g., selective serotonin reuptake inhibitors (SSRIs), selective serotonin- norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs));

9) predisposition to priapism;

10) currently participating in another longitudinal intervention research study;

11) body mass index (BMI) ≥ 30 with desire to use weight management medication, *or* BMI > 40;

12) BMI < 15; 13) anticipated use of agents that are associated with valvulopathy and/or pulmonary hypertension

7. CONCURRENT MEDICATIONS

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

7.1 Allowed Medications and Treatments

Standard therapy is allowed except for treatments noted in the exclusion criteria described above and as noted in the prohibited medications section below.

7.2 Prohibited Medication and Treatments

No prohibited medication or treatment besides those in the exclusion criteria.

8. STUDY TREATMENTS

8.1 Method of Assigning Subjects to Treatment Groups

Up to 45 eligible participants will be randomly assigned to lorcaserin or placebo treatment groups in a 2:1 allocation ratio (lorcaserin and placebo), using the computer-generated randomization code for the study blocks. Assignment of two-thirds of participants to the lorcaserin arm was specifically chosen to improve our ability to detect adverse events in the active treatment arm, while preserving our ability to assess recruitment in a study in which randomization to placebo is likely. The study biostatistician, Dr.

Vittinghoff, will generate and provide the randomization code directly to the pharmacy. No study staff will have access to the code.

8.2 Blinding

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

Access to the randomization code will be strictly controlled.

Packaging and labeling of test and control treatments will be identical to maintain the blind.

The study blind will be broken on completion of the clinical study and after the study database has been locked.

During the study, the blind may be broken **only** in emergencies when knowledge of the patient's treatment group is necessary for further patient management. When possible, the Investigator should discuss the emergency with the Medical Director prior to unblinding.

8.3 Formulation of Test and Control Products

Drug Name and Active Ingredients

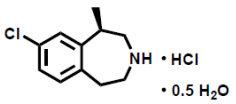
Name(s): BELVIQ® XR

Active Ingredients: lorcaserin hydrochloride

Pharmacological Class
BELVIQ® XR (lorcaserin hydrochloride) is a serotonin 2C receptor agonist for oral administration used for chronic weight management. [1]

Structural and Chemical Formula
Its chemical name is (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride hemihydrate. The empirical formula is C H Cl N·0.5H O, and the molecular weight of the hemihydrate form is 241.16 g/mol.[1]

The structural formula is:



Formulation of Dosage
This drug is in the form of an orange, film-coated, round, film-coated, 20 mg extended release tablet. The tablets are biconvex, debossed with "A" on one side and "20" on the other side

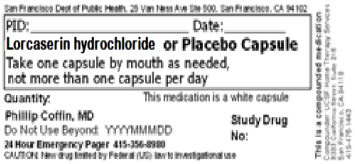
For this investigation, BELVIQ® XR will not be compounded. We will have Safeway Pharmacy (located at 6100 Hellyer Avenue, Suite 100 San Jose, CA 95138) encapsulate the BELVIQ® XR pill in whole form and create identical placebo capsules.[1]

Route of Administration

Packaging and Labeling

Safeway Compounding Pharmacy, 6100 Hellyer Ave Ste 100, San Jose, CA, 95138, is used to provide study drug. Each treatment bottle from the UCSF pharmacy was labeled with the study drug number, prescribing physician name (medical director), required FDA warning statement, emergency pager number, directions for participant use and storage, and expiration information. Each treatment bottle from Safeway pharmacy is labeled with the study drug number, principal investigator name, prescribing physician name (medical director), required FDA warning statement, emergency pager number, directions for participant use and storage, and lot and expiration information.

Sample Label:



8.4 Supply of Study Drug at the Site

The Safeway Compounding Pharmacy (San Jose, CA), which is currently supplying the study drug for our ongoing trials, will prepare and supply lorcaserin and placebo in identical-looking gel capsules to maintain blinding. The initial study drug shipment will be shipped after site activation (i.e., all required regulatory documentation has been completed). Subsequent study drug shipments will be made after site request for resupply.

8.4.1Dosage/Dosage Regimen

The recommended dose of BELVIQ® XR is one 20mg tablet administered orally once daily.[1]

8.4.2 Dispensing

Study medications will be dispensed by the study clinician (licensed medical practitioner) in treatment bottles that are labeled with the study drug number, principal investigator name, prescribing physician name (medical director), required FDA warning statement, emergency pager number, directions for participant use and storage, and lot and expiration information.

Further, at time of study drug dispensing, the study clinician will review with the participant how to take the study medication, possible side effects they may encounter, and how to access the study clinician by emergency pager if necessary. The study clinician will also answer any questions the participant might have.

