University of Pennsylvania

A PHASE II, DOUBLE-BLIND, PLACEBO-CONTROLLED, TRIAL OF NS2359 FOR THE TREATMENT OF COCAINE DEPENDENCE

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Study Product: NS2359

Protocol Number: 1.6

IND Number: 116053

Date: **7/2/2019**
Amended:
Administrative Change:

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Study Summary

Title	A Phase II, Double-Blind, Placebo-Controlled, Trial of NS2359 For The Treatment of Cocaine Use Disorder
Short Title	NS2359 for cocaine dependence
Protocol Number	NS2359 1.3
Phase	Phase 2
Methodology	Double-blind placebo-controlled parallel group clinical trial.
Study Duration	24 months
Study Center(s)	University of Pennsylvania
Objectives	Exploratory trial examining the efficacy and tolerability of NS2359 for the treatment of patients with cocaine use disorder
Number of Subjects	80 subjects
Diagnosis and Main Inclusion Criteria	Cocaine use disorder. Men and women over 18 years of age. Subjects must have current DSM V diagnosis of cocaine use disorder. Subjects must be in good health and psychiatrically stable. They must have no other substance use disorder except tobacco use disorder or cannabis use disorder. Comorbid alcohol use disorder will be accepted if alcohol use disorder is not severe enough to require a medical alcohol detoxification.
Study Product, Dose, Route, Regimen	NS2359 2 mg daily
Duration of administration	8 weeks of medication
Reference therapy	Placebo
Statistical Methodology	Cocaine use will be measured using three-times-weekly qualitative urine benzoylecgonine (BE) levels. More NS2359-treated subjects (compared to placebo-treated subjects) will achieve 3 consecutive weeks of cocaine abstinence during the last three weeks of the medication trial, as measured by the Timeline Follow-Back method and qualitative urine benzoylecgonine (BE) levels

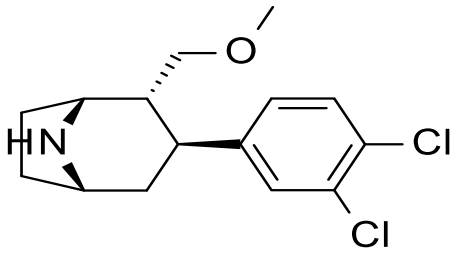
1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background

The 2008 National Household Survey on Drug Abuse (SAMHSA) reported that 1.9 million Americans were regular cocaine users, making cocaine one of the most commonly abused illicit drugs in the US, with ~250,000 individuals in treatment at any one time (SAMSHA, 2008). 5-6% of recent cocaine users will develop cocaine dependence (CD) (O'Brien and Anthony, 2005). There is no FDA approved pharmacotherapy for CD. CD standard treatment consists of individual and group psychotherapy and self-help groups, which do not provide substantial benefit for many patients (Kampman et al, 2001; Alterman et al, 1996; Caroll et al, 2004). Dropout rates in outpatient treatment programs are very high (Kampman et al, 2002). Among patients who complete treatment, relapse is common (McKay et al, 2010). In other addictive disorders (eg, nicotine and opioid dependence), medications have been employed usefully to improve treatment outcomes. With these two addictions as models, investigators have searched for medications to treat CD (Kampman et al, 1996, 2000, 2003 and 2006; Pettinati et al, 2008; Plebani et al, 2012).

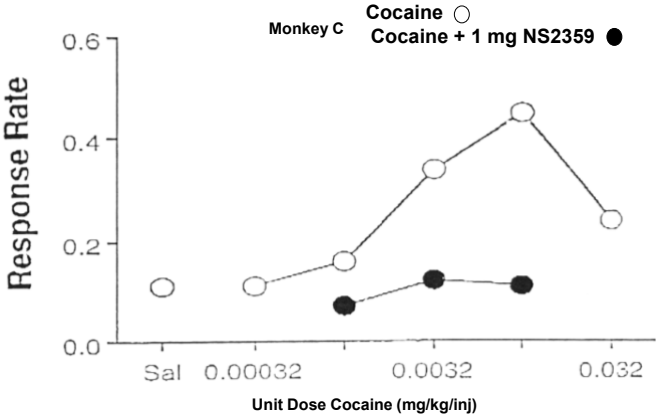
Structure of NS2359



Cocaine's rewarding effect is mediated by inhibition of transporters for DA, NE and 5HT, a mechanism which is qualitatively similar to that of NS2359, a compound synthesized and characterized pharmacologically by NeuroSearch (Copenhagen). NS2359 (structure at right), unlike cocaine, has slow dissociation kinetics at all three transporters and a long half-life in humans (~ 7 days). Thus it has the potential to block the binding of cocaine to these transporters and the euphoria associated with cocaine.

The effect of NS2359 acute pretreatment (0.064 mg/kg to 2.05 mg/kg IM) on cocaine self-administration was examined in four rhesus monkeys trained to lever press for cocaine (eg, 0.0032 mg/kg IV per lever press). NS2359 potently and dose-dependently inhibited responding for IV cocaine (ED50 = 0.45 mg/kg) in 3/4 rhesus monkeys (see figure). In a monkey given 2 mg/kg, cocaine responding did not recover for 22 hours after the NS2359 dose. This dose does not block responding for food (data not shown).

NS2359 Blocks Cocaine Self-administration in Monkeys



A cocaine-NS2359 safety interaction study, was conducted with 24 psychostimulant users. Participants received 20 mg IV cocaine 6 hours after placebo (n=6) or after acute pretreatment with a single oral dose of NS2359 (1.5, 3 or 6 mg, n = 6/dose). ~24 hours later, subjects received 40 mg cocaine IV. No evidence of toxicity was seen; NS2359 attenuated heart rate and blood pressure increases after 40 mg cocaine. However, there was no overall significant effect of NS2359 on the cardiovascular or subjective responses to cocaine. While lower NS2359 doses had little

influence on subjective responses to cocaine, there is evidence that the 6 mg dose blocked cocaine's effects. Mean (+/- SD) maximal subjective ratings, from visual analog scales, suggest an NS2359 effect at the 6 mg dose (Appendix 4, Tables 21-30, pp 64-72). Absence of overall statistical significance is due to the lack of influence of cocaine subjective effects at the two lower NS2359 doses, the small sample sizes (n = 6) at each dose, and the large variances in subjective ratings. Given the expected large variances in subjective ratings, the study was not powered adequately for this endpoint.

cocaine dose	NS2359 dose	any effect	high	good effect	liking	desire	stimulated	likely to use	amount you would pay
20 mg	0 mg	33 +/- 24	27+/-20	24 +/- 22	26 +/- 27	28+/- 28	33 +/- 27	27+/-33	19 +/- 31
20 mg	6 mg	7.2+/-8.8	6.6+/11	6.3+/-7.7	4.4+/-8.2	6.3+/-11	7.4 +/-13	7.2+/11	5.8 +/- 3.8
40 mg	0 mg	60 +/- 26	53+/-28	52 +/- 33	52+/- 36	50+/- 38	48 +/- 30	50+/-37	33 +/- 37
40 mg	6 mg	32 +/- 34	28+/-27	22 +/-20	12 +/- 16	18+/- 26	28 +/- 33	16+/-23	13 +/- 9.3

The 6 mg NS2359 dose (but not the lower doses) attenuated 40 mg cocaine-induced increases in heart rate (p = 0.0018) and systolic blood pressure (p = 0.024), with a trend to do so for diastolic blood pressure (p = 0.11, Table 8, p 46, Appendix 1, cocaine interaction study). *This suggests that NS2359 might have a protective effect on the major source of morbidity and mortality in cocaine overdose (stroke and myocardial infarction) due to rapid rise in blood pressure.*

NS2359 was licensed to GlaxoSmithKline (GSK), where it (as GSK472375) was examined in phase 1 and 2 trials. At single oral doses of 9 mg, unacceptable levels of insomnia and impaired concentration were observed (Appendix 1, p 91), but a single 6 mg oral dose was moderately well tolerated (Appendix 1, p 91). 2 mg/day for 28 days was well-tolerated among healthy volunteers (Appendix 1, p91).

GSK conducted several phase 2 clinical trials. NS2359 (at 0.5 mg/day) did not show efficacy in an adult attention deficit disorder (ADD) placebo-controlled study (Willens et al, 2008). Absence of efficacy probably was due to the low NS2359 dose of 0.5 mg/day. NS2359 (at 1.5-2 mg/day) did not differentiate from placebo in two major depressive disorder (MDD) trials (Appendix 1, pp 104-114), in which the active comparators were superior to placebo and NS2359 (Learned et al, 2011). The reasons for lack of efficacy are unclear. In these trials, insomnia, loss of appetite and anxiety were common CNS adverse events. Insomnia, loss of appetite and anxiety may be particularly difficult for MDD patients to tolerate, as these adverse events are common depressive symptoms, and they could have led to the excess discontinuation rate among patients randomized to NS2359 (Appendix 1; Learned et al, 2011). However, the total adverse event reports were not greater for NS2359 than for the active comparators (Learned et al, 2011). No serious adverse events were attributed to NS2359 in ~ 500 persons exposed in the phase 1 and phase 2 studies (Appendix 1; Learned et al, 2011; Wilens et al, 2008).

After the disappointing results in MDD and adult ADD, the NS2359 license reverted from GSK back to NeuroSearch, which is making the medication available to us for a phase two trial in CD (letter from Pierandrea Muglia, MD). NeuroSearch has supported our application to the FDA for an IND for this trial, allowing us to cross-reference their existing IND. NeuroSearch has supplied the NS2359 for purification and stability testing, while packaging will be done by the University of Pennsylvania Investigational Drug Service (www.med.upenn.edu/cores/investigational_drug_service.shtml) into 1.0 mg pills with matching placebo.

1.2 Investigational Agents

NS2359 (from Investigators Brochure)

NS2359 is a novel drug candidate that exhibits potent in vitro and in vivo inhibition of re-uptake transporters for the neurotransmitters serotonin (5-HT), norepinephrine (NE) and dopamine (DA). It was developed under the name NS2359 by NeuroSearch. Therefore GlaxoSmithKline had in-licensed NS2359 (as GSK372475) and performed non clinical and clinical studies. This compound was investigated for its potential as an antidepressant agent and for the treatment for adults with attention deficit hyperactivity disorder. Currently, Neurosearch is planning to investigate the potential of NS2359 in the treatment of addiction.

Nonclinical Pharmacology Studies

In vitro and in vivo studies have clearly demonstrated NS2359 (also known as GSK372475) to potently and selectively inhibit the re-uptake of the 3 monoamines, serotonin, norepinephrine and dopamine, in the central nervous system. Studies in rodents have shown low doses of NS2359 to increase the extracellular levels of these monoamines in the frontal cortex, hippocampus, striata and nucleus accumbens. In addition, NS2359 increased cortical and hippocampal levels of acetylcholine.

