

CLINICAL PROTOCOL

STUDY NIDA-CTO-0001

PHASE 2, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF RESERPINE FOR THE TREATMENT OF COCAINE DEPENDENCE

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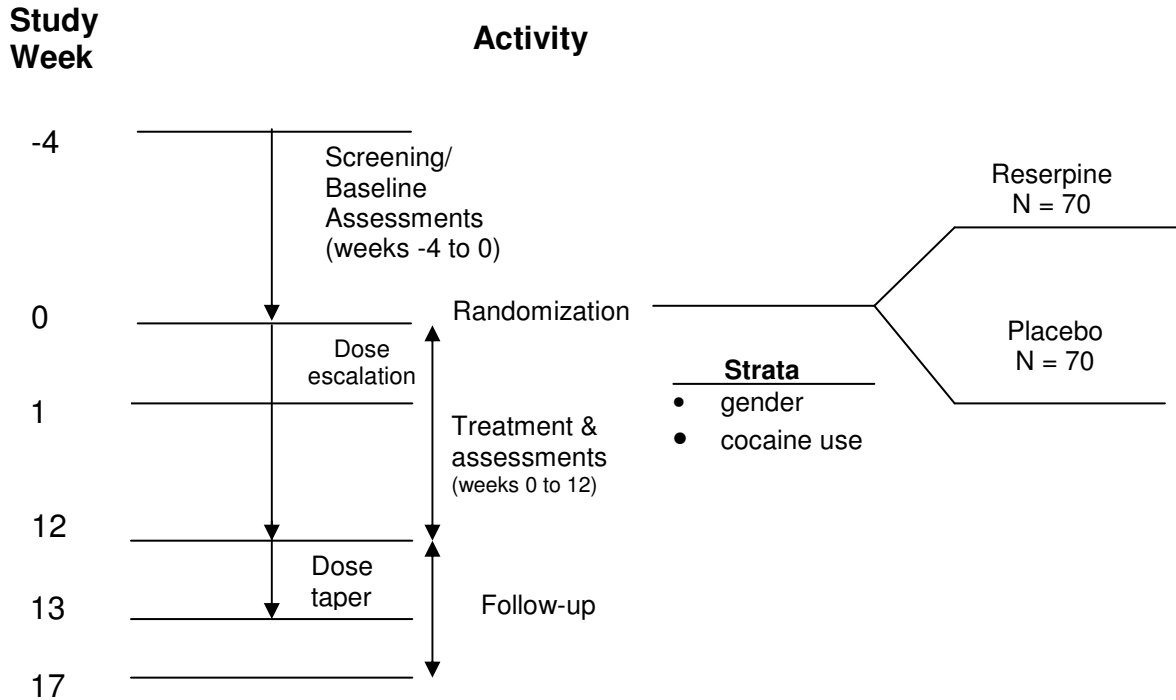
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1 LIST OF ABBREVIATIONS

Abbreviation	Definition
ADD	attention deficit disorder
AE	adverse event
ALP	alkaline phosphatase
ALT/SGPT	alanine aminotransferase/serum glutamic pyruvic transaminase
ASI-Lite	Addiction Severity Index-Lite
AST/SGOT	aspartate aminotransferase/serum glutamic oxaloacetic transaminase
BE	benzoylecgonine
BSCS	Brief Substance Craving Scale
BUN	blood urea nitrogen
CA	classification accuracy
CAP	College of American Pathologists
CCQ-NOW	Cocaine Craving Questionnaire-Now
CGI-O	Clinical Global Impression Scale – Observer
CGI-S	Clinical Global Impression Scale – Self
CLIA	Clinical Laboratory Improvement Amendment of 1988
CNS	Central Nervous System
CRF	Case Report Form
CPK	creatinine phosphokinase
CSEQ	Cocaine Subjective Effects Questionnaire
CSSA	Cocaine Selective Severity Assessment
DA	dopamine
DSMB	Data and Safety and Monitoring Board
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders Fourth Edition
DTR&D	Division of Treatment Research and Development
ECG	electrocardiogram
FEV ₁	forced expiratory volume in 1 second
GGT	gamma glutamyltranspeptidase
HAM-D	Hamilton Depression Rating Scale
HIV	human immunodeficiency virus
HRBS	HIV Risk-Taking Behavior Scale
IRB	Institutional Review Board
LAAM	levomethadyl acetate (L-alpha acetylmethadol)
LDH	Lactic dehydrogenase
LOQ	limit of quantification
mg	milligrams
mL	milliliter
NIDA	National Institute on Drug Abuse
PCP	phencyclidine
RPR	Rapid plasma reagin (test for syphilis)
SAE	serious adverse event
SCID	structured clinical interview for DSM-IV
SFQ	State of Feelings Questionnaire
SUI	substance use inventory

2 STUDY SCHEMA



Double blind dosing consists of:

- dose escalation week 1 with 0.25 mg reserpine daily or matched placebo
- treatment weeks 2 through 12 with 0.5 mg reserpine daily or matched placebo
- dose taper week 13 with 0.25 mg reserpine daily or matched placebo with both groups receiving weekly psychotherapy.