8.4.3 Administration Instructions

Participants will receive training on dosing at enrollment. Participants will be given a week's supply of 20mg tablets at enrollment and at weekly visits; they will be instructed to only take 1 tablet every 24 hours. This optimal dose was informed by pharmacokinetic studies which estimated that 20mg of lorcaserin has a mean plasma half-life of 11 hours and once daily 20mg dosing of lorcaserin will lead to steady state within 3 days of treatment.[104]

8.4.4 Storage

Study drug should be stored by the study site at controlled room temperature, 15 to 30ºC (59 to 86ºF). If the temperature of study drug storage in the clinic/pharmacy exceeds or falls below this range, this should be reported to the Principal Investigator and captured as a deviation. Subjects will be instructed to store the medication in original packaging at room temperature according to the instructions outlined on the Drug Administration Instructions.

8.5 Study Drug Accountability

An accurate and current accounting of the dispensing and return of study drug for each subject will be maintained on an ongoing basis by a member of the study site staff. The number of study drug dispensed and returned by the subject will be recorded on the Investigational Drug Accountability Record.

8.6 Measures of Treatment Compliance

Study medications will be dispensed by the study clinician in MEMs cap dispensers with dosing instructions, date of dispensing, prescribing clinician, a 24-hour telephone study phone number for medical emergencies, and advisements against drug combinations. MEMS Caps will track adherence daily; each dispenser opening is recorded as a medication event sent to a remote database in real time

9. STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is diagrammed in Appendix 1.

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject or subject's legal representative. If appropriate, assent must also be obtained prior to conducting any study-related activities.

9.1 Clinical Assessments

Concomitant Medications

All concomitant medication and concurrent therapies will be documented at Baseline/Screening and at Month 1, Month 2 and Month 3 visits. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

Demographics

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

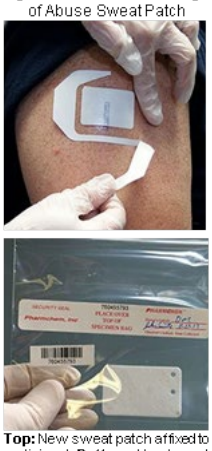
Balloon Analogue Risk Tast (BART)

To better understand the mechanism in which lorcaserin may reduce cocaine and cocaine-associated sexual risk behaviors, we will evaluate lorcaserin's effect on impulsivity through two validated measures of impulsivity: the state impulsivity scale (the STIMP)[183] and the Balloon Analogue Risk Task (BART).[182] We will evaluate changes in cocaine craving by arm using the visual analog scale for craving[187] and the Minnesota cocaine craving scale.[188]

Medical History

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

Figure 6: PharmChek Drugs of Abuse Sweat Patch



Top: New sweat patch affixed to participant. **Bottom:** Used sweat patch collected, placed in sterile pouch and labeled before being shipped for testing (adapted from[9]).

Physical Examination

A complete physical examination will be performed by the study clinician at Screening, Enrollment, Month 1, Month 2, and Month 3 visits. Qualified staff (MD, NP, RN, and PA) may complete the abbreviated physical exam at all other visits. New abnormal physical exam findings must be documented and will be followed by a physician or other qualified staff at the next scheduled visit.

Vital Signs

Body temperature, blood pressure, pulse and respirations will be performed after resting for 5 minutes at Enrollment, Month 1, Month 2 and Month 3 visits

Electrocardiogram (ECG):

The ECG will be administered during screening to assist in determination of participant eligibility and again at study exit (ie. week 12/Month 3) to assess safety at termination. The ECG tracings will be reviewed by a qualified medical clinician for accuracy at the site.

Urinalysis for Cocaine Use

Urinalysis for Cocaine Use**:** Urine samples will be collected once a week and tested for cocaine metabolites (benzoylecgonine) with EZ-SCREEN screening assays (MedTox Diagnostics, Inc., Burlington, NC). On average, cocaine is detectable in urine for approximately 72 hours. To detect use over weekends, when cocaine use is likely to be higher compared to the remainder of the week. Furthermore, the MedTox assays we will use for urine toxicology tests can also detect the following classes of substances: amphetamine, barbiturates, benzodiazepines, buprenorphine, methadone, methamphetamine, opiates, oxycodone, phencyclidine, propoxyphene and THC (cannabinoids).