At similarly low doses, NS2359 enhanced learning and memory and did not induce anxiety or influence explorative open field behavior in the rat. NS2359 was also active in mouse models of depression and showed a unique anti-Parkinson activity in the monkey. NS2359 was active in the cocaine drug discrimination paradigm, attenuated experimental alcohol craving and demonstrated anti-nociceptive properties.

High doses of NS2359 caused an increase in locomotor activity in rodents, and at still higher doses, induced typical dopaminergic stereotypic behavior.

A series of cardiovascular safety studies conducted with NS2359 in dogs demonstrated dose-dependent increases in blood pressure. In one study in conscious restrained dogs, NS2359 caused an increase in QTc interval; however, only one animal was outside the historical QTc interval range. In another study in dogs fitted with atrial pacemakers, much higher plasma concentrations produced no effect on QT interval, when heart rate was controlled. Similarly, 28 days administration in dogs did not affect any of the cardiovascular parameters measured, including QT interval. NS2359 inhibited hERG currents at 37°C with an IC50 value of 1.4 μM (420 ng/mL). NS2359 did not affect respiratory rates in the dog and did not affect gastrointestinal transport in the rat. In a rat respiratory study, single oral doses of ≥4.8 mg/kg NS2359 produced increases in total pulmonary ventilation.

Nonclinical Pharmacokinetic Studies

In the mouse, rat, rabbit, dog and monkey, NS2359 was shown to be well absorbed, with a moderate to high clearance. NS2359 was highly distributed with variable half-lives in the rat, dog and monkey ranging between 1 and 24 hours.

Systemic exposure to NS2359 typically increased in a supraproportional fashion following administration to rat and rabbit, whilst in mouse, minipig, dog and monkey, exposure increased in a generally proportional manner. In the rat, systemic exposure was greater in females than males, whilst in the mouse, exposure tended to be greater in males than females. In the other pre-clinical species, where assessed, no sex differences were observed. There was evidence of accumulation upon repeat administration in the rat and dog. Notable exposure to GSK459151 (the O-desmethyl metabolite) was observed in rat (exposure greater than to NS2359) and dog, and to a lesser degree in monkey and mouse.

The distribution of drug-related material was widespread following oral and/or intravenous administration of [14C]NS2359 to rats (albino and pigmented). By 35 days post dose, concentrations were below the limit of quantification in most tissues except in uveal tract/retina (suggesting some association with melanin), epididymes and testes. Liver concentrations were

approximately 50-fold or greater than those in plasma in the rat, and there was also evidence of notable CNS penetration of drug-related material in the rat, mouse and hamster. The plasma protein binding and the association of NS2359 with blood cells were moderate.

NS2359 and GSK459151 were determined to have high and moderate passive membrane permeability, respectively, at pH 7.4 (which decreased notably at lower pH). NS2359 and GSK459151 were shown to be inhibitors and substrates of human P glycoprotein. Pgp was shown not to have a biologically important role in the absorption of NS2359 or to contribute to the distribution into the kidney or liver. Pgp was shown to have a role in the efflux of NS2359 from the brain and in its urinary elimination.

Preliminary information in man indicates that the major metabolic routes of NS2359 are demethylation (to form GSK459151), hydroxylation, N-oxidation and glucuronidation. This is generally consistent with the routes observed in nonclinical species (rat, mouse and hamster). However, in the minipig desmethylation to GSK459151 was only a minor route. In rat liver, the major component present was GSK459151, although NS2359 was also seen. Drug-related material in the brains of rats and mice was predominantly attributable to NS2359, although GSK459151 was also observed in rats.

Following oral administration of [14C]NS2359 to rat, minipig, dog and monkey, urinary elimination was the major route of elimination in female rat, minipig and monkey, whereas in male rat and dog the fecal route predominated. In the rat, the majority of the fecal elimination can be accounted for by biliary secretion.

In vitro, NS2359 showed inhibition of CYP2C19, CYP2D6 and CYP3A4, but with no evidence for any metabolism-dependent inhibition of any of the activities investigated. There was evidence of induction of CYP1A and CYP2B following repeat oral administration for 13 weeks in the rat but not in the monkey.

Toxicology Studies

The maximum non-lethal single oral doses in the rat and mouse were 30.5 mg/kg and 6.4 mg/kg, respectively. At these doses, treatment-related effects were limited to behavioural signs (stereotypy) and reduced appetite with an associated decrease in weight gain, and were attributable to the pharmacological effects of NS2359.

Similar findings were seen following repeated oral administration of NS2359 for up to 15 weeks in minipigs, 13 weeks in rats and monkeys, and 28 days in dogs, and were reversible. Three episodes of convulsions were observed in two minipigs after 17, 27 and 29 weeks of treatment in a 52 weeks toxicity study, suspended after completion of the in life treatment. They have been considered isolated and not dose or exposure related.

Target organ toxicity was not identified in any species tested. The behavioural effects limited the maximum dose employed, and hence systemic exposure in all species.

NS2359 had no effect on embryofetal development in either the rat or the rabbit. Rat female fertility was also unaffected by NS2359. Maternal toxicity in rats was comprised of hyperactivity and increased body weight and food consumption.

NS2359 was considered not to be genotoxic. Polyploidy highlights the potential for aneuploidy, but as both the mouse lymphoma assay and in vivo micronucleus assay detect aneuploidy, and all of these results were negative, this data is not considered to be biologically relevant.

Clinical Studies

The maximum acute dose level achieved within the Phase I single escalating-dose study in healthy volunteers was 9 mg [study 1253/127]. Although single doses of 6 mg and 9 mg were associated with a number of adverse events (AEs) including pronounced insomnia and impaired concentration, no clinically significant drug or dose-related findings on clinical laboratory

measures, electrocardiograms (ECGs) or vital signs were reported in Phase I single-dose studies [studies: 1253/127; SND101811; SND102340; SND110117; CA2359-002].

In the six Phase I repeat-dose studies conducted with NS2359, doses up to 2 mg/day for up to 28 days were evaluated and considered generally well tolerated [studies: DDS633554; GDRS-QGUY; PBR-022341; CA2359-003; SND103869; SND108813] .

One serious adverse event (SAE) has been recorded in Phase I studies (exacerbation of cholelithiasis), which occurred in the SND103869 study. The SAE was considered to be unrelated to the study drug by the investigator and the subject was not withdrawn from the study.

Three studies in patient populations have also been completed. An 8-week ADHD study with 0.5 mg NS2359 [study: NS2359-001], and two 10-week MDD studies with NS2359 flexible doses of 1.0 to 1.5 and 1.5 to 2.0 mg/day respectively [studies: SND103288; SND103285].

The most frequently reported AE in these studies were insomnia, headache, fatigue, dizziness, palpitations, and constipation. The majority of AEs were of mild or moderate intensity.

No SAEs emerged in the 8-week ADHD study in which the dose was 0.5 mg/day (NS2359-001).

In the two 10-weeks MDD clinical efficacy studies (SND103285 and SND103288), a total 12 SAEs were observed in NS2359 groups, including one death (completed suicide); 3 SAEs in the Paroxetine active comparator group (SND103288); and a total of 3 SAEs in the Placebo groups (SND103285 and SND103288); no SAEs were observed in the Venlafaxine group (SND103285). Two of the 12 SAEs (i.e. completed suicide, and mania in the NS2359 group of study SND103288) were considered by the Investigator to be potentially related to the investigational product.

Clinically significant elevations in some hepatic enzymes (e.g., AST and ALT) were recorded in one healthy volunteer Phase I study, but were considered unlikely to have been caused by NS2359. A relatively modest, apparently dose-related, overall trend for NS2359-associated increases in mean blood pressure and/or heart rate was observed, and one subject (receiving 2 mg for 3 days and then 1 mg per day for 25 days) had more notably elevated blood pressure and heart rate values (PBR-022341). However, within the other Phase I studies, no vital signs were otherwise identified as clinically significant. Increases in mean change from baseline in heart rate and sitting blood pressure were grater for NS2359 than observed for either placebo or active control groups in the MDD studies. A relationship between changes from Baseline in vital signs and median concentrations was shown by the exploratory PK/PD analysis only in the SND103288 study.

In one repeat-dose phase I study (PBR-022341) and in the ADHD study and in the two MDD studies there was a trend towards decreasing weight in subjects receiving NS2359 when compared to placebo groups.

Studies of the pharmacokinetics of NS2359 in man indicate that the absorption is fairly slow with Tmax ranging from 6 to 7 hours. The elimination phase is also slow with a terminal elimination half-life of 8-10 days. There is a high degree of accumulation of NS2359 observed with repeated dosing, in line with the long half-life of the compound. The AUC0-∞ and Cmax appeared to increase in a dose-proportional manner. PK findings in the clinical efficacy studies (ADHD and MDD) indicated slightly lower exposure and higher variability as compared to studies in healty volunteers.

Two imaging studies with NS2359 demonstrated excellent CNS penetration and dose-dependent specific binding to brain dopamine and serotonin transporter sites in healthy male

subjects at well-tolerated doses. The plasma concentration/receptor occupancy data indicated equivalent potency across the monoaminergic transporters tested.

The abuse liability of NS2359 was evaluated in experienced users of stimulant drugs in a randomized, double-blind, placebo controlled cross-over study, comparing NS2359 to placebo and to two active controls, pseudoephedrine and d-amphetamine (SND101811). The overall pattern of pharmacodynamic responses demonstrated that NS2359 is unlike d-amphetamine and more like placebo. The results from this study indicate that the abuse potential of NS2359 is likely to be very low.

The results of the clinical efficacy studies showed that there were no significant differences between NS2359 and placebo groups for any of the primary or secondary efficacy endpoints, for either ADHD or MDD. In the two MDD phase II studies, venlafaxine (study SND103285 or paroxetine (study SND103288) were the active comparators, in addition to a placebo arm. Total adverse events were not significantly greater for NS2359, compared to venlafaxine or paroxetine. Voluntary withdrawal was 13% for NS2359, compared to 8% for placebo and 2% for venlafaxine. Physician withdrawal was 14% for NS2359 versus 14% for venlafaxine and 15% for NS2359 versus 6% for paroxetine.

In summary, the available data from Phase I and II studies did not show compound safety and tolerability issues. The studies in MDD indicated a possible dose-dependent effect in increasing blood pressure and heart rate. Also a possible effect in lowering body weight has been detected in the MDD studies, with similar results for the ADHD study. Efficacy data indicate that NS2359 does not warrant further study as treatment in MDD.

Data from one human abuse liability study (SND101811) and a human cocaine interaction study (CA2359-002) indicate that NS2359 has low abuse potential and no significant effect on the PK of cocaine. These data allow clinical testing of NS2359 in addiction.