3 ABSTRACT

STUDY OBJECTIVES: To assess the efficacy and safety of reserpine in reducing cocaine use in subjects with cocaine dependence. It is hypothesized that reserpine treatment, compared to placebo, will be associated with fewer days of cocaine use as assessed by self-report confirmed with urine assays for benzoylecgonine (BE).

STUDY DESIGN: This is a double-blind, placebo-controlled, parallel-group design study in which, after screening and a 2-week baseline assessment period, subjects will be equally randomly assigned to one of two treatment groups, reserpine or placebo. Dosing will occur over 13 weeks with the first week being dose escalation and the last week being dose taper. Follow-up will consist of assessments at the ends of weeks 13 and 17. Randomization stratum include gender and frequency of cocaine use 30 days prior to screening.

STUDY POPULATION: One hundred forty (140) subjects with Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria for cocaine dependence determined by structured clinical interview (SCID) will be randomized into one of two treatment groups (70 per group). Males and females, at least 18 years-of-age, with at least 1 urine BE positive specimen provided during the 2-week baseline period prior to randomization with the ability to understand and provide written informed consent will be included.

TREATMENTS: Subjects will take one tablet of 0.25 mg of reserpine or one matched placebo tablet per day week 1, two tablets of 0.25 mg of reserpine or two placebo tablets per day weeks 2 through 12, and one tablet of 0.25 mg of reserpine or one matched placebo tablet per day week 13. All subjects will take study agents daily and receive once weekly manual-guided cognitive behavioral therapy during the 13 weeks of dosing. After completion of the treatment phase (week 13), subjects will be asked to return to the clinic for one follow-up assessment four weeks later (week 17).

SAFETY ASSESSMENTS: All candidates for study enrollment will have a physical examination, a 12-lead electrocardiograph (ECG), clinical laboratory studies (blood chemistry, hematology, urinalysis, and pregnancy test, if female), and Hamilton Depression Rating Scale (HAM-D) completed during screening or baseline. Assessment of vital signs will be performed at each visit during screening and during the first two weeks of treatment. Vital signs will be checked weekly thereafter. Concomitant medication use will be assessed weekly during baseline and treatment. Adverse events (AEs) will be assessed at each study visit and recorded weekly. The HAM-D will be performed weekly the first two weeks then every other week thereafter during treatment. Clinical laboratory studies including a pregnancy test, if female, will be assessed at weeks 4, 8, and 12. An ECG will be performed at week 4 and 12. At treatment week 12 or at the time of study discontinuation, subjects will be evaluated by AE assessment, vital signs, physical examination, and clinical laboratory studies. AEs and concomitant medications will be assessed at week 13 and 17 during follow-up. A human immunodeficiency virus (HIV) Risk-Taking Behavior Scale (HRBS) interview will be performed at baseline and week 12

EFFICACY ASSESSMENTS: Success in reduction of cocaine use will be determined by comparing cocaine non-use days (self-report confirmed or disproved by urine BE levels)

expressed as the weekly mean proportion of non-use days to the total number of non-missing study days that week. Secondary assessments include overall proportion of cocaine non-use days, proportion of successful subjects, the largest number of consecutive cocaine non-use days, weekly median quantitative urine BE levels. Severity of cocaine dependence will be assessed by Addiction Severity Index (ASI)-Lite, Brief Substance Craving Scale (BSCS), Cocaine Craving Questionnaire (CCQ-NOW), and Clinical Global Impression as assessed by the subject (CGI-S) and an observer (CGI-O). ASI-Lite is assessed at baseline, at the first visit of weeks 4, 8, and 12. The BSCS, CGI-S, and CGI-O are assessed twice weekly during baseline and the first visit of each study week. The CCQ-NOW questionnaire is assessed once at baseline and week 12. Sweat patches will also be applied twice weekly to assess cocaine use. A State of Feelings Questionnaire (SFQ) and a Cocaine Subjective Effects Questionnaire (CSEQ) will be completed twice during baseline and weekly during treatment. A Cocaine Selective Severity Assessment (CSSA) interview will be conducted three times during baseline and once per week during treatment.