Sweat Testing Using Perspiration Patches

To further enhance our ability to detect cocaine use, we will also utilize tamper evident sweat patches—PharmChek Drugs of Abuse Sweat Patch (PharmChem, Inc., Fort Worth, Texas)—that absorb perspiration 24 hours per day, for up to 10 days of continuous wear.[8] These patches will be tested for the presence of cocaine and cocaine metabolites, using testing procedures approved by the FDA since 1995.[8] Pharmchek patch enzyme immunoassays to detect cocaine in sweat have been found to have 94-95% sensitivity and 91-99% specificity rates, compared to gas chromatography-mass spectrometry.[166,167] At baseline visit, we will affix patches on all participants (see **Figure 6**). These patches have a semi-permeable membrane to allow oxygen, carbon dioxide and water vapor to pass through the patch, keeping the skin underneath sterile and healthy. At each weekly follow-up visit, we will replace the used patch worn since the prior visit and send those used patches for
cocaine testing to PharmChem's laboratories. These patches will retain cocaine and cocaine metabolites for any use during the period it was worn. Hence, we anticipate no gaps in the window of detection for cocaine use. *Extra replacement patches* will be provided to participants at weekly visits, in anticipation of the rare event that a patch falls off prematurely; participants will be instructed to use a replacement patch when needed. Used patches will be collected and tested weekly. In sensitivity analyses, we will impute cocaine-positive results for weeks in which multiple patches were used or when patches fell off.

HIV Testing and Counseling:

Participants will receive standard HIV risk reduction counseling[168] at screening and at month 3 visits with HIV rapid test and pooled viral load (HIV-negative participants) or CD4 and viral load testing (HIV-positive participants). Participants with positive rapid tests will have a confirmatory Western Blot assay performed and will receive HIV counseling and referrals to HIV service providers. Participants newly diagnosed with HIV at screen will be referred to community resources. Consistent with our prior trials, after obtaining the participant's permission, we will contact LINCS (Linkage, Integration, Navigation, and Comprehensive Services), a program of the San Francisco Department of Public Health (SFDPH), which provides coordinated comprehensive linkage to care, navigation and partner services for HIV-positive people living in San Francisco, particularly those who are newly HIV-positive and those who have fallen out of care.

Substance Use Counseling

In addition to HIV risk-reduction counseling done at screening and month 3 visits, all participants will receive weekly 30-minute substance use counseling. This standardized protocol is based on a manual-driven psychosocial treatment program using cognitive behavioral therapy,[169] motivational interviewing techniques,[170,171] and incorporating the Stages of Change Model.[172] This platform has been used to treat substance use and has high acceptability among substance-using MSM.[122,173-175] Counseling will be provided by trained study staff closely supervised by a licensed clinical psychologist in weekly quality assurance session.

Ecological Momentary Assessments (EMA) Messages:

As with our *Project iN* and *Better THAN* pharmacologic trials, participants will receive daily EMA texts to collect data on cocaine use patterns and medication compliance (see sample texts shown **Figure 5**).[163] Messages will use shorthand notations to maintain participant confidentiality. Participants will be trained on text messaging procedures and receive a reference guide during enrollment (sample guide from The Project iN Study included in the Appendix). Participants will be encouraged to regularly delete text messages and encrypt their phone with passwords for privacy. Our current studies already utilize this technology with great success and the majority of our participants prefer text appointment reminders. Moreover, text messaging has been highly acceptable in health and research settings.[110]

Medical Safety and AE Assessments:

Blood specimens will be collected via venipuncture using universal precautions. Medications taken in the 30 days prior to enrollment and while enrolled in the study will be documented. Because lorcaserin is not approved for cocaine use, we include *extensive safety parameters*, as is required by the Food and Drug Administration when testing a medication for a new indication. AEs and concomitant medications will be elicited from participants verbally and *documented weekly*. As previously noted, participants will also be given the 24-hour study phone number to communicate with the study clinician in the event of an emergency. Clinicians will follow the "Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events" (version 2.0) and UCSF IRB reporting guidelines.[179] Safety monitoring will include assessment, follow-up, and reporting of clinical and serious AEs, and abnormal lab results.

Addressing Medical/Social Needs:

While our study will not provide direct medical care, we may identify problems and will provide referrals, identifying community providers suited for individual participants (sample list of resources referrals). Clinical staff will be available as needed for clinical consultation.

Qualitative Interviews:

All participants will be scheduled for in-depth semi-structured interviews at their 12-week treatment visit. Qualitative experts, Drs. Wilson and Matheson will conduct interviews to explore participant treatment and study acceptability and assess medication adherence challenges. Semi-structured interview guides will begin with a discussion of motivations for treatment seeking and ask about the participant's history of drug use and treatment programs. The guide will then assess overall experiences as part of the study (e.g., frequency of study visits, frequency of medication dosing, appraisal of study activities and staff, study location). Participants who have experience with pharmacologic interventions for substance use treatment will be asked to compare their experiences

Adverse Events

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

9.2 Clinical Laboratory Measurements

Hematology

Blood will be obtained and sent to each site's clinical hematology lab for a complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count, white blood cell differential, and platelet count)

Blood Chemistry Profile

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

Pregnancy Test

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

Urinalysis

Urine will be obtained and sent to each site's clinical laboratory for determination of cocaine metabolites (benzoylecgonine). On average, cocaine is detectable in urine for approximately 72 hours.