1.3 Dose Rationale and Risk/Benefits

The overriding principle for NS2359 dosing is that the daily dose will not exceed the maximum dose or duration in the phase II studies of major depressive disorder (Learned, et al, 2012). The daily NS2359 doses of 1-2 mg/day will not exceed the maximum daily dose given in phase I and phase II studies, 2 mg/day, as detailed in Appendix 2, Investigators' Brochure. This 2 mg/day dose was well tolerated by normal volunteers in phase I for 28 days (see Appendix 2, Investigators Brochure, Study SND103869, p 76-77). Mean C_{max} plasma level was 36 ng/ml in that phase I study (Table 18, p 77, Investigators' Brochure, Appendix 2). Further, in study SND103285 – MDD (p 79, in Appendix 2, Investigators' Brochure) patients received 1.5 mg/day for 6 weeks (mean plasma NS2359 C_{ave} = 16 ng/ml) or 2 mg/day for 6 weeks (mean C_{ave} plasma NS2359 = 23 ng/ml; p 81, Table 21, Investigators' Brochure, Appendix 2). In neither of these investigations was there a serious adverse event.

Medications will be started at the beginning of week 2 and stopped at the end of week 9. At each clinic visit (Monday, Wednesday and Friday), patients will be asked to take the medication under the direct observation of staff. Subjects will take 2 mg of NS2359. Depending on tolerability, the dose may be reduced to 1 mg once daily. Thus, the dosing regimen chosen will not exceed the NS2359 exposure at 2 mg/day for the phase I and II trials in which there were no serious adverse events. Patients experiencing intolerable adverse events at the 2 mg/day dose will be allowed to reduce the dose to 1 mg/day. This flexible dose strategy is designed to enhance patient retention while providing adequate exposure to NS2359 to attenuate the rewarding and cardio-vascular effects of cocaine.

Potential risks. The potential risks of this study include adverse reactions to NS2359, potential adverse interactions between NS2359 and cocaine, and the small risk incurred by venipuncture.

Risks associated with NS2359. NS2359 has been shown to be safe and well tolerated in a number of Phase I and Phase II trials, including two relatively large trials for the treatment of depression and ADHD, involving 1200 subjects. These studies were characterized by NS2359 plasma levels similar to those proposed here. The most common side effects of NS2359 noted in clinical trials include: insomnia, weight loss, dizziness, headache, constipation, dry mouth, anxiety, increased heart rate and increased blood pressure. The heart rate and blood pressure increases were small and not clinically significant. There were no medication associated serious adverse events in any of the clinical trials conducted thus far. As described in Preliminary Studies in Research Strategy, a safety interaction trial of NS2359 and cocaine was conducted and no adverse interactions between NS2359 and cocaine were found (see Appendix I). The preliminary data support the safety of NS2359 for this trial. In the proposed trial, patients will be monitored closely (three times per week) to ensure that any adverse events will be identified and treated appropriately. Vital signs and weight will be monitored weekly by a nurse practitioner.

Consent procedures. All study procedures will be described in detail for the subjects by one of the project investigators in an individual consent session. The consent form and session will include the following information: Detailed information about the study medication; that is, a description of the medication, rationale for why it is being studied, frequency of dosing and length of treatment, potential side effects, safeguards and emergency procedures. Information will also be provided about the psychosocial treatment, frequency of visits and length of treatment, safeguards and emergency procedures, etc. Collection of lab specimens (number of venipunctures and urine specimens required) will be reviewed. Eligibility will be reviewed. The number and frequency of the research interviews and self-assessments will be reviewed.

In addition, subjects will be assured that their participation is voluntary and that withdrawal from the study does not jeopardize current or future treatment. Patients will also be told that if at any time during the study the research team and the clinical treatment team feel that the patient needs more intensive, standard treatment, the patient will be referred to one of the available inpatient treatment programs in Philadelphia. All subjects will be informed of potential risks and benefits involved in the study. Potential medication side effects will be described to all subjects. Patients will be informed that their participation in the treatment trial may be discontinued at any time because of serious medication side effects, their noncompliance with treatment, missing appointments or if continued participation is considered an endangerment to their welfare.

At the end of the consent session, a quiz is given. Subjects scoring below 100% correct will receive additional instruction regarding the study and consent form. Incorrect questions from the quiz will be administered again until all questions are answered correctly. All participants are provided with a hard copy of the consent form that includes the name and telephone numbers of the investigative team, and the Chair of Penn's Institutional Review Board (IRB). A 24-hour Emergency contact is provided in case of an adverse consequence or any other emergency.

Protection of Subjects. Potential subjects will be screened for medical illnesses that would preclude the use of NS2359, eg, untreated hypertension and untreated cardiac disease detected by EKG and/or physical exam. Subjects selected for the study will be monitored closely. Adverse events will be monitored by a nurse practitioner at weekly visits. Individuals with urine drug screen results indicating recent cocaine ingestion will be questioned closely about adverse events. At the conclusion of medications, an end of study physical will be completed and the baseline laboratory tests, including EKG, will be repeated. Subjects will be given a 24-hour emergency number they can call if necessary. Adverse events: If the patient is discontinued in treatment due to a serious adverse event, the patient will be followed clinically by medical staff until the adverse experience resolves itself and becomes stable.

Subjects taking other concomitant medications will be monitored closely for signs of toxicity. Subjects with a history of current severe psychiatric symptoms, impaired renal function or known liver disease, use of any investigational medication within the last 30 days, or AIDS or any other serious illness which may require hospitalization during the study, will be excluded. Pregnant females or women who refuse to use acceptable forms of birth control will be excluded from the study. Should a participant become pregnant while participating in the study, outcome data will be collected via self report and any medical charts made available. A pregnant partner authorization form will be signed so data may be collected from female subjects and female partners of male subjects who become pregnant while in the study.

Venipuncture will be carried out with good aseptic technique by a nurse practitioner or physician. Venipuncture sites will be monitored carefully for signs of infection.

If a patient experiences an adverse event, appropriate evaluation and management will be undertaken. This may include medical management, a reduction in study of medication, a temporary cessation of study drug, or early termination from the trial if necessary.

HIV antibody testing will be available to all research patients on a voluntary basis. Pre and post-test counseling is conducted for all subjects by the nurse practitioner. Informed consent is signed and maintained in the patient's clinical chart. Subjects who have positive tests have access to supportive counseling by the nurse practitioner with psychiatric consultation available through Dr. Kampman and/or Dr. Berrettini. Subjects have the option of medical follow-up through their personal physician or through referral to the Infectious Disease Clinic of The Hospital of the University of Pennsylvania.

Confidentiality. No information about subjects will be disclosed to others without their prior written permission, except as stated in the informed consent, or if necessary to protect the rights or welfare of a subject in accordance with the law. Subject names or unique identifying information are never used in the publication of research data. Procedures designed to maintain confidentiality include: (1) formal training sessions for all research staff emphasizing the importance of confidentiality; (2) specific procedures developed to protect a patient's confidentiality; and (3) formal mechanisms limiting access to information that can link data to individual patients. Data forms that include identifying information are kept in locked cabinets. Only the unique identification (ID) number, assigned at the time of initial contact represents patients during data entry, data transfer, data analysis, or other file management procedures. To facilitate tracking, a password-protected computer file on a secure server is maintained containing the identity of patients, their ID numbers, and information about how they can be reached. This file, however, contains no clinical data. All data are stored in a securely locked area accessible only to authorized research personnel. The Principal Investigator (PI) is required to allow trial-related monitoring, audits, IRB review, and regulatory inspection by providing direct access to source documents. The FDA, IRB, and other regulatory authorities will also have access to source documents. We inform subjects of this access in the informed consent. Finally, HIPPA regulations are followed.

With respect to minimizing the discomfort that may result from the interview, research assistants are selected on the basis of their personal attributes and interpersonal skills as well as their substantive knowledge. They are further trained and periodically observed to ensure that they are respectful and sensitive to the needs and feelings of the patients in all contacts. Furthermore, they are trained to recognize signs of significant stress or enervation in patients, and are instructed that they should gently terminate the interview and schedule the patient for another time or request assistance from a trained clinician.

HIPPA compliance. Penn investigators support the appropriate privacy of all clinical and research data collected as part of any study. We follow NIH policy in the use and disclosure of protected health information in research in a manner that respects the subject's privacy in accordance with the "Privacy Rule" promulgated under the Health Insurance Portability and Accountability Act (HIPPA) and other applicable laws. All staff receive appropriate HIPPA training. All subjects sign a HIPPA-authorization form, receive a copy of this form, and receive a notice of the site's privacy practice. HIPPA signed forms are retained in locked file cabinets with patients' source documents.

2 Study Objectives

The primary objective of this single site trial is to evaluate the efficacy of NS2359 for the treatment of cocaine use disorder. The study will be double-blind, and placebo-controlled. The project proposes to randomize 80 treatment-seeking subjects with DSM-V diagnoses of cocaine use disorder to NS2359 or placebo. All subjects will receive weekly sessions of Medical Management (MM) and Cognitive Behavioral Therapy (CBT). We chose to use the MM from the NIAAA-funded COMBINE national study because of its distinctive procedures for maximizing medication adherence. We also plan to provide once weekly sessions of CBT as a psychosocial treatment in our exploratory trials because CBT has been shown to be effective for promoting treatment retention in prior medication trials for the treatment of cocaine dependence.

Following the treatment trial, there will be one follow-up visit conducted with subjects at 12 weeks after starting study medications (four weeks after completing the medication phase of the trial).

3 Study Design

3.1 General Design

Study Design: The hypotheses in the proposed study will be tested with a 2-group design to assess the efficacy of NS2359 compared to placebo. We will follow NIAAA's COMBINE Medical Management (MM) manual in weekly dispensing medications, safety checks and medication adherence. The psychosocial treatment will be Cognitive Behavioral Coping Skills Therapy (CBT). Subjects will be 80 men and women with current DSM-V diagnoses of cocaine use disorder who will be randomized to NS2359 or placebo (40 subjects per group). All subjects will receive weekly sessions of CBT. The study length for each subject is comprised of 1-week of screening and baseline evaluations, an 8-week double-blind, placebo-controlled trial with CBT (medication phase), and one follow-up visit 4 weeks after end of medication phase.

3.2 Primary Study Endpoints

Primary Hypothesis: More NS2359-treated subjects (compared to placebo-treated subjects) will achieve 3 consecutive weeks of cocaine abstinence during the last three weeks of the medication trial, as measured by the Timeline Follow-Back method and qualitative urine benzoylecgonine (BE) levels.

3.3 Secondary Study Endpoints

1. NS2359-treated subjects will have reduced craving for cocaine, compared to placebo-treated subjects, as measured by the Brief Substance Craving Scale.
2. NS2359-treated subjects will have reduced cocaine withdrawal symptom severity, as measured by the Cocaine Selective Severity Assessment (CSSA).
3. NS2359-treated subjects will have higher rates of cocaine abstinence at the final appointment, four weeks after the 8 weeks of medication treatment has been completed, as measured by self-report and by urine drug screen for BE levels.