ANALYSIS: Each primary and secondary outcome variable will be analyzed using appropriate statistical methods for the intent-to-treat population and for the evaluable population. The intent-to-treat population is defined as the subjects who are randomized to treatment and who receive the first day's study agent. The evaluable study population is defined as the subjects who are randomized and properly qualified to participate in the study in accordance with the inclusion and exclusion criteria and who contribute at least four (4) usable on-study urine samples, 21 days of self-report, and who do not have reserpine dose adjustments made due to side effects. The individual effects, if any, of gender, age, prior cocaine use, diagnosis of attention deficit disorder (ADD), and race on the primary treatment effects will be determined where numbers permit. No attempt will be made to determine the effect of two or more of these variables acting together. Statistical tests will be two-sided at a 5% Type I error rate. Confidence intervals will be two-sided with a 95% confidence coefficient.

Summaries of the characteristics of the subject population in both treatment arms at baseline will be prepared for both the intent-to-treat and evaluable subjects. A summary will be prepared to show dropouts/retention over time in each treatment group and for major subgroups. The number of missing observations will be compared between treatments and for major subgroups. Weekly treatment compliance will be summarized. All adverse events will be reported in tabular form indicating the frequency and severity of each type of event.

Some data is being collected for scientific use and population descriptive purposes such as the HRBS, CSSA, SFQ, CSEQ, and sweat patch data.

4 INTRODUCTION AND RATIONALE

Cocaine dependence is a significant public health problem associated with serious medical, psychiatric, social, and economic consequences. Although many compounds have been evaluated for the treatment of cocaine dependence, none has been approved by the Food and Drug Administration (FDA) for this indication. Psychosocial and behavioral therapy are currently the treatments of choice for cocaine dependence. Unlike methadone or naltrexone treatment for heroin addiction, disulfiram for alcohol dependence, and bupropion (Zyban) for cigarette smoking, no pharmacological agent is currently approved for the treatment of cocaine

dependence. NIDA has to identify and/or develop pharmacological agents to treat cocaine dependence in conjunction with psychosocial interventions. Current strategies to treat cocaine dependence include: 1) blocking its effects, 2) restoration of central nervous system homeostasis, 3) reducing craving or enhancing the addict's ability to manage his/her response to craving, 4) treating underlying conditions (or consequences of use) that may predispose targeted subpopulations toward dependence.

The drug to be studied in this clinical trial is reserpine. Reserpine is an alkaloid extracted from the roots of a plant, *Rauwolfia serpentina*. Reserpine has been used since the 1950's for the treatment of mild to moderate hypertension and was one of the first antipsychotic drugs. However, its present use in psychiatry is almost obsolete as other neuroleptics are more effective.

Reserpine binds tightly to aminergic transmitter secretory vesicles in central and peripheral nerve endings and blocks their ability to take up and store biogenic amines, probably by interfering with an uptake mechanism. This effect occurs throughout the body, resulting in depletion of dopamine (DA), serotonin and norepinephrine in both central and peripheral neurons. Administration of reserpine (2.5 mg/kg) reduces DA levels in the rat limbic system (frontal and cingulate cortices, nucleus accumbens and caudate-putamen) by more than 80% (Karoum *et al.*, 1997). Reserpine's effects on dopaminergic vesicles appear irreversible, and trace amounts of the drug remain bound to vesicular membranes for many days. Thus, reserpine is a DA depletor that lowers brain DA levels by disrupting storage vesicles function (Carlson, 1975).

In contrast, cocaine induces accumulation of DA in the synaptic cleft. Pharmacologically, cocaine is a potent inhibitor of the DA transporter, and neuroimaging studies indicate fewer DA transporter receptors in the prefrontal cortex of cocaine users (Hitri *et al.*, 1994). Cocaine binds at the DA transporter and inhibits neurotransmitter reuptake, thus leading to a build-up of extracellular DA levels. The resulting potentiation of mesolimbocortical pathways ultimately causes reinforcement (Kuhar *et al.*, 1991). Thus, it is logical to conclude that the cocaine-induced increase of DA and other amines in the synaptic cleft will be greatly attenuated if the subject is pretreated with reserpine, for the storage vesicles will already have been depleted of dopamine. Pretreatment of rats with reserpine (2.5 mg/kg, 24 hours) prevented both the hippocampus norepinephrine and the caudate putamen dopamine responses to cocaine (20 mg/kg) (Florin *et al.*, 1995).

Absorption, clearance and metabolism of reserpine have not been well studied. It disappears rapidly from the circulation, but its effects persist much longer, due to irreversible inactivation of catecholamine storage granules. The usual daily dose of reserpine is less than 1 mg (typically, 0.25 – 0.5 mg), administered orally.