10. EVALUATIONS BY VISIT

10.1 VISIT 1 (SCREENING VISIT—WEEK 1)

Review the study with the subject (subject's legal representative) and obtain written informed consent and HIPAA authorization and assent, if appropriate.

Assign the subject a unique screening number.

Record demographics data.

Record medical history, including a history of mental health, sexual behaviors and substance use, diagnosis date, and prior cocaine treatments.

Record concomitant medications.

Perform a complete physical examination.

Collect urine sample for cocaine use and other substances test. If capable of becoming pregnant then a pregnancy test. Record results.

If urine is not positive for cocaine metabolites then place a sweat patch on participant.

10.2 Visit 2 (Screening Visit – week 2)

Perform and record vital signs (including weight and height for calculating BMI)

Perform and record results of blood pressure testing.

Perform and record results of ECG

Collect blood for clinical laboratory tests (chemistry, hematology, HIV test, pooled viral load test. If HIV positive, a CD4 test).

Collect and record contact information

Collect urine sample for cocaine use and other substances test. If capable of becoming pregnant then a pregnancy test. Record results.

If urine is not positive for cocaine metabolites then place a sweat patch on participant.

10.3 Visit 3 (Enrollment Visit – month 1)

Assign randomization. You are assigned by a computer by chance to either the lorcaserin hydrochloride or placebo groups.

Collect urine to test for cocaine metabolites and other substances.

If capable of becoming pregnant, we will collect urine and perform a pregnancy test.

Perform and record results for the BART test.

Provide study medication (lorcaserin or placebo) in medical monitoring devices ("MEMS" containers). MEMS devices will record each time you open the container to retrieve a study medication capsule.

Provided with a Wallet Card that explains that you may or may not be on a study medication (lorcaserin or placebo). This card will provide the study clinician's pager number who can provide information to other doctors in the event of an emergency. The card will also instruct the emergency room or other doctor providing treatment to provide information to the study clinician about the care they provide.

Perform ACASI questionnaire on a computer.

Meet with counselor about cocaine use.

Initiate Ecological Momentary Assessments

10.4 Visit 4 (weeks 1, 2, 3, 5, 6, 7, 9, 10, and 11))

Record any Adverse Experiences and dosing compliance by downloading MEMs cap dispenser.

Meet with the counselor regarding cocaine use and use of the study medication.

Collect urine sample to test for cocaine use and other substances. If capable of becoming pregnant, we will also conduct a pregnancy test.

Answer ACASI questions on a compute

Receive the study medication: if needed, you will be given more of the study medication (except at the week 12 visit).

Meet with the study doctor or nurse: to talk about any problems with the study medication or any changes in your health or medications if needed. A physical exam may be done.

10.5 Visit 5 (Month 1, 2 and 3 with visit window 2 weeks before visit and 2 weeks after visit)

All the same procedures as the weekly visits **PLUS** these additional procedures:

Answer ACASI questions on a computer about your mood, your recent sexual behavior and drug use, and your feelings about being in the study.

Record any Adverse Experiences and dosing compliance.

Record changes to concomitant medications.

Perform and record results for the BART test.

Meet with the study doctor or nurse: to talk about any problems with the study medication or any changes in your health or medications if needed. A physical exam may be done.

Collect blood for clinical laboratory tests (chemistry, hematology).

At month 3 visit, collect blood for HIV test, pooled viral load test. If HIV positive, a CD4 test.

At month 3 visit, perform and record ECG results.

At month 3, perform qualitative exit interview.

10.6 Early Withdrawal Visit

Record any Adverse Experiences and/or Review for adverse experiences and exclusionary medication use.

Record changes to concomitant medications.

Perform complete physical examination.

Perform and record vital signs.

Collect blood for clinical laboratory tests: Chemistry, Hematology, Urinalysis, Pregnancy (urine or serum).

11. ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

11.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

The Investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. Adverse events will be recorded in the patient CRF. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause.

11.2 AE Severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. The modified criteria can be found in the study manual. If the experience is not covered in the modified criteria, the guidelines shown in Table 1 below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 1. AE Severity Grading

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

AE Relationship to Study Drug

The relationship of an AE to the study drug should be assessed using the following the guidelines in Table 2.

Table 2. AE Relationship to Study Drug

Relationship to Drug	Comment
Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.

Possibly	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

11.3 Serious Adverse Experiences (SAE)

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

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

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

11.3 Medical Monitoring

John Walker, RN, FNP-C, research clinician, should be contacted directly at these numbers to report medical concerns or questions regarding safety.

Phone: (628) 217-6227
Pager: (415) 356-8980

Phillip Coffin, MD MIA FACP FIDSA, medical director, should be contacted directly at this number to report medical concerns or questions regarding safety.