3.4 Primary Safety Endpoints

NS2359 adverse events: NS2359 has been shown to be safe and well tolerated in a number of Phase I and Phase II trials, including two relatively large trials for the treatment of depression and ADHD, involving 1200 subjects. The most common side effects of NS2359 noted in clinical trials include: insomnia, weight loss, dizziness, headache, constipation, dry mouth, anxiety, increased heart rate and increased blood pressure. The heart rate and blood pressure increases were small and not clinically significant. There were no medication associated serious adverse events in any of the clinical trials conducted thus far. As described in Preliminary Studies in Research Strategy, a safety interaction trial of NS2359 and cocaine was conducted and no adverse interactions between NS2359 and cocaine were found (see Appendix I). The preliminary data support the safety of NS2359 for this trial. In the proposed trial, patients will be monitored closely (three times per week) to ensure that any adverse events will be identified and treated appropriately. Vital signs and weight will be monitored weekly by a nurse practitioner.

Clinical deterioration and/or suicide risk management: All of the investigators have had experience managing and referring subjects under these conditions. The TRC follows standing emergency policy when managing clinical deterioration related to addiction or psychiatric symptomatology for all of our subjects. At the weekly visit, subjects are evaluated for the presence or persistence of any symptoms indicative of clinical deterioration due to a rapidly increasing problem with cocaine use, alcohol use, and/or psychiatric symptoms, including suicidality. Between visits, subjects are instructed to contact their treating physician or an authorized research staff member in the event that disturbing symptoms become evident. In all cases, these subjects are immediately evaluated, and if deemed appropriate, are referred to clinical treatment. If possible, they will be maintained in the trial as long as it is deemed safe to do so. Also, any additional treatment is recorded for data analysis purposes. At any time, subjects who are severely suicidal or at high risk of medical or physical harm will be immediately discontinued from the trial and appropriate medical treatment instituted. All subjects who are discontinued from the trial are still encouraged to attend the follow-up visits.

4. Subject Selection and Withdrawal

4.1 Inclusion Criteria

1. Male and females, 18-70 years old.
2. Meets DSM-5 criteria for current diagnosis of cocaine use disorder moderate or severe, as determined by the SCID -5 semi-structured interview.
3. In the past 30 days, used no less than $100-worth of cocaine
4. Speaks, understands, and prints in English.

4.2 Exclusion Criteria

1. Meets DSM-5 criteria for a substance use disorder, moderate or severe on any substance other than cocaine, alcohol, marijuana or nicotine as determined by the SCID. Subjects with comorbid alcohol use disorder will be accepted if their alcohol use disorder is not severe enough to require a medical alcohol detoxification.
2. Needs treatment with any psychoactive medications (with the exception of diphenhydramine or melatonin, if necessary, for sleep).
3. Meets current or lifetime DSM-5 criteria for schizophrenia or any psychotic disorder, or organic mental disorder.
4. Has another Axis I psychiatric disorder that in the opinion of the PI will interfere with completion of the study or place the patient at heightened risk through participation in the trial.
5. Has evidence of a history of significant hematological, pulmonary, endocrine, cardiovascular, renal or gastrointestinal disease such as AIDS, active hepatitis, significant hepatocellular injury as evidenced by elevated bilirubin levels (>1.3), or elevated levels (over 3.5x normal) of aspartate aminotransferase (AST), and serum alanine aminotransferase (ALT).
6. Use of an investigational medication in the 30 days prior to randomization.
7. History of hypersensitivity to NS2359.
8. Is female and tests positive on a pregnancy test, is contemplating pregnancy in the next 6 months, is nursing, or is not using an effective contraceptive method (if relevant).
9. Has a self-reported gambling problem. This exclusion criterion is required because of the fishbowl technique of contingency management.

4.3 Subject Recruitment and Screening

Screening, consent and subject eligibility. After signing a screening consent, persons will be screened to verify that they meet all inclusion/exclusion criteria. A medical history, physical and laboratory examination will be conducted. The research clinician will offer eligible patients participation in the study. The study clinician will ensure that the patient understands the risks/potential benefits of the study prior to signing the consent form.

Contacting Subjects: Subjects are informed during the informed consent process that contact information provided to the research staff may be used at a later date to contact them by phone or mail. Reasons for contact include but are not limited to: missed appointments, appointment reminders, requests for follow-up visits, notifications of medical testing results, or other clinical reasons. Subjects are instructed to notify study staff if they no longer wish to be contacted.

4.4. Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Clinical trial discontinuation criteria: All randomized subjects are included in the intent-to-treat analysis. After the completion of Week 9, or at the termination for patients who discontinue from the trial prematurely, we will conduct the following procedures: physical exam, vital signs and weight, electrocardiogram, monitor adverse events and concomitant medications, obtain blood samples for chemistry, CBC, liver function tests, obtain a urinalysis (and a pregnancy test for women), Clinical Global Impression and the Treatment Opinion Form. They will also be scheduled for an end-of trial visit (unless it falls within 2 weeks of the final evaluation), and the follow up visit. Subjects will also be given appropriate treatment referrals. Subjects are not dropped from all study activity unless they request they not be contacted, or the subject cannot be located for assessment by the follow-up. Subjects will be informed at the consent session that medications may be discontinued (discretion of principal investigator and study doctor) due to: 1) Intolerable side effects; or 2) Extreme lab values with a repeat test. (AST or ALT levels greater than 5 times the upper limit of normal and bilirubin above 1.5 mg./dl). 3) If the participant develops signs of cardiovascular instability (vital signs and clinical evaluation; pulse at rest > 100 or BP at rest >140/90 mm Hg for more than 2 weeks or SBP>160, DBP>110, sitting quietly HR>110 on any visit will result in immediate discontinuation of study medications). In these cases, the subjects may continue with the CBT part of the treatment. Subjects will be informed at the consent session that he or she may be discontinued from all treatment due to: 1) Development or exacerbation of significant psychiatric or medical symptoms which necessitate inpatient admission or a more aggressive therapeutic intervention than provided by the protocol; these subjects would not be invited back to take study medication but will be followed for data collection and may remain eligible for psychosocial treatment; Psychiatric symptoms that would require inpatient treatment would include suicidal ideation acute psychosis or acute mania. 2) Emergence of another substance abuse problem which necessitates inpatient admission or a more aggressive treatment than provided by the protocol; subjects who are admitted for inpatient stabilization for alcohol and cocaine use may return for data collection and psychosocial treatment after discharge to complete the 11 week medication phase of the trial; 3) Clinical deterioration for any reason or a clinical status which necessitates inpatient admission; subjects may return for data collection and psychosocial treatment after discharge to complete the 9 week medication phase of the trial 4) Incarceration > 1 week; subjects may return for data collection and psychosocial treatment after discharge to complete the 11 week medication phase of the trial 5) subject behaviors compromise subject's safety. The reason the subjects are discontinued from medication and/or the clinical trial and any referrals made are documented on the Final Evaluation Form in the subject's casebooks.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

Standard procedures developed at the treatment sites are used to help locate missing subjects. These include the identification and verification of home and work phone numbers, emergency contacts and locators. Subjects who have missed an appointment are recontacted initially by phone, then by letter and finally by registered mail. Emergency and other locators are used when subjects themselves cannot be contacted. Contacts are attempted at least two times a week for a minimum of two weeks then less frequently by mail. Subjects are not considered lost to follow up until the entire study is completed and the database is ready to be closed.

5. Study Drug

5.1 Description

NS2359 is a novel drug candidate that exhibits potent in vitro and in vivo inhibition of re-uptake transporters for the neurotransmitters serotonin (5-HT), norepinephrine (NE) and dopamine (DA). It was developed under the name, NS2359, by NeuroSearch (now Saniona). GlaxoSmithKline had in-licensed NS2359 (as GSK372475) and performed pre-clinical and clinical studies. This compound was investigated for its potential as an antidepressant agent and for the treatment for adults with attention deficit hyperactivity disorder. Saniona has provided us with the API to investigate the potential of NS2359 in the treatment of cocaine addiction.

Study medication has been supplied by Saniona. Study medication will be maintained and dispensed by the Investigational Drug Service of the Hospital of the University of Pennsylvania.

5.2 Treatment Regimen

Three visits weekly will be scheduled for dispensing medication, and treatment evaluation will be scheduled so that patients have three visits per week. Medications will be started at the beginning of week 2 and stopped at the end of week 9. At each clinic visit (Monday, Wednesday and Friday), patients will be asked to take the medication under the direct observation of staff. The initial dose of the medication during week 2 will be 2 mg orally on days 1-7. Patients with intolerable adverse events at the 2 mg/day dose will be allowed to reduce the dose to 1 mg/day. Subjects with intolerable adverse events at the 1 mg/day dose will be allowed to reduce the dose to 1 mg every other day.

The Director of the Investigational Drug Service of the Hospital of the University of Pennsylvania will conduct the randomization using a computer-generated program of urn randomization, based on specified criteria that have been described below:

5.3 Method for Assigning Subjects to Treatment Groups

Urn Randomization. We plan to use urn randomization to stratify subjects across the two treatment conditions. We will stratify subjects on four baseline variables: 1) a co-morbid DSM-IV diagnosis of alcohol dependence; 2) gender; 3) high cocaine withdrawal symptom severity, as measured by a score above 22 on the Cocaine Selective Severity Assessment (CSSA, Kampman et al, 1998); 4) urine drug screen results on the day of randomization. Subjects with high CSSA scores and patients who enter a trial with cocaine positive urines often have poor outcomes during pharmacotherapy trials (Kampman et al, 2001, 2002).

An off-site statistician will work with the research pharmacist at IDS in setting up the urn randomization sequences, and will ensure that the codes linking subject's ID numbers to treatments are secure. IDS uses an electronic emergency-unmasking database that works off the PennKey and is accessible 24/7 from any computer with internet access. Tables are uploaded by IDS and pocket cards are issued to investigators when access is granted. The system only provides access for one subject at a time and all transactions are recorded. If a subject is prematurely discontinued from the trial, all attempts will be made to not break the blind. If an emergency necessitates that the blind be broken, only the pharmacist will have access to the blind to do so. He will be given the name of the staff members who have authority to request that the blind be broken. The IDS pharmacist can be reached 24 hours a day and can access a subject's code rapidly.

5.4 Preparation and Administration of Study Drug

Study medication will be prepared, stored and dispensed by the Research Pharmacist at Investigational Drug Services. Ken Rockwell 215 349 8817.

5.5 Subject Compliance Monitoring

Medication adherence. Adherence will be reinforced in several ways. There will be observed medication ingestion at each clinic visit, three times weekly. In addition, an automated telephone reminder system, utilizing either voice or text, will be used to remind patients to attend scheduled appointments and take medication on days between clinic appointments. Telephone voice reminders have been successfully used to enhance compliance in geriatric patients taking HIV medications and in patients taking asthma medications (Hayes et al., 2009; Strandbygaard et al, 2010, Pop-Eleches et al, 2011). Medication adherence will further be enhanced using weekly Medical Management (MM) sessions.