Reserpine has been investigated in a pilot clinical study for the treatment of cocaine dependence. A Clinical Rapid Evaluation Screening Trial (CREST) was conducted at one of NIDA's medications research units and completed in 1999. This 60-subject four-arm study compared the safety and efficacy of reserpine (at a 0.50 mg dose), together with two additional drugs, gabapentin and lamotrigine, against a single unmatched placebo (15 subjects per group). Analysis of self-report of cocaine use and interviewer-administered instruments suggested that all four study groups decreased their cocaine use and craving. However, only the subjects in the

reserpine group significantly decreased their cocaine use as assessed by urine BE levels at endpoint when compared to baseline ($p = 0.014$; BE levels were normalized by natural logarithm transformation). Although the reserpine group decreased their urine BE levels compared to their baseline values, the reserpine group's urine BE levels were not significantly different from the placebo group's BE levels at endpoint (analysis of variance $p = 0.16$). However, this study was not powered to detect statistically significant differences given the large variance in urine BE measurements and the small sample sizes (15 per group). The results of this study were reported by Liederman *et al.*, (2000).

Since reserpine has been in clinical use for decades, its adverse as well as therapeutic effects have been well documented (Oates, 1966). Sedation and impaired concentration are the most common adverse effects of reserpine. Depression traditionally has been considered to be the most serious adverse effect associated with reserpine's use, moreover, there have been reports of suicide associated with its use. Significant depression has been estimated to occur in 5 to 25% of patients and is thought to be dose related, leading to the recommendation that only doses at or below 0.25 mg should be used (Medical Letter, 1976, Long and Kathol, 1993). However, it should be noted that reserpine was used widely for treating hypertension in a population (generally older middle age to geriatric) where the prevalence of depression tends to be high.

Studies do not support a causal relationship between reserpine and depression [Goodwin and Bunney (1971), Wendy (1974), Bant (1985) Widmer (1985)] especially in the case of subjects with no history of depression taking low doses (under 0.5 mg/day) of reserpine. In reviewing the relationship between depression and reserpine, Goodwin and Bunney (1971) reported that in the last decade in which reserpine was widely used for hypertension, there was "a virtual absence of reports on depression." Their interpretation of this statistic was that by the time reserpine was used at dosages of 0.5 mg/day (or less), it was seldomly used in patients with a history of depression.

In the CREST study, patients with a history of depression were excluded from participation. The CREST results indicated that depression, as measured by the Beck Depression Scale, significantly decreased during the course of the study for all study groups, including the reserpine group. However, scores on the HAM-D Scale, which places greater emphasis on the vegetative symptoms of depression, increased for both the placebo and reserpine groups with the increase in the reserpine group reaching marginal significance.

The dose of reserpine selected for the current clinical investigation was selected based on two factors. First, because the prolonged use of reserpine in doses higher than 0.5 mg has been associated with major depression, the recommended daily dose of 0.5 mg was selected to minimize adverse events. This is supported by the lack of clinical depression observed in the CREST study when this dose was given for 8 weeks. Secondly, this dose should have limited sedative and dysphoric effects and had suggested efficacy in the CREST study.

5 STUDY OBJECTIVES

5.1 PRIMARY OBJECTIVES

The primary objective of this study is to assess the efficacy of reserpine in reducing cocaine use in subjects with cocaine dependence (DSM-IV criteria). The hypothesis is that reserpine will increase the weekly mean proportion of cocaine non-use days over the treatment period when compared to placebo as determined by self-report of cocaine use confirmed with urine assays for BE.

5.2 SECONDARY OBJECTIVES

Secondary objectives include:

1. Determining the safety of reserpine in the study population.
2. Assessing the efficacy of reserpine in reducing the weekly mean proportion of cocaine use-days as determined by self-report alone.
3. Assessing the efficacy of reserpine in increasing the proportion of subjects that achieve measured reductions in cocaine use (25 and 50% reductions in the number of use-days compared to baseline use).
4. Assessing the efficacy of reserpine in reducing the weekly median urine BE level.
5. Assessing the efficacy of reserpine in the reduction in the severity of cocaine dependence (assessed by ASI-Lite and self and observer scored CGI) and craving (assessed by BSCS and CCQ-NOW).
6. Assessing the efficacy of reserpine in reducing the self-reported use of other drugs of abuse and in reducing the proportion of urines positive for amphetamines, barbiturates, benzodiazepines, and opiates.
7. Assessing the utility of sweat patches as an alternative to urine toxicology in measuring reductions in cocaine use.

6 STUDY SPONSOR

Eugene Somoza, M.D., Ph.D., Cincinnati Addiction Research Center, University of Cincinnati, 3210 Jefferson Avenue, Cincinnati, OH 45220 is the study sponsor.

7 STUDY SITES

This study will be conducted at three sites, the Veterans Administration Medical Center, Cincinnati, Ohio, the Veterans Administration Medical Center, Dayton, Ohio, and the Boston University Medical Center, Boston, Massachusetts. It is anticipated that the Cincinnati, Dayton and Boston sites will enroll 40, 50 and 50 subjects, respectively.