Phone: (510) 407-2603

12. DISCONTINUATION AND REPLACEMENT OF SUBJECTS

12.1 Early Discontinuation of Study Drug

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

- Subject withdrawal of consent (or assent)
- Subject is not compliant with study procedures
- Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment

- Protocol violation requiring discontinuation of study treatment
- Lost to follow-up
- PI or clinician request for early termination of study
- Positive pregnancy test (females)

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

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

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

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents Refer to Section 10 for early termination procedures.

12.2 Withdrawal of Subjects from the Study

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

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

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents. As noted above, subjects who discontinue study treatment early (i.e., they withdraw prior to Week 8 Visit) should have an early discontinuation visit. Refer to Section 10 for early termination procedures. Subjects who withdraw after Week 8 Visit but prior to Week 12 Visit should be encouraged to come in for a final visit (and the procedures to be followed would include those for their next scheduled visit).

12.3 Replacement of Subjects

Subjects who withdraw from the study treatment will not be replaced.

13. PROTOCOL VIOLATIONS

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

- Failure to meet inclusion/exclusion criteria
- Use of a prohibited concomitant medication (such as those listed in the exclusion criteria)

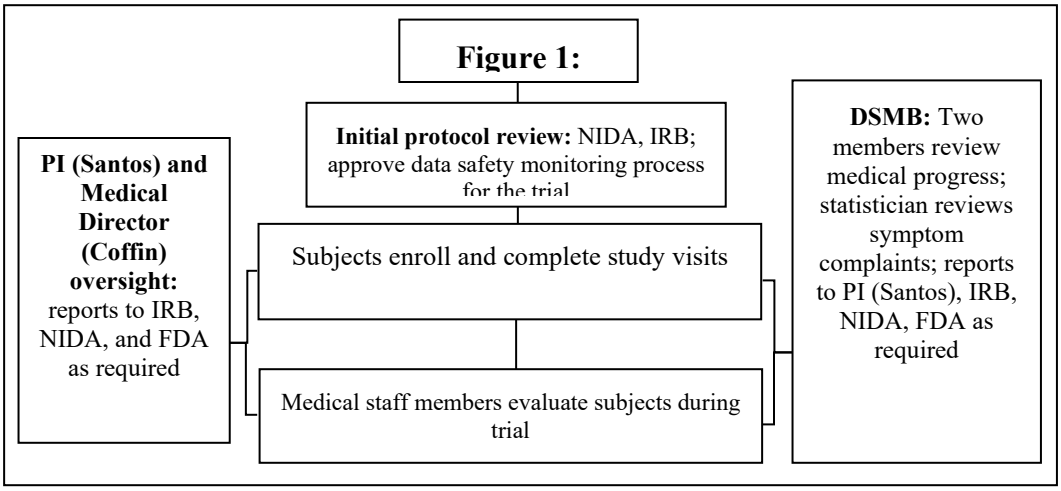
Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The PI will determine if a protocol violation will result in withdrawal of a subject.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by a Sponsor representative and the Investigator. A copy of the form will be filed in the site's regulatory binder and in the Sponsor's files.

14. DATA SAFETY MONITORING

The PI along with the site physician Dr. Coffin, will be responsible for ensuring proper monitoring of the safety and efficacy of this trial, including the execution of the DSM plan, and complying with the reporting requirements, including reports to the IRB, DSMB, NIDA and (where applicable) the FDA (see Figure 1 below).

Figure 1:



The research team including the PI, clinicians, data manager, research associates, and recruitment coordinator, meets weekly to discuss all aspects of the study such as recruitment and retention, clinical or counseling issues, and any regulatory or operation issues. All study documents are monitored by the study coordinator for quality assurance on a weekly basis to ensure timely corrections to charting such as missing initials or cross-outs with error-correction. Although there is no outside monitor, the clinicians review each other's charts for accuracy, consistency, and adherence to protocol. Regular audits will be conducted as well on consent forms, laboratory logs and other data collection forms.

The interim DSMB report will contain a brief description of the trial, baseline socio-demographic characteristics of participants, retention and disposition of study participants, a description of any quality assurance or regulatory issues, a report of AEs and SAES, and the status of outcome data.

Members and affiliation: We will use the existing University of California, Los Angeles (UCLA) Data & Safety Monitoring Board for Addiction Medicine (DSMBAM), which has extensive experience in monitoring pharmacologic interventions, including among vulnerable populations. The DSMBAM has monitored all of our pharmacologic trials for substance users.

To ensure that the DSMB oversight of the study remains independent from the proposed study, the PI(Santos) as well as others who serve on the DSMBAM that might be linked with the study in some way recuse themselves from review of the present study.