5.6 Prior and Concomitant Therapy

Concomitant medications will be recorded for the time period of one month before the initial screening visit throughout the follow up phase.

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Additional psychosocial therapies including self-help groups will be allowed during the randomized medication phase but will be measured using the Treatment Services Review (TSR).

5.7 Packaging

Study drug will be dispensed weekly in blister packs. Subjects will be instructed to bring their blister pack to each visit and dosing will be observed at each visit (three times weekly)

5.8 Blinding of Study Drug

Integrity of the blind. All research and clinical staff will be blind to the medication status until the end of the study. An off-site statistician will work with the research pharmacist in the urn randomization sequences, and will ensure that the codes linking subject's ID numbers to treatments are secured. If a patient is prematurely discontinued from the trial, all attempts will be made to maintain the blind. If an emergency necessitates that the blind be broken, study personnel who received access to the electronic unmasking database or the Penn pharmacist will have access to the blind. The Penn pharmacist will have the name(s) of the staff at all sites who have authority to request that the blind be broken. The Penn pharmacist is "on call" 24 hours a day.

5.9 Receiving, Storage, Dispensing and Return

5.9.1 Receipt of Drug Supplies

Study drug has been supplied by Saniona. It will be stored, and dispensed by the Research Pharmacy at the Hospital of the University of Pennsylvania consistent with regulations governing a Schedule II medication.

Upon receipt of the of the study treatment supplies, an inventory will be performed and a drug receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment (active drug or comparator) will be documented in the study files.

5.9.2 Storage

Study medication will be stored at the Research Pharmacy at the Hospital of the University of Pennsylvania as a Schedule II medication.

5.9.3 Dispensing of Study Drug

After randomization, study drug will be dispensed to each subject according to his or her randomization number. Medication will be dispensed on Mondays, Wednesdays and Fridays during clinic appointments by research staff who will observe ingestion. Ingestion of drug by each patient will be recorded in the CRF by research staff who observed ingestion by that patient. A dispensing log will be maintained at the Research Pharmacy. Sufficient medication in blister packs will be given to each patient weekly. Patients will be required to bring their blister packs to each clinic visit.

Regular study drug reconciliation will be performed to document drug assigned, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, and signed and dated by the study team.

5.9.4 Return of Study Drug

All unused study drug will be returned to the Research Pharmacy. At the completion of the study, there will be a final reconciliation of drug obtained from the Research Pharmacy, drug consumed, and drug returned. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented. Unused study drug will be destroyed in a manner consistent with regulations governing Schedule II medications.

6 Study Procedures.

Table 1. Schedule of Assessments

Assessment	*Week 1*	**Weeks 2-9**	**End of Trial**	**F/U**
Medical Exam and ECG ,CBC and blood chemistry Urinalysis (UA) Risk Assessment Battery	1X		1X	
Pregnancy Test (women),	1X	2X	1X	
Structured clinical Interview for DSM 5	1X			
Cocaine Selective Severity Assessment (CSSA)	3X	9X	1X	
Columbia Suicide Severity Rating Scale	1x	1x	1X	x
Vital Signs, Weight,	3X	24X	1X	1X
Clinical Global Impression Scale (CGI) Treatment Services Review (TSR) ,Concomitant Medications, Minnesota Cocaine Craving (MCC) scale, Urine Toxicology-other than cocaine	1X	9X	1X	1X
Urinary BE,Breathalyzer (BAL),Timeline Follow back (TLFB), SAFTEE	3X	24X	1X	1X
Addiction Severity Index (ASI),HAM A and D, Standard Form 36	1X	1X	1X	1X
Pill Counts		9X	1X	
Treatment Opinion Form		1X, week 5	1X	
Medical Management	1X	9X	1X	
Blood for NS2359 level		1X, week 5	1X	

DESCRIPTION OF INSTRUMENTS (See Table 1 for timing)

Measures to be used (See table below for timing)

Addiction Severity Index (ASI) (McLellan, 1992b). The ASI is a 45-minute interview which yields composite scores, ranging from 0 to 1, of problem severity over the past 30 days in 7 areas: medical, employment, drug use, alcohol use, legal, family/social, and psychiatric. The ASI will be used to characterize baseline demographic and drug use variables for each subject. The composite scores will be used as secondary outcome measures. The ASI is administered on four occasions spaced throughout the trial.

Clinical Global Impression Scale (CGI) (Guy, 1976). The CGI is a brief clinical rating of severity of illness (at time of interview) and global improvement (from admission) using a 7-point Likert scale. The CGI is completed by the MM practitioner, and the subject to assess clinical progress, global improvement and to assess the severity of the subject's illness at regular contacts over the course of the study. The CGI is done at baseline, weekly during the medication phase of the trial, at the end of the medication phase of the trial and at follow up.

Cocaine Selective Severity Assessment (CSSA) (Kampman, 1998). The CSSA is a 10-minute, 18-item clinician-administered cocaine withdrawal scale developed at the TRC. The CSSA will be used to stratify subjects at the start of the trial and to measure cocaine withdrawal symptom severity during the trial. The CSSA is administered at each visit during baseline and weekly during the medication phase of the trial.

Columbia Suicide Severity Rating Scale (C-SSRS) (Chappell, 2012). This is a 5-item scale with additional questions that may be asked based on the participant's responses to the core items. This questionnaire will assess both lifetime and recent suicidal ideation and behavior, including both passive and active thoughts/plans. It is extensively used across clinical practices, hospitals, research institutions and schools to address potential thoughts of suicide expressed by the client. This questionnaire will be administered at baseline, and once a week through the trial and at follow-up.

Hamilton Anxiety Rating Scale (Ham-A) (Hamilton, 1959). The Ham-A is a 15-minute, 14-item, clinician-administered instrument that measures current anxiety and changes in anxiety symptoms. The Ham-A is administered at baseline, end of medication phase, and at follow up.

Hamilton Depression Rating Scale (Ham-D) (Hamilton, 1967). The Ham-D is a 20-minute, 24-item interview that measures the severity of depression and changes in depressive symptoms. The Ham-D is administered at baseline, end of medication phase and at follow up.

Brief Substance Craving Scale (BSCS) (Somoza 1995). The BSCS is a valid and reliable measure of cocaine craving. The BSCS is administered at baseline, weekly during weeks 2-9 and at follow up.

Risk Assessment Battery (RAB) (Metzger, 1993). The RAB is a self-administered questionnaire designed for use with substance using populations. It provides a rapid and confidential method of assessing needle use practices and sexual activity associated with HIV transmission. The RAB is given at baseline and at week 9.

Short Form-36 Health Status Questionnaire (SF-36) (Jenkinson, 1994). The SF-36 is a 36-item self-report of the subject's quality of life, and will be completed at baseline, end of medication phase and at follow up.

Structured Clinical Interview for DSM- 5 (SCID) The SCID 5 is a 60-minute, semi-structured interview that yields current and lifetime DSM-IV Axis I diagnoses for the major psychiatric disorders including cocaine and alcohol dependence. The SCID is administered once during week 1.

Systematic Assessment for Treatment Emergent Effects (SAFTEE) (Rabkin et al., 1992). Adverse events are queried and documented at each visit by the SAFTEE. This constitutes our primary measure of safety.

Timeline Follow-Back Interview (TLFB, Sobell, 1995). The TLFB is a 15-30 minute, semi-structured interview that measures self reported cocaine use and other drug use. The TLFB will be administered at each visit.

Treatment Opinion Form (TOF) The TOF questionnaire asks the MM clinician and subject whether they think the subject is receiving active medication or placebo. It will be administered twice (mid- and end-trial).

Treatment Services Review (TSR) (McLellan, 1992a). The measure is given at baseline, weekly throughout the medication phase and at follow up, providing a record of non-study treatment services throughout the trial.

Laboratory Measurements (in alphabetical order)

Blood chemistry and CBC are obtained to assess for adverse events. Enzyme levels will be obtained once at baseline and at the beginning of week 7 and at the end of week 9.

Pregnancy Testing Urine pregnancy tests will be obtained from all women at weeks 1, 5, 9, and end of study.

Plasma NS2359 Level A blood sample will be obtained at the end of week 5 (steady state for 1mg/day) and at the end of week 9 (steady state for 1.5 mg/day). Plasma NS2359 levels will be measured using a reverse phase high performance liquid chromatography/tandem mass spectrometry method (Appendix 3). All samples (n = 2 samples each for patients treated with NS2359) will be assayed in one batch in a commercial lab (www.aptuit.com) by the individual who developed the assay for GSK, Luca Ferrari, PhD (letter attached). Values will be reported to Drs. Berrettini and Kampman, then entered into the database. Because all patients will take medication under direct study staff observation three times weekly, it is not expected that any sample will have undetectable levels of NS2359, given its long half-life of ~ 7 days. Any samples with undetectable NS2359 will be re-assayed. Plasma levels will be used in data analysis (see below) as quantitative co-variates.

Urine Drug Screen and Urine Benzoylecgonine (BE) Qualitative urine BE will be assessed three times weekly throughout the trial. Qualitative (emit) urine toxicology for other drugs (benzodiazepines, barbiturates, opiates, marijuana, and amphetamine) is done at baseline and weekly throughout the trial.

Regular evaluation visits. Subjects will have appointments with study staff three times weekly throughout the 8-week medication phase of the trial, Monday, Wednesday and Friday. An automated telephone system will provide reminder calls and/or text messages to enhance attendance. Urine drug screens (UDS) for benzoylecgonine (BE) will be obtained at each visit, along with vital signs and weight, CSSA, adverse events (SAFTEE) and time line follow back (TLFB). Clinical Global Impression (CGI), the Minnesota Cocaine Craving Scale (MCCS), the Columbia Suicide Severity Rating Scale (CSSRS) and Treatment Services Review (TSR) will be obtained weekly. Other measures completed routinely but not weekly are as follows: Addiction Severity Index (ASI), Short Form 36 (SF36), Hamilton Anxiety Rating Scale (HAM-A), and a Hamilton Depression Rating Scale (HAM-D), the Risk Assessment Battery (RAB), and the Treatment Opinion Form (TOF) from the MM clinicians. A description and schedule of assessments is provided below. Each patient will meet weekly with the MM clinician who will assess clinical status, dispense study medications and monitor adverse events and concomitant medications.

After the completion of Week 9, or at the termination for patients who discontinue from the trial prematurely, we will conduct the following procedures: physical exam, vital signs and weight, electrocardiogram, monitor adverse events and concomitant medications, obtain blood samples for chemistry, CBC, liver function tests, obtain a urinalysis (and a pregnancy test for women), CGI, and the TOF. A safety follow up visit will be conducted one month after the completion of the medication phase at week 9. At this follow-up visit, a nurse practitioner will

collect the following: vital signs and weight, monitor adverse events and concomitant medications. A research technician will conduct the following procedures: breathalyzer, ASI, TSR, PACS, MCCS, SF36, TLFB, and a UDS for BE and other drugs.