8 STUDY DESIGN

8.1 EXPERIMENTAL DESIGN

This protocol is a double-blind, placebo-controlled, parallel-group study design. After screening and a 2-week baseline period, subjects will be randomly assigned approximately equally to dosing with either placebo or reserpine for 13 weeks (the first week is reserpine dose escalation and the 13th week is dose taper). A final follow-up assessment will be performed 4 weeks after the last dose.

8.2 OUTCOME/RESPONSE MEASURES

Primary Outcome Measure. The principal outcome measure is the cocaine use or non-use day. Cocaine use and non-use days will be defined by subject's self-report of use, confirmed or disproved by quantification of urine BE. For the primary efficacy response, each day of the 11-weeks of full dose treatment will be coded as either a use or a non-use day based on the self-reports and on the urine BE data. Because of the pharmacokinetics of cocaine and BE, carryover from previous cocaine use may be difficult to distinguish from new use. The rules enunciated by Preston *et al.* (1997), modified to meet the conditions of this study, will be used as described in section 15 to facilitate classification of each assessment day as use or no-use. The weekly mean proportion of non-use days for weeks 2 through 12 (when the subjects are treated with the 0.5 mg dose) will be compared between treatment groups by Generalized Estimating Equations (GEE).

Secondary Outcome Measures. Secondary outcome measures include other measures of the pattern of cocaine use (overall proportion of non-use days, proportion of successful subjects, and weekly median urine BE levels), measures of severity of cocaine dependence (assessed by ASI-Lite and self and observer scored CGI) and craving (assessed by BSCS and CCQ-NOW), self-reported use and non-use days of other substances of abuse, and percentage of negative urines by drug (for amphetamines, barbiturates, benzodiazepines, and opiates).

Other Measures. Several measures will be included for population descriptive purposes and other scientific use. These include the HRBS, the CSSA, SFQ, cocaine subjective effects and the sweat patch test for cocaine use (see below).

Sweat Patch Test for Cocaine Use. Urine toxicology is frequently used as a primary outcome measure for cocaine dependence clinical trials. While urine toxicology offers the advantage of providing an objective measure of substance use, it has the disadvantages of being particularly susceptible to data loss due to missed clinic visits (Lavori *et al.*, 1999), of being prone to patient falsification (Eskridge and Guthrie, 1997), and of being objectionable to some study subjects and staff. In addition, urine toxicology is problematic in that qualitative assessments are likely to underestimate decreases in the quantity of cocaine use (Preston *et al.*, 1997) while quantitative measures are prone to large variability based on the timing between cocaine use and sample collection (Li *et al.*, 1995). Finally, adequate assessment of cocaine use entails the collection of urine samples every few days, which results in subjects being scheduled for clinic visits three times per week. This time demanding schedule may serve to reduce the pool of subjects willing to participate in the study and, thus, the generalizability of the study findings. Given the difficulties associated with urine toxicology, researchers have investigated the use of other

biological matrices for detecting substance use. Sweat, collected with the PharmCheck™ Sweat Patch, has been the focus of several dosing (Cone *et al.*, 1994; Burns and Baselt, 1995) and outpatient studies (Preston *et al.*, 1999; Taylor *et al.*, 1998; Skopp *et al.*, 1996; Baer and Booher, 1994; Winhusin *et al.*, 2000). The results of these studies suggest that the sweat patch may be useful as an objective measure of substance use.

The present protocol will seek to replicate and expand upon the findings of a recent cocaine dependence study in which participants wore two sweat patches, one applied three times per week (per-visit) and one applied weekly (Winhusin *et al.*, 2000). The results suggested that the qualitative and quantitative sweat patch measures had good reliability and validity and that the concurrent validity of the qualitative patch results could be improved by selecting a cutoff score according to classification accuracy (CA) rather than the limit of quantitation. The results revealed no significant degradation of cocaine to BE associated with wearing the patch for a longer time. Finally, compared to urine, sweat patches allowed for more data to be collected in fewer study visits.

8.3 BLINDING PLAN

The investigational agents, reserpine and placebo, will be supplied by the research pharmacist in high density polyethylene bottles with child resistant caps that do not reveal the identity of the investigational agent. The bottles will be labeled with a product label and a subject label. The product label will include the protocol number; the following statement – Caution: New Drug – Limited by federal law to investigational use; expiration date and lot number. The subject label will include the subject number; week of study; number of tablets and directions for use. All subjects will receive one tablet per day (i.e., one 0.25 mg tablet of reserpine or one placebo tablet) during dose escalation (week 1) and dose taper (week 13). During weeks 2 through 12, all subjects will receive two tablets per day (i.e., two placebo tablets or two 0.25 mg tablets of reserpine). When reserpine dose reduction is warranted from the 0.5 mg dose to the 0.25 mg dose, subjects will be given one 0.25 mg tablet of reserpine. Subjects in the placebo arm that report side effects will also have their dose reduced from two to one tablet. As dose reductions are permissible in both groups, this will not break the blind for a subject, however; subjects that have dose reductions will not be included in the efficacy analysis of the evaluable population.