The purpose of the DSMBAM is to provide oversight and monitoring of Phase I and Phase II clinical trials of pharmacological and behavioral treatments for stimulant dependence. There are three fundamental charges of the board, which are:

- To ensure the safety of trial participants
- To preserve validity and integrity of research data
- To facilitate the availability of timely as well as reliable findings to the broader clinical community

Below are members who serve as committee chairs as well as clinical research experts:

• Steven Shoptaw, PhD, is Professor in both the Department of Family Medicine and the Department of Psychiatry and Biobehavioral Sciences at UCLA. Over the past 20 years, Dr. Shoptaw has conducted a series of clinical studies in community clinic settings, primarily on topics that involve developing medical and behavioral interventions to treat substance abusers.

• Timothy M. Hall, MD, PhD, is Health Sciences Assistant Clinical Professor at UCLA Department of Family Medicine and Center for Behavioral and Addiction Medicine. His research expertise is in sexual identity formation, social/sexual MSM networks, non-gay-identified MSM, ethnography and MSM substance use.

• Gayle Baldwin, PhD, is Associate Professor in the Department of Medicine at the University of California, Los Angeles. Her research focuses on how specific immune cells fight infectious diseases and cancer.

• Dominick Frosch, PhD, is an Associate Staff Scientist in the Department of Health Services Research at the Palo Alto Medical Foundation's Research Institute. He is also an Assistant Professor of Medicine at the University of California, Los Angeles. His research is focused on developing and implementing interventions to increase patient participation in clinical decision making and understanding the effects of health information in the media on behavior.

Below are members who serve as experts in biostatistics and epidemiology:

• Scott Comulada, PhD

• Sung-Jae Lee, PhD

• Jesse Fletcher, PhD

Below are members who serve as clinical research experts:

• Adam Carrico, PhD

• David Farabee, PhD

• Timothy Fong, MD

• Liz Evans, PhD

• Lara Ray, PhD

Administrative support staff:

• Uyen Kao, MPH, Director

• Oluwadamilola O. Jolayemi, MSc, Coordinator

The DSMC evaluates known risks to subjects' participation, the safety of the subjects as pre-specified in the protocol, and monitors the operational performance of the trial. The DSMC makes recommendations to continue, amend, or terminate the trial based on their findings. Recommendations are made in writing to the study investigators. The DSMC are given blinded trial data, but may request unblinding if safety data warrant. The initial review includes a review of the following items: statement of the protocol design, characteristics of the study data collection site, inclusion/exclusion criteria, randomization plan, definition of participants (e.g., screened, enrolled, randomized, treated, drop-out, lost to follow-up), intervention definition, dosage and frequency of study drug, reasons to discontinue study or to terminate individual

participants, reasons to discontinue treatment, outcome measures, sample size target, key adherence and safety variables, and the data analysis plan.

Subsequent ongoing reviews include: enrollment data, including those screened, enrolled, and active; subject eligibility; demographic characteristics of participants (total, and by group), recruitment and retention (total and by group). Protocol compliance are evaluated by reviewing: the expected recruitment rate, study drop-outs and reasons for leaving the study, data quality assurance reports, overall data flow procedures, CRFs collected, received, and entered; protocol deviations; protocol violations; missing data; staff omissions; subject refusal to provide data; adherence to stopping rules. The data safety report are provided in total and by group, and include any relevant medical, psychosocial or laboratory data, AEs summarized in tables, individual SAE reports, concomitant medications, and concomitant illnesses. The outcome data report includes outcome data analyzed by group, masked or unblended, with or without statistical analyses, and include all outcome variables.

15. STATISTICAL METHODS AND CONSIDERATIONS

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

15.1 Data Sets Analyzed

All eligible patients who are randomized into the study and receive at least one dose of the study drug (the Safety Population) will be included in the safety analysis.

15.2 Demographic and Baseline Characteristics

The following demographic variables at screening will be summarized by treatment group: race, gender, age, educational attainment, employed, and HIV positivity.

15.3 Analysis of Primary Endpoint

To establish the feasibility of enrolling and retaining 45 MSM with cocaine use disorder in a 12 week with 2:1 randomized, double-blind study of lorcaserin versus placebo. We will calculate the following feasibility measures: 1) proportion of those eligible among those screened; 2) proportion enrolled among those eligible; and 3) study completion rate. Process measures (e.g., visit length, counseling session completion) and reactions to study procedures will also be collected and reported. Between-group differences will be assessed using Fisher's exact and Wilcoxon rank sum tests. We will also calculate Kaplan-Meier curves for time to dropout, by group, and test for differences using the log-rank test. Precision: In the overall sample of 45, proportions will be estimated with margins of sampling error (MSEs; i.e., half widths of 95% confidence intervals) of ≤14.4 percentage points, and means with MSEs of 0.30 standard deviations, both typical for a small pilot study. While the study will only be powered to detect large between-group differences in process measures, it will provide warning of potential problems.