Psychosocial Treatment. Subjects will participate in weekly manualized individual cognitive behavioral relapse prevention psychotherapy from week 2 through week 9. (Carroll, 1998). They will also receive weekly Medication Management (MM), an intervention developed as part of NIAAA's Project COMBINE study, that provides advice and support from medical practitioners concomitantly with dispensing medications, safety checking and compliance (Pettinati et al., 2004). The main goal of MM is to increase the likelihood that patients will reduce their cocaine use. The initial MM session is an hour; subsequent sessions are 15-30 minutes.

7 Statistical Plan

7.1 Sample Size Determination

Power Analyses: We have one primary hypothesis and will test it at a 5% level of significance. Our principal interest is in the comparison of urine drug screen BE results between the placebo group and the NS2359 group during the final three weeks of the medication phase (weeks 7-9). To ensure an intent-to-treat comparison, we will test this in the context of a model that uses all data. Power will largely depend on the amount of data available for the final period, so we focus on that. Given our assumptions on dropout rate and missing data, about 60 people will yield a response for the final period, and 20 will be missing. For the case when missing data are regarded as indicative of use, then we have a full sample of 80 subjects. This yields 80% power for an odds ratio of 3.6 or larger (corresponding to a difference such as 30% versus 61%). If missing data are ignored, then we have 80% power for an odds ratio of 4.5.

7.2 Statistical Methods

Data Management. Data will be gathered using Penn's Center for the Study of Addiction's (CSA) direct-entry data system, and will be stored on the data management unit (DMU) network. Interview data and self-report data are entered directly onto computers at the research sites, by research technicians and study subjects respectively. Field validation (eg, no out of range or otherwise invalid responses will be accepted) and form validation (e.g. logically impossible responses to different questions will not be accepted) are built into this entry process. Data are transmitted (128-bit encrypted form) over the internet to the DMU servers. After online reviews, the data are archived on the servers. No identifying information is stored on the DMU servers. Certain DMU staff members have permission to modify the archived data. Audit logs record any modification to the original entry. Password protection allows members of the research team appropriate levels of data access.

Data Analyses. Kevin Lynch, PhD, the CSA Statistician, and his staff will perform the data analyses. Prior to analyses, standard data screening/cleaning procedures will be applied [53]. These procedures will screen the data for data-entry errors, check for outliers, assess the extent and pattern of missing data, and check that appropriate assumptions of normality are met whenever necessary. Due to sample size, it is unlikely that the randomization will result in significant imbalance of the distributions of demographic or other variables across treatment groups. Additional covariates will be considered for inclusion in the analyses, to improve the precision of estimation for the treatment effects. Covariates describing levels of cocaine use prior to the study may be included. Assumptions underlying the application of statistical methods will be examined, through use of standardized residuals, influence diagnostics, and graphical displays. **Primary Hypothesis:** More subjects treated with active medication will

achieve 3 consecutive weeks of cocaine abstinence during the last three weeks of the medication trial compared to placebo-treated subjects Abstinence will be determined by self-report using the TLFB method and urine BE levels. Cocaine use will be measured by three-times-weekly urine BE levels, so the total urine BE data will be 24 binary indicators of cocaine use, accompanied by TLFB data. These data will be employed to assign a binary use/no-new-use measure for each day of the treatment period. To explicitly address the primary hypothesis of abstinence during the final three weeks, we will model time as a four-level discrete variable, corresponding to weeks 2-4, 4-6, and 7-9, and will determine whether subjects show complete abstinence during those periods. This will yield a binary response for each subject for each of the three periods. We will use a generalized linear mixed effects model to estimate the effects of medication group and time on the log-odds of complete abstinence across the periods, and in particular during the last three weeks of the treatment phase. The explanatory variables in these models will be a binary indicator of medication group, variables representing time effects, together with possible interaction terms. Possible interaction terms include gender and plasma NS2359 levels at week 5 and week 9. The group by time interactions will yield an estimate of the log odds of complete abstinence for the final three weeks, for the active medication group versus the placebo group, explicitly addressing the primary hypothesis. If we find that these interaction terms are not significant, then we will remove them from the model and compare the two groups across the entire 8-week treatment period.

Secondary Hypotheses:

Secondary Hypothesis 1: Subjects treated with the active medication will have reduced craving for cocaine, compared to placebo-treated subjects, as measured by the Brief Substance Craving Scale (BSCS) Scale. The BSCS scale will provide weekly measures of cocaine craving. The scale provides a six-category Likert response, and it is likely that we will collapse some adjacent categories prior to the analyses, and regard the responses as ordinal. We will compare the two medication groups across the treatment weeks using mixed-effects models for ordinal responses [54]. The fixed effects are the medication group, and time, together with possible interaction terms. The effect of time will be broken into linear, quadratic and, possibly, cubic, trends across the weekly time points. These analyses will be performed using PROC GLIMMIX in SAS.

Secondary Hypothesis 2: Subjects treated with the active medication will have reduced cocaine withdrawal symptom severity, as measured by the Cocaine Selective Severity Assessment (CSSA). The CSSA provides weekly measures of the severity cocaine withdrawal, whose distribution is likely to be skewed towards higher values. Based on our experiences with these responses in other studies, we expect that a log transformation of these responses will yield approximately normally distributed responses. The hypothesis (that medication will decrease CSSA scores) will be tested using linear mixed effects models, following the same approach described for Hypothesis 2. These models will be fit using PROC MIXED in SAS, or PROC GLIMMIX if transformations fail to reduce skewness enough for the assumption of a Normal response to be valid..

Secondary Hypothesis 3: subjects treated with the active medication will have higher rates of cocaine abstinence during the treatment period, and at the final appointment, four weeks after the 8 weeks of medication treatment has been completed, as measured by self-report and by urine drug screen for BE levels. The analyses will use the same type of generalized linear mixed effects models as described for the Primary hypothesis above. In contrast to the earlier analyses, where the focus was on three-week periods, we will examine weekly time-periods, and will include the week 15 follow up as an additional time point.

Missing Data and Nonadherence: For the longitudinal analyses described above, premature discontinuation from treatment and occasional missing daily use indicators will lead

to incomplete data. The mixed effects models described above can make use of all available data provided by subjects, but the inferences drawn from them will be unaffected by the missing data only if the missing data can be regarded as ignorable, in the sense of Laird [55]. To assess the sensitivity of our analyses to this assumption, we will use shared parameter models, which allow for correlated random effects underlying the cocaine use measurements and the pattern of dropout [56]**.** We will also use selection models to examine the effects of missing data [57,58]. We will explicitly model the probability of premature discontinuation at a time point as a function of baseline characteristics and responses at previous time points, using a logistic regression model, and incorporate the predicted probabilities into a weighted analysis of the main hypotheses. We will do analyses in a range of assumptions and assess the sensitivity of results to them [58]. We will use self-report of pill ingestion, and blood levels of NS2359 as measures of compliance with assigned medication regime. We will use the methods of Nagelkerke et al [59] and Small et al [60], to obtain estimates of the intervention effect in a population compliant with treatment i.e. the Complier Average Causal Effect (CACE).

Safety: The SAFTEE responses will be analyzed as a measure of safety. Total number of adverse events, adverse events leading to discontinuation (in the judgment of the study physician), % of patients reporting at least one adverse event, clinical lab assessments, ECG, vital signs, BMI and evidence of clinical worsening (by urine drug screen results and TLFB results) will be considered in assessment of safety. In a manner parallel to the analysis for therapeutic response, medication group, plasma NS2359 levels, gender, age and other clinical variables will be entered into a generalized linear mixed effects model to predict adverse events. Body weight is measured weekly, as NS2359 may cause weight loss is some individuals [6].

7.3 Subject Population(s) for Analysis

All-treated population: Any subject randomized into the study that received at least one dose of study drug

8. Safety and Adverse Events

8.1 Definitions

Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity

- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period
The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an adverse event if <u>any one of the following</u> conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events

8.3.1 Study Sponsor Notification by Investigator

A serious adverse event must be reported to the study sponsor (Penn) by email or telephone within 72 hours of when the event is reported to any of the study staff. A Serious Adverse Event (SAE) form must be completed by the investigator and faxed to the study sponsor within 72 hours. The investigator will keep a copy of this SAE form on file at the study site. Report serious adverse events by phone and facsimile to the study sponsor:

Kyle M. Kampman, M.D. 215 222 3200 x 109 215 386 6770 fax

kampman@upenn.edu

At the time of the initial report, the following information should be provided:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

Within the following 48 hours, the investigator must provide further information on the serious adverse event in the form of a written narrative. This should include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing serious adverse events should be provided promptly to the study sponsor.

8.3.2 EC/IRB Notification by Investigator

Reports of all serious adverse events (including follow-up information) must be submitted to the EC/IRB based on the IRBs current AE/SAE reporting requirements and timeline for reporting (e.g. 5 business days). Copies of each report and documentation of EC/IRB notification and receipt will be kept in the study regulatory binder.

8.3.3 FDA Notification by Sponsor

The study sponsor (Penn) shall notify the FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible based on the FDAs current SAE reporting requirements and timeline for reporting (e.g. no later than 7 calendar days from the sponsor's original receipt of the information).

If a previous adverse event that was not initially deemed reportable is later found to fit the criteria for reporting, the study sponsor (Penn) will submit the adverse event in a written report to the FDA as soon as possible based on the FDAs reporting requirements and timeline for reporting (e.g. but no later than 15 calendar days from the time the determination is made).

8.4 Unblinding Procedures

All research staff will be blind to the medication status until the end of the study. An off-site statistician will work with the research pharmacist at IDS in setting up the urn randomization sequences, and will ensure that the codes linking subject's ID numbers to treatments are secure. *IDS uses* an electronic emergency-unmasking database that works off the PennKey and is accessible 24/7 from any computer with internet access. Tables are uploaded by IDS and pocket cards are issued to investigators when access is granted. The system only provides access for one subject at a time and all transactions are recorded. If a subject is prematurely discontinued from the trial, all attempts will be made to not break the blind. If an emergency necessitates that the blind be broken, only the pharmacist or approved study personnel will have access to the blind to do so. He will be given the names of the staff members who have authority to request that the blind be broken (Dr. Kampman or the TRC Doctor-On-Call). The IDS pharmacist can be reached 24 hours a day by beeper and can access a subject's code rapidly. The CBT therapist and subject will be asked for their opinion twice (mid- and end-trial) about whether they think the subject is receiving NS2359 or placebo.