The pharmacy will prepare 14 bottles of study medications for each subject. This reflects 13 weeks of study medication and one extra bottle of 20 tablets. The number of tablets per each bottle is as follows: 1st week: 10 tablets of 0.25 mg reserpine or placebo; weeks 2-12: 20 tablets of 0.25 mg reserpine or placebo and week 13: 10 tablets of 0.25 mg reserpine or placebo.

8.4 RANDOMIZATION PLAN

Stratified randomization will be used in order to distribute non-random characteristics known to influence outcomes in substance abuse trials equally across groups. The treatment groups within sites will be balanced with respect to gender and historical self-report of cocaine use (< 18 or ≥ 18 days of use in the last 30 days). The randomization process will be performed by computer at the data coordinating center and treatment assignments provided to the study pharmacist for investigational agent distribution.

8.5 CONCURRENT CONTROLS

As the study design is double-blind (neither the investigator nor the subject know the treatment arm assignment), subjects in the control arm will be given matching placebo agent along with cognitive behavioral therapy according to the same schedule as those in the test agent arm.

8.6 DEFINITION OF STUDY POPULATIONS (INTENT-TO-TREAT AND EVALUABLE)

The intent-to-treat study population is defined as the subjects who are enrolled, randomized, and receive the first day's study investigational agent. The evaluable study population is defined as the subjects who are randomized and properly qualified to participate in the study in accordance with the inclusion and exclusion criteria and who contribute at least four (4) usable on-study urine samples, 21 days of self-report, and who do not have reserpine dose adjustments made due to side effects.

9 SUBJECT SELECTION

A total of 140 male and female subjects with cocaine dependence will be enrolled in the study (70/group). Entry into this study is open to both men and women and to all racial and ethnic subgroups. At least 30%-percent female subjects will be enrolled. Subjects will be recruited from a variety of sources. The primary source will be subjects seeking treatment for cocaine dependence at the site's hospital/outpatient clinic. Additional subjects will be recruited from the community by means of referrals from local treatment providers, advertising in local media, and word of mouth among subjects themselves. Recruitment advertisements will be approved by the site's and subsites' Institutional Review Board (IRB).

9.1 INCLUSION CRITERIA

Potential subjects must:

1. Be at least 18 years-of-age.
2. Have a DSM-IV diagnosis of cocaine dependence as determined by SCID.
3. Be seeking treatment for cocaine dependence.
4. Have at least 1 positive urine BE specimen (> 300 ng/mL) within the two-week baseline period prior to randomization with a minimum of 4 samples tested.
5. Have the ability to understand, and having understood, provide written informed consent.
6. If female, use one of the following methods of birth control:
 - a. oral contraceptives
 - b. barrier (diaphragm or condom) with spermicide
 - c. intrauterine progesterone contraceptive system

- d. levonorgestrel implant
- e. medroxyprogesterone acetate contraceptive injection
- f. surgical sterilization
- g. complete abstinence from sexual intercourse

9.2 EXCLUSION CRITERIA

Potential subjects must not:

1. Have current dependence, defined by DSM IV criteria, on any psychoactive substance other than cocaine, alcohol, nicotine, or marijuana or physiological dependence on alcohol requiring medical detoxification.
2. Have neurological or psychiatric disorders, such as psychosis, bipolar illness, major depression or a HAM-D score >15 or history of depression as assessed by SCID, organic brain disease, or dementia, which require ongoing treatment or which would make treatment compliance difficult or have a past history of suicide attempts as determined by history/SCID and/or current suicidal ideation/plan as assessed by SCID interview or HAM-D question #3.
3. Have serious medical illnesses including, but not limited to:
 - uncontrolled hypertension,
 - significant heart disease (including myocardial infarction within one year of enrollment), or any clinically significant cardiovascular abnormality (ECG).
 - angina,
 - hepatic or renal disorders,
 - potentially life-threatening or progressive medical illness other than addiction that may compromise subject safety or study conduct.
4. Be mandated by the court to obtain treatment for cocaine-dependence.
5. Have ulcerative colitis, history of peptic ulcer, or gall stones. Reserpine increases activity of the stomach, which may make the condition worse.
6. Have Parkinson's disease.
7. Be anyone who in the opinion of the investigator would not be expected to complete the study protocol due to probable incarceration or relocation from the clinic area.
8. Have AIDS.
9. Have active syphilis that has not been treated or refuse treatment for syphilis (see note below).
10. Have history of neuroleptic malignant syndrome.