To explore the tolerability of lorcaserin versus placebo among MSM with cocaine use disorders**,** as determined by the number of adverse clinical events in the cocaine and placebo arms. We will compute the proportions of those experiencing adverse events, both overall and by type. Adverse clinical events, AEs and SAEs, and other binary safety outcomes will be presented as percent of participants that experience the safety outcome by treatment assignment. We will also classify AEs as any AE that results in stopping study medication, specific common AEs (>2% in both groups), AEs for general organ system categories, and AEs potentially related to study drug. The probability of observing at least one AE with population incidence of 1, 2, and 5% in the active arm will be 26, 45, and 70% with 2:1 randomization, respectively.

To describe the acceptability and adherence for lorcaserin versus placebo MSM with cocaine use disorders. We will measure the acceptability of lorcaserin compared to placebo among participants through a qualitative interview and survey evaluations of the study procedures, study drug characteristics, and dosing schedule at the final visit. We will determine medication adherence via MEMs Cap data, pill count, and self-report from TLFB and SMS texts. Measures of interest will include percent of doses taken, patterns of adherence, and time to stopping medication. We will assess how these measures of adherence track with patterns of cocaine use as measured in TLFB and urinalysis. Concordance of the adherence measures will be examined using weighted Kappa and correlations. Qualitative Analysis: In-depth, semi-structured qualitative interviews will be analyzed to establish the acceptability of study procedures and study medication, and identify key factors affecting treatment adherence for MSM with cocaine use disorders. Transcribed semi-structured interviews will be imported into *Atlas.ti,* a qualitative research software program. Data will be separated by study arm initially to determine if adherence differed between groups. If it appears there were no differences between placebo and study drug arms, then we will collapse data to assess study acceptability and adherence challenges together. If there are noticeable differences, we will analyze each set of data separately. In either scenario, we will utilize two qualitative analytic methods to interpret data.[190] First, content analysis to assess *a priori* themes using a structured codebook will allow us to focus on answering study questions about acceptability of study procedures and medication adherence. Second, thematic analysis primarily focused on adherence challenges will be conducted using open coding to allow themes to emerge from the data.[191] A coding system for the thematic analysis will be developed using an iterative process. In the initial phase, Drs. Wilson and Matheson will review transcripts and field notes to become familiar with the data, and the analytic team will make notes of their observations and potential codes for use in the initial analysis meeting. Then a thematic codebook consisting of the code definition and inclusion and exclusion criteria will be created to aid analysis. In addition to anticipated adherence challenges, additional codes will be developed independently by each analytic team member through an inductive process of identifying themes that emerge from the data. Group analysis meetings will be held to compare independently developed codes for similarity and further definition. A consensus will be reached regarding each code, its application, and definition. To ensure consistency, a codebook and dictionary will be developed with universal definitions for each code. *Inter-rater reliability:* The two coders will assess inter-rater reliability by calculating the correlation between a set of ratings done by two independent raters for the initial set of 3–6 transcripts, and then again on the next set of 6 transcripts. After each inter-rater reliability assessment, the codebook and codes will be revised based on reconciliation of findings done between coders. Inter-rater reliability will be assessed as a team twice during the analysis process and again at the end of analysis as a post-hoc evaluation of reliability and validity. This evolving analysis process will ensure high quality of research decisions, the rationale behind decisions, and the responsiveness of investigators to the data.[192] Once the thematic analysis codebook is developed and verified all remaining transcripts will be coded by study staff under the direction of Dr. Wilson. Further meetings will be held to discuss any differences in coding and to ensure consistency in the application of codes. Final analysis will begin with data reduction, then display, analysis and conclusion drawing using a conceptual framework in which hypothesized factors affecting adherence are assessed and unanticipated findings are identified.[193] The analytic team will work from the coded data to merge findings into a final summary and a consensus of major themes, relationships between themes, and ranking of items of most importance to adherence. This method of data reduction encompassing both site- and team-based analysis creates a robust iterative process through which the data is thoroughly discussed and analytical consensus achieved. *Atlas.ti* software will be used to both code and develop data displays used in the analysis