8.5 Stopping Rules

Clinical trial discontinuation criteria: All randomized subjects are included in the intent-to-treat analysis. All subjects who prematurely discontinue treatment will be scheduled for a final evaluation, end-of trial visit (unless these two fall within 2 weeks of each other), and the follow up visit. Subjects will also be given appropriate treatment referrals. Subjects are not dropped from all study activity unless they request they not be contacted, or the subject cannot be located for assessment by the follow-up. Subjects will be informed at the consent session that medications may be discontinued due to: 1) Intolerable side effects; or 2) Extreme lab values with a repeat test. (AST or ALT levels greater than 5 times the upper limit of normal and bilirubin above 1.5 mg./dl) In these two cases, the subjects may continue with the CBT part of the treatment. Subjects will be informed at the consent session that he or she may be discontinued from all treatment due to: 1) Development or exacerbation of significant psychiatric or medical symptoms which necessitate inpatient admission or a more aggressive therapeutic intervention than provided by the protocol; these subjects would not be invited back to take study medication but will be followed for data collection and may remain eligible for psychosocial treatment; 2) An emergence of another substance abuse problem which necessitates inpatient admission or a more aggressive treatment than provided by the protocol; subjects who are admitted for inpatient stabilization for alcohol and cocaine use may return for data collection and psychosocial treatment after discharge to complete the 8 week medication phase of the trial 3) Clinical deterioration for any reason or a clinical status which necessitates inpatient admission; subjects may return for data collection and psychosocial treatment after discharge to complete the 8 week medication phase of the trial 4) Incarceration > 1 week; subjects may return for data collection and psychosocial treatment after discharge to complete the 8 week medication phase of the trial 5) subject behaviors compromise subject's safety. 6) signs of cardiovascular instability (vital signs and clinical evaluation; pulse at rest > 100 or BP at rest >140/90 mm Hg for more than 2 weeks or SBP>160, DBP>110, sitting quietly HR>110 on any visit will result in immediate discontinuation of study medications). Subjects who experience elevated blood pressure as a result of exposure to study medications will be allowed to continue to participate in psychosocial treatment. The reason the subjects are discontinued from medication and/or the clinical trial and any referrals made are documented on the Final Evaluation Form in the subject's casebooks.

Study Stopping Criteria: In addition to oversight by the University of Pennsylvania IRB and Office of Human Research , the trial will be conducted under the supervision of a Data Safety and Monitoring Board, as outlined below in section 8.6.1. This independent board will review the study every 6 months. The DSMB is charged with monitoring the safety of participants and the quality of the data, as well as the appropriate termination of studies either when significant benefits or risks have been uncovered or when it appears that a clinical trial cannot be concluded successfully. The DSMB will review all adverse events and will have access to unblinded data in order to determine the association between adverse events and study medication. If a pattern of significant adverse events is uncovered that suggests that the risks of continuing the trial outweigh the expected benefits of the trial then the DSMB will recommend that the study be stopped.

8.6 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data

and safety-monitoring plan (see section 9 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

8.6.1 Internal Data and Safety Monitoring Board

Purpose: The monitoring of a clinical trial is necessary to ensure the protection of the patient's rights, the safety of the patients enrolled in the trial and the integrity and quality of the resulting data. This monitoring plan details the source data verification of efficacy and safety parameters, the frequency of monitoring visits, regulatory document review and drug accountability/patient compliance.

Protocol summary: This trial is intended to explore the potential efficacy and tolerability of NS2359 for the treatment of cocaine dependent patients. Patients admitted to this trial will be men and women with cocaine dependence. Treatment will consist of 8 weeks of NS2359 or placebo plus weekly individual cognitive behavioral relapse prevention therapy and medical management therapy.

Monitor selection and training: One monitor will be assigned for this trial and will be responsible to complete the monitoring process. The monitor will be selected from one of the Study Coordinators working at the University of Pennsylvania Center for the Studies of Addictions. A CV for the monitor will be obtained and updated bi-annually. The CV will be kept in the regulatory binder to document the qualifications of the monitor. Monitors will be trained by the Administrative Director of the TRC. Monitors will meet with the Administrative director and review the protocol, CRF and the monitoring checklists to be completed by the monitor. The monitoring process will be reviewed and approved by the University of Pennsylvania Office of Human Research.

Study initiation visit: The Principal Investigator will be responsible for assuring through personal contact between the co-investigators, the monitor and the clinical staff that each clearly understands and accepts the obligations incurred in the undertaking of this clinical trial.

The co-Principal Investigators (Drs. Kampman and Berrettini) and the assigned monitor will meet with the clinical staff (research nurses and study technician) to ensure that they understand and accept the following: the nature of the protocol and the requirements for an adequate and well-controlled study; the obligation to conduct the clinical investigation in accordance with 21 CFR Parts 312, 511, 812, 813 and any other applicable regulations; the obligation to obtain informed consent in accordance with 21 CFR Part 50; the obligation to obtain IRB review and approval of a clinical investigation before the investigation may be initiated and to ensure continuing review of the study by the IRB in accordance with 21 CFR Part 56; and to keep the sponsor informed of such IRB approval and subsequent IRB actions concerning the study.

Training will consist of an explanation of the protocol and review of the CRF. In addition the duties of each member of the staff outlined in all applicable regulations will be reviewed. All questions will be answered.

A report of the Study Initiation will be written by the monitor detailing the visit, specifically noting the information reviewed with the clinical staff and any questions generated during the training. The report will be filed in the regulatory binder. A copy of the Study Initiation Report will be sent to the Office of Human Research, University of Pennsylvania School of Medicine, Room 150 Anatomy-Chemistry Building, Philadelphia, PA 19104-6061.

Monitoring Visits: Monitoring will be conducted in accordance with University of Pennsylvania Sponsor-Investigator Standard Operating Procedure PM 504. Enrollment will be complete when 80 patients are randomized into the trial. Approximately 4 patients will be randomized per month. Monitoring visits will be conducted periodically

throughout the study. The first monitoring visit will occur no more than two weeks after the first patient is entered. Subsequent monitoring visits will be conducted quarterly.

Monitoring log: At the beginning of each monitoring visit, the monitor and any representative of the Sponsor participating in any aspect of monitoring the study is required to sign and date the monitoring log documenting the visit.

Monitoring report: All monitoring visits will be documented on the Monitor's Report and Visit Checklist. The original report for each visit will be filed with in the regulatory binder and copies of the report will be sent to the Data Safety Monitoring Board (DSMB) and the Office of Human Research at the aforementioned address**.**

Routine Monitoring Visits:

Monitoring visits are conducted periodically throughout the study as described below.

- Visit 1: Initiation Visit
- Visit 2: Approximately 25% of subjects to be randomized have completed the trial and 100% Source Document Verification for the first two randomized subjects
- Visit 3: Approximately 50% of subjects to be randomized have completed the trial.
- Visit 4: Approximately 100% of subjects to be randomized have completed the trial. This visit serves as the closeout-monitoring visit.

Study initiation visit: The Principal Investigator will be responsible for assuring through personal contact between the co-investigators, the monitor and the clinical staff that each clearly understands and accepts the obligations incurred in the undertaking of this clinical trial.

The Principal Investigator and the assigned monitor will meet with the clinical staff (research nurses and study technician) to ensure that they understand and accept the following: the nature of the protocol and the requirements for an adequate and well-controlled study; the obligation to conduct the clinical investigation in accordance with 21 CFR Parts 312, 511, 812, 813 and any other applicable regulations; the obligation to obtain informed consent in accordance with 21 CFR Part 50; the obligation to obtain IRB review and approval of a clinical investigation before the investigation may be initiated and to ensure continuing review of the study by the IRB in accordance with 21 CFR Part 56; and to keep the sponsor informed of such IRB approval and subsequent IRB actions concerning the study.

Training will consist of an explanation of the protocol and review of the CRF. In addition the duties of each member of the staff outlined in all applicable regulations will be reviewed. All questions will be answered.

A report of the Study Initiation will be written by the monitor detailing the visit, specifically noting the information reviewed with the clinical staff and any questions generated during the training. The report will be filed in the regulatory binder. A copy of the Study Initiation Report will be sent to the Office of Human Research, University of Pennsylvania School of Medicine, Room 150 Anatomy-Chemistry Building, Philadelphia, PA 19104-6061.

Visits 2, 3 and 4:

Regulatory binders and Case Report Forms

All regulatory documents are maintained in the Regulatory Binder. The monitor at monitoring visit 2, 3 and 4 will review the Regulatory Binder.

==> The **Compliance Assessment Checklist**, developed by the University of Pennsylvania Office of Human Research, will be used for monitoring the Regulatory Binders. This form is located on the OHR website.

==> The monitor will also ensure that the CRFs are being completed and Final QA'd in a timely manner and that FMPro is up to date and complete.

For all Randomized subjects the following will be reviewed:

1) Screening consent

==> Source document verify (SDV) that consent is on file with signature, date, and proper version.

2) Informed consent

==> SDV that consent on file with signature, date, and proper version.

3) Inclusion/Exclusion Criteria

==> SVD for completeness and accuracy.

4) Severe Adverse Events (SAEs)

==> Verify study specific reporting requirements were followed for reportable SAEs according to section 8.3 above and proper follow-up and resolution of SAE was documented.

5) Adverse Events

==> Verify an annual blinded report of all AEs was reviewed by study PI and M.D.

==> Review all AEs collected during the study reported as severe were reported to appropriate agency and resolved.

6) Drug accountability

==> Verify all drug accountability form are complete for subjects finished the treatment phase of the study and medication is returned to pharmacy.

7) Stopping Rules

==> Verify documentation of Final Evaluation Form for subjects finished the treatment phase.

8) Prohibited Concomitant Medication

==> Verify restricted concomitant meds were not taken.

9) Review gross clinical indicators for all subjects lost to follow-up during the treatment phase of the trial.

==> Review of drug use captured on TLFB and UDS;

==> Review of HAMS for high scores;

==> Review of Clinical notes by the Director of Operations or his designee;

==> Summary of relevant findings will be written by monitor and Director of Operations and included in the report.

10) Review of key safety & efficacy data for those subjects discontinued due to AEs

==> Specifically a thorough review of Clinical Notes by the Director of Operations or his designee. Relevant findings will be summarized and included in the monitoring report.

Additional 100% Source Data Verification (SDV) for Randomized subjects with the DMU, Clinical Chart, and Case Report Form

==> At the second visit the monitor will 100% SDV 1 subject among the first 25% of participants;

==> At the third visit the monitor will 100% SDV 1 subject between 25% and 50% of participants randomized;

==> At the fourth visit the monitor will 100% SDV 1 subject between 50% and 75% of participants randomized.

If a greater than 10% error rate is noted during the data review, the monitor will source data verify 100% of the data on a larger sample at the following monitoring visit.

Visit 4: Close-Out Visit:

The monitor will conduct the Close-Out Visit at the time of the fifth monitoring visit. The monitor will complete the following activities at visit 5 in addition to the above items to close out the study:

==> Ensure all data have been reviewed and collected;

==> Ensure all outstanding queries are answered;

==> Perform drug accountability and return any unused drug to the Penn Pharmacy;

==> Review requirements for record retention with the investigator and the clinical staff;

==> The **Close-Out Visit Report,** developed by the University of Pennsylvania Office of Research, will be used for monitoring the Regulatory Binders. This form is located on the OHR website.