11. Have known or suspected hypersensitivity to reserpine or other rauwolfia alkaloids (rauwolfia serpentina or yohimbine), salicylate, or tartrazine dyes (FD&C Yellow).
12. Be taking reserpine for any condition.
13. Have pheochromocytoma.
14. Be using a medication that could interact adversely with reserpine, with the time of administration of study medication and other medications based on the longest time interval of A, B, or C, below:
 - A) Five half lives of other medication or active metabolite(s), whichever is longer
 - B) Two weeks
 - C) Interval recommended by other medication's product labeling

Medications that fall into this category include:

- a. Monoamine oxidase (MAO) inhibitors (furazolidone [e.g., FUROXONE], isocarboxazid [e.g., MARPLAN], phenelzine [e.g., NARDIL], procarbazine [e.g., MATULANE], selegiline [e.g., ELDEPRYL], tranylcypromine [e.g., PARNATE]). Taking a rauwolfia alkaloid while taking or within 2 weeks of taking MAO inhibitors may increase the risk of central nervous system (CNS) depression or may cause a severe high blood pressure reaction.
 - b. CNS depressants (e.g., antihistamines, sedatives, neuroleptics, benzodiazepines, hypnotics, barbiturates, anti-convulsants, muscle relaxants, tricyclic antidepressants, or anesthetics).
15. Have participated in any experimental study within 2 months preceding screening.
 16. Be pregnant or lactating.
 17. Have clinically significant abnormal laboratory values (Appendix I).
 18. Have had electroconvulsive therapy within the past 3 months preceding screening.
 19. Have been enrolled in an opiate substitution therapy program (methadone, LAAM, buprenorphine) within 2 months of enrollment.
 20. Have a diagnosis of adult asthma, including those with a history of acute asthma within the past two years, and those with current or recent (past 2 years) treatment with inhaled or oral beta-agonist or steroid therapy (due to potential serious adverse interactions with cocaine).

21. Be actively using albuterol or other beta agonist medications, regardless of formal diagnosis of asthma. (Inhalers are sometimes used by cocaine addicts to enhance cocaine delivery to the lungs). A subject without respiratory disease who will consent to discontinue agonist use, may be considered for inclusion.
22. For subjects suspected to have asthma but without a formal diagnosis, 1) have history of coughing and/or wheezing, 2) have history of asthma and/or asthma treatment two or more years before, 3) have history of other respiratory illness, e.g., complications of pulmonary disease (exclude if on beta agonist), or 4) use over-the-counter agonist or allergy medications for respiratory problems (e.g., Primatene Mist): a detailed history and physical exam, pulmonary consult, and pulmonary function tests should be performed prior to including or excluding from the study (an FEV₁ <70 % will exclude a subject from participation).

Notes on inclusion/exclusion criteria: Although AIDS is an exclusion criteria, a positive antibody titer to HIV is not. Prospective subjects will be offered HIV testing during screening but may not have the test performed until after enrollment. This test is offered as a courtesy to the prospective subject along with HIV education.

Prospective subjects who are positive for syphilis by the RPR test will have a fluorescent treponemal antibody absorbant assay (FTA-abs) confirmatory test performed. If this test is positive, prospective subjects must be treated for syphilis to be enrolled on the study or provide evidence of previous treatment for syphilis.

The infectious disease panel for hepatitis is performed as an aid to determine if the prospective subject has been exposed to the hepatitis virus. Positive hepatitis results do not exclude a prospective subject from participation. However, if liver function tests (e.g. ALT and AST) are over three times normal it is presumptive evidence that the subject has active hepatitis and should be excluded from the study (exclusion criterion number 3). Similarly, a positive tuberculin (PPD) result does not exclude a prospective subject from participation, but if diagnostic tests (e.g. chest x-ray) indicate that active disease is present, subjects may be excluded from participation.

10 INVESTIGATIONAL AGENTS

Reserpine: Reserpine, 0.25 mg tablets, will be provided by a NIDA contract manufacturer.

Placebo: Matched placebo tablets will be supplied by a NIDA contract manufacturer.

10.1 DISPENSING INVESTIGATIONAL AGENTS

Investigational agents will be dispensed once per week at the first clinic visit of the week. Unused investigational agents will be collected and inventoried each week. The subject will be thoroughly instructed on how to administer investigational agents. Investigational agents will be distributed by the research pharmacist directly to the subject or to the investigator for dispensing to the subject.

10.2 LABELING

Investigational agents will be packaged in high density polyethylene bottles with a 10 day supply being provided. The bottles will be labeled with a product label and a subject label. The product label will include the protocol number; following statement – Caution: New Drug – Limited by federal law to investigational use; expiration date and lot number. The subject label will include the subject number; week of study; number of tablets and directions for use.