15.4 Analysis of Secondary Endpoints

To evaluate the ***preliminary efficacy*** of lorcaserin versus placebo to reduce cocaine use and HIV-related sexual risk behaviors among MSM with cocaine use disorders, as determined by the proportion of cocaine-positivity from twice weekly urine samples and self-reported sexual behaviors. Minimum detectable effects (MDE) of the intervention on cocaine use outcomes will be substantial, as is typical of a pilot study. In our prior trial for MSM actively using stimulants, [68] the within-subject correlation of the repeated measures for urine positivity was 0.45, the urine positivity in the control group was 55%, and the retention was 93% at the end of the study. On this basis, we conservatively estimate that the sample will provide 80% power to detect reductions of 29 percentage points in the rate of cocaine urine positivity. In preparation for a larger trial, we will conduct exploratory assessments using GEE Poisson models to assess treatment effects on cocaine urine positivity.[194] In sensitivity analyses, we will also evaluate between-group differences on changes in: 1) any cocaine positive samples, defined as having a positive urine or sweat patch sample, over follow-up; 2) any cocaine positive samples or self-report of cocaine use in text messages; and 3) cocaine positivity from sweat samples only. Concordance of the urine testing, sweat testing, and self-reported measures will be examined using weighted Kappa and correlations. To evaluate treatment effects on cocaine-associated sexual risk behaviors, GEE Poisson, binomial, and negative binomial models will be used to assess treatment effects on HIV sexual risk behaviors including high-risk sexual behaviors while under the influence of cocaine. **Findings from these analyses will be used to determine whether a linearly increasing or constant treatment effect best describes outcome patterns.**

Safety and tolerability data will be summarized by treatment group.

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

15.5 Interim Analysis

No planned interim analysis.

15.6 Sample Size and Randomization

16 DATA COLLECTION, RETENTION AND MONITORING

16.1 Data Collection Instruments

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

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

For eCRFs: If a correction is required for an eCRF, the time and date stamps track the person entering or updating eCRF data and creates an electronic audit trail. *For paper CRFs:* If a correction is made on a CRF, the study staff member will line through the incorrect data, write in the correct data and initial and date the change.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. A copy of the CRF will remain at the Investigator's site at the completion of the study.

16.2 Data Management Procedures

The data will be entered into a validated database. The Data Management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

16.3 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. *For paper studies:* Query reports (Data Clarification Requests) pertaining to data omissions and discrepancies will be forwarded to the Investigators and study monitors for resolution. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

16.4 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

16.5 Availability and Retention of Investigational Records

The Investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of two years following marketing of the investigational product or for two years after centers have been notified that the IND has been discontinued. There may be other circumstances for which the Sponsor is required to maintain

study records and, therefore, the Sponsor should be contacted prior to removing study records for any reason.

16.6 Monitoring

Monitoring visits will be conducted by representatives of the Sponsor according to the U.S. CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6). By signing this protocol, the Investigator grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

16.7 Subject Confidentiality

In order to maintain subject confidentiality, only a subject number and subject initials will identify all study subjects on CRFs and other documentation submitted to the Sponsor. Additional subject confidentiality issues (if applicable) are covered in the Clinical Study Agreement.

17 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

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

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

17.1 Protocol Amendments

Any amendment to the protocol will be written by the Principal Investigator. Protocol amendments cannot be implemented without prior written IRB approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

17.2 Institutional Review Boards

The protocol and consent form will be reviewed and approved by the IRB of each participating center prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB/IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the Investigator will keep the IRB/IEC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC. The IRB/IECs written unconditional approval of the study protocol

and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB/IECs unconditional approval statement will be transmitted by the Investigator to prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

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

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

17.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form, assent and HIPAA authorization and provide the documents to the Sponsor or designee for approval prior to submission to the IRB/IEC. The consent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations. The Investigator will send an IRB-approved copy of the Informed Consent Form to the Sponsor (or designee) for the study file.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects (or their legal representatives) must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB, assent from the subject will also be obtained. If a subject is unable to sign the informed consent form (ICF) and the HIPAA authorization, a legal representative may sign for the subject. A copy of the signed consent form (and assent) will be given to the subject or legal representative of the subject and the original will be maintained with the subject's records.

17.4 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the Principal Investigator and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

17.5 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of subjects.

2. Personally conduct or supervise the study (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
8. Promptly report to the IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
9. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

18 APPENDICES

Appendix 1: Study Procedures

Table 2. The TLC Study Procedures	Scr 1&2	Enr	Wk	Bi-wk	Dly	M 1&2	M 3
Informed consent	X						
Safety lab assessment	X					X	X
Rapid HIV test*, CD4, viral load	X						X
HIV risk reduction counseling	X						X
Medical history and SCID	X						
Vital signs, weight	X	X				X	X
Physical exam		X					X
Medication Training		X					
Randomization		X					
Urine testing for cocaine	X	X	X	X		X	X
Sweat patch testing for cocaine		X	X			X	X
CAPI assessments		X	X			X	X
AE assessments			X			X	X
Substance use counseling			X				
Qualitative Interviews							X
Text Messaging					X		

Notes: *Confirmatory HIV testing will be performed for reactive tests. Scr=Screening, Enr=Enrollment, Wk=Weekly, Bi-wk=Biweekly/twice weekly, Dly=Daily, M=Monthly

18.2 Appendix 2: References:

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