Content of monitoring report;

Monitoring visits can be documented on the **Monitoring Visit Report**, developed by the University of Pennsylvania Office of Human Research. This form is located on the OHR website. After each visit is complete the monitor and investigator will review the report. The original report for each visit will be filed in the Monitoring Binder maintained by the Regulatory Coordinator. In addition to the Monitoring Visit Report, the monitor will write a letter to the PI addressing each component of the visit. Queries will be given to the study staff to complete within 1 month of the report.

8.6.2 Independent Data and Safety Monitoring Board

A safety monitoring board has been established at the Center for the Studies of Addiction with the following purpose (according to NIDA guidelines): to assure that the safety of study subjects is protected while the scientific goals of the ongoing studies are being met. Specifically, the DSMB is charged with monitoring the safety of participants and the quality of the data, as well as the appropriate termination of studies either when significant benefits or risks have been uncovered or when it appears that a clinical trial cannot be concluded successfully.

All board members will meet NIDA requirements regarding background and experience, and none will have ethical conflicts, including financial interest related to study outcome.

Individuals invited to serve on the board will disclose any potential conflicts in writing. The board will meet every six months (unless more frequent meeting are deemed necessary) and will be chaired by David Oslin, M.D., a faculty member within the Department of Psychiatry at the University of Pennsylvania. Other members of the board include Kevin Lynch, Ph.D. (senior statistician), and David Metzger, PhD., who are faculty members of the University of Pennsylvania School of Medicine, Department of Psychiatry. When the current study is reviewed, Dr. Kampman will open the meeting with a report on the trial status, followed by a closed session under the direction of Dr. Oslin. Issues related to recruitment, subject safety and efficacy, whether the primary study question is being answered, conflict of interest, confidentiality, and ongoing study review (including AEs, SAEs, and regulatory issues) will be assessed. Following each DSM Board meeting, Dr. Oslin will make recommendations to Dr. Kampman, and a final report (edited by all Board members) will be prepared and submitted to NIDA, the Penn IRB, and (if required) the FDA.

In addition to semiannual reviews, at the occurrence of the second medication associated serious adverse event or after the first fatal medication associated adverse event the protocol will be reviewed by the DSMB the DSMB to consider modifications to the protocol or discontinuation.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

Research data will be collected electronically on the internet at <https://dmu.trc.upenn.edu/dmumain>, a password-protected website run by the University of Pennsylvania's Data Management Unit. Binders will also be kept for each participant. These will contain checklists for study assessments to be administered online, as well as source documents.

9.4 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

This study will be monitored according to the monitoring plan as noted above. The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Attachments for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12 Study Finances

12.1 Funding Source

This study is financed through a grant from the DANA Foundatio. Saniona has provided study drug.

12.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All University of Pennsylvania investigators will follow the University conflict of interest policy.

12.3 Subject Stipends or Payments

Attendance and Adherence Contingencies. Contingency management (CM), where tangible reinforcement is provided in close temporal proximity to a subject performing a target behavior (e.g., on-time attendance, drug abstinence, medication compliance) is highly efficacious in engendering abstinence and other target behaviors among many patients engaged in substance abuse treatment. During screening, participants will receive $30 total cash (two payments of $15 if screening is completed over two days, or three payments of $10 if screening assessments span three days). Participants will receive $25 cash for the follow up study visit at week 13. During the active phase, CM will be provided in the form of an opaque “fishbowl” with a high proportion of chips with little ($1) monetary value. Subjects draw from the fishbowl upon completion of an objectively verified target behavior, and bonuses are often provided for continued performance. Petry and colleagues have seen success with the fishbowl for attendance in prior studies, and our recently completed trial of varenicline for CA used a fishbowl for attendance and treatment visit compliance, resulting in attendance rates of 80% 42, as compared to the <60% attendance rates seen in many of our prior clinical trials.

For each visit, subjects will provide a urine sample, take medication and complete assessment paperwork. Upon completion of all requirements for a given visit, patients will receive fishbowl draws for that visit. Draws will be available on an escalating schedule with a bonus contingency. Attendance at all three visits earns subjects bonus draws for that week.

Failure to attend a visit without prior approval or failure to complete all visit requirements results in no draws earned for that visit and results in loss of bonus draws for that week.

The fishbowl contains 500 chips, half (250) with no value that simply say “good job”, 219 of which have a value of $1, 30 of which have a value of $5, 2 have a value of $25, and 1 of which has a value of $50. Patient will earn five draws per visit, for week 2 (visits 4-6), with draws increasing by one each week. The weekly bonus draws will remain constant at 5 draws. Subjects who attend all required visits will have the opportunity to make 203 draws from the fishbowl, for maximum possible earnings of $800 during the trial. Based on prior use of this fishbowl schedule, actual earnings based on the statistics of drawing chips with dollar value for each patient are expected to be approximately $400. Subjects will receive vouchers redeemable for gift cards from local merchants contingent on attendance at each visit and completing all required activities. Gift cards are used to avoid giving cash to CUD patients, as cash is often a trigger for drug craving and relapse. Patients will receive $5.00 for each medication pack they return for a total of up to $40 in cash.

Financially compensation for travel Patients will receive 2 transit tokens at each visit totaling ; 56 transit tokens valued at $112..

13 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

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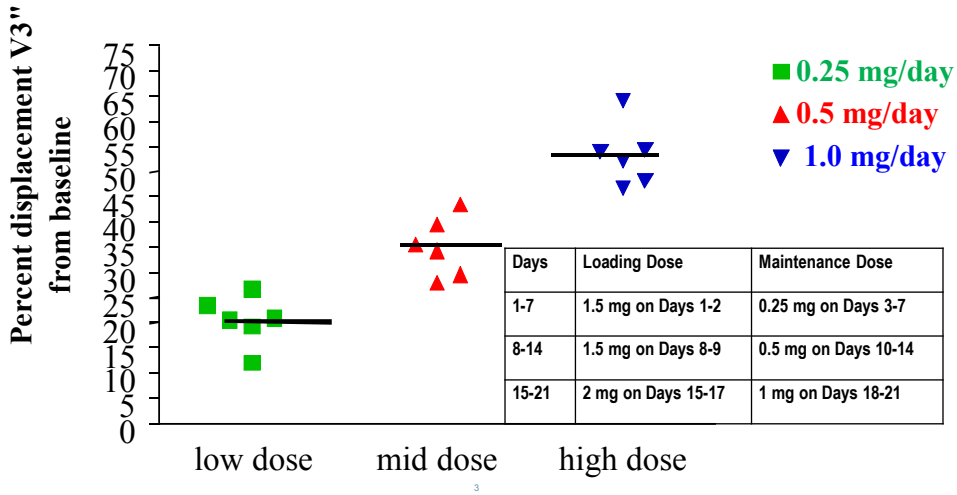
Introduction to Amendment 1

In this phase II 8 week randomized double-blind, placebo-controlled trial of NS2359 in cocaine use disorder, with a dose of 1.3 mg/day of the free base (2.0 mg of the tartrate monohydrate), interim blinded analysis of 40 persons (19 from group 1 and 21 from group 2) provided sufficient toxicology and self-report data to determine whether any of those weeks were cocaine use weeks, according to the same weekly-use definition described in the main protocol, (section 3.2). For these 40, 89% of group 1 and 90% of group 2 had cocaine use in the final three weeks (Chi-square=0.01, p=0.92). There were no serious adverse events and this dose was well-tolerated.

SPECT Study of Human Striatal Dopamine Transporter Occupancy at 0.25, 0.50 and 1 mg Doses of NS2359.

~90% DA transporter occupancy is estimated for steady state plasma levels of 25-30 ng/ml at 2 mg/day by extrapolation.



Days	Loading Dose	Maintenance Dose
1-7	1.5 mg on Days 1-2	0.25 mg on Days 3-7
8-14	1.5 mg on Days 8-9	0.5 mg on Days 10-14
15-21	2 mg on Days 15-17	1 mg on Days 18-21

We propose to continue the trial using 2.0 mg/day of the free base (equivalent to 2.7 mg/day of the tartrate monohydrate). The rationale for continuing the trial at this higher dose is found in evidence for target engagement only at this higher dose, based on a brain-imaging study. At an oral dose of 1 mg/day free base, mean trough steady-state plasma values are approximately 12 ng/ml, and dopamine transporter occupancy is only 55%. At an oral dose of 2.0 mg/day free base, mean trough steady-state plasma values are approximately 30 ng/ml, and the extrapolated estimated dopamine transporter occupancy is ~90%. A high degree of DA transporter occupancy is characteristic of compounds which block cocaine self-administration in primates (Lindsey et al, 2004).

Study Design

The overall design of the trial will remain the same except where specifically noted below. There will be no changes in subject selection, primary and secondary endpoints, subject selection and withdrawal. There will be no changes to Section 8 of the protocol Safety and Adverse Events. There will be no changes to Sections 10, 11, 12, or 13.

Study Medication

Capsules containing 2.7 mg of NS2359 tartrate monohydrate will be manufactured using the techniques described Section 5 of the main protocol and further described in the CMC of the IND 112053.

Procedures

In addition to the 55 of subjects already enrolled in the trial, an additional 36 subjects will be randomized to either 2.7 mg of NS2359 or identical placebo capsules in a ratio of 4:1. Twenty seven subjects will receive 2.7 mg and 9 subjects will receive placebo. For these 36 subjects all other study procedures will be identical to those described in the main protocol.

Statistical Plan

Sample Size Determination

Power Analyses: *For this renewal, we will combine the planned nine new placebo participants with the 21 already recruited, and compare their outcomes with those of the 36 participants recruited into the high dose group. We have the same primary hypothesis as in the original study, namely that during the final three weeks of the medication phase (weeks 7-9), the high dose NS2359 group will have a lower rate of positive urine drug screen BE results than the placebo group. If we regard missing UDS tests as positive for use, then we will compare 36 to 30 participants, which yields 80% power for an odds ratio of 4.1 or larger (corresponding to a difference such as 30% versus 64%); if missing data are ignored, resulting in a 25% loss in sample size, then we have 80% power for an odds ratio of 5.2.*

Statistical Methods

Data Management. The data will be managed using Penn's Center for the Study of Addiction's (CSA) direct-entry data system, and will be stored on the data management unit (DMU) network, as described in the original proposal.

Data Analyses. The data analysis procedures will closely parallel those described in the original proposal. Dr. Kevin Lynch, PhD, the CSA Statistician, and his staff will perform the data analyses. The main change will be that we will combine the placebo and low dose NS2359 participants from the current study with the additional placebo and high dose NS2359 participants, yielding a three-group (placebo, low dose, high dose) trial. The primary comparison for the new proposal (high-dose versus placebo) will be tested using contrasts from the three-group model. Apart from the change from a binary (placebo, low-dose) treatment factor to a three-level factor, the analytic approach for the primary and secondary analyses will exactly parallel that described in the original proposal.

Missing Data and Nonadherence: Same as original proposal

Safety: Same as original proposal

Reference

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