10.3 STORAGE

Investigational agents will be stored at room temperature in a secure location at the dispensing pharmacy.

10.4 RECORD OF ADMINISTRATION

Accurate recording of all investigational agent dispensing/administration will be made in the appropriate section of the CRF.

10.5 USED/UNUSED SUPPLIES

During the study, all investigational agents not used by the subject must be returned to the investigator or designee for assessment of subject compliance. At the end of the study, all unused investigational agents must be inventoried. If any investigational agent is lost or damaged, its disposition should be documented. Unused investigational agents will be retained at the clinic site pending instructions for disposition by the Sponsor at the end of the study.

10.6 SAFETY OF RESERPINE

The most common adverse reactions (occurring in >10% of subjects) associated with reserpine are drowsiness, sedation, nervousness, paradoxical anxiety, nightmares, depression, bradycardia, syncope, nasal congestion, hyperacidity, nausea, vomiting, dry mouth, impotence, weight gain and thrombocytopenic purpura. For the present study, subjects with a diagnosis of major depression, HAM-D > 15, or a history of depression by SCID will be excluded from participation. The development of depressive symptoms will be monitored by the completion of a HAM-D on a weekly basis for the first two weeks, then every other week (weeks 4, 6, 8, 10, 12) and during follow-up assessment at week 17. In addition, subjects will be assessed for the development of clinical depression, as defined by DSM-IV criteria, at study weeks 4, 8, and 12. Any subject exhibiting signs of clinical depression will be withdrawn from the study agent.

Subjects should be told to take the investigational agent with meals and not to discontinue agent suddenly but to contact the study staff if adverse reactions occur. Subjects should be warned not to perform hazardous tasks that require alertness and coordination until the drug's CNS effects are known. The subjects should be advised to minimize orthostatic hypotension by rising slowly and avoiding sudden position changes. Dry mouth can be relieved with chewing gum, sour hard candy, or ice.

Another risk is the worsening of the symptoms of cocaine dependence. The condition may not respond to the study agent or may become worse. The condition may also worsen if subjects

receive placebo. There is a possibility that subjects may have an allergic reaction to the study drug. Subjects' conditions will be monitored closely by the study doctor and his or her staff. If the subjects or the study doctor decide to stop subject participation in the study due to increased symptoms of cocaine dependence or adverse experiences with study agent, subjects will receive appropriate follow-up treatment as determined by the study physician.

11 TREATMENT PLAN

11.1 INVESTIGATIONAL AGENTS

Blinded supplies of reserpine and/or matched placebo tablets will be dispensed by the research pharmacist weekly for daily administration in subjects. Subjects will be instructed to take investigational agents with food once per day. The investigational pharmacist will be unblinded. AEs will be assessed at each visit, and AE CRF completed weekly. The subject will be seen by study physician weekly to assess AEs. If subject-reported adverse events (AE) are deemed treatment-related, the site study physician will evaluate the AE and if necessary instruct the subject to reduce the number of tablets taken daily or to stop the medication, based on clinical judgment. Likewise, study subjects receiving placebo will also have study agents reduced from two to one placebo tablets if complaining of side effects or other symptoms.

11.2 DOSE ADJUSTMENTS

Those subjects, who are unable to tolerate the maximum dose of reserpine (0.5 mg), will be allowed to continue in the study at a reduced dose (0.25 mg). These subjects will be given one 0.25 mg reserpine tablet to take daily.

Situations considered indicative of dose intolerance are:

1. Significant/symptomatic hypotension (drop of more than 10 mm Hg on either diastolic or systolic blood pressure with postural changes). If this happens at the 0.5 mg dose, the dose is reduced to the 0.25.
2. Any other AE which in the opinion of the investigator warrants a dose reduction.

In the case of severe side effects, rising HAM-D scores indicating depression, or suicidal ideations, discontinuation of the study agent all together may be necessary. In such a situation, a study psychiatrist should evaluate the subject to determine if the medication should be tapered or discontinued, and if further treatment such as an antidepressant or hospitalization is warranted.

In this intent-to-treat study design, inability to tolerate study drugs is not a reason for termination from the study. These subjects may continue to participate in all other aspects of the study. However, every attempt will be made to maintain subjects at the maximum drug dose. AEs will be assessed at each visit. AE CRFs will be completed weekly, and the patient will be seen by study physician weekly to assess AEs.

11.3 COGNITIVE BEHAVIORAL THERAPY

All subjects will receive standardized, manual-guided individual cognitive behavioral therapy by a certified therapist once per week during the double-blind phase of the study. The cognitive behavioral manual, to be provided in the study operation manual, is the 2000 version of the Cognitive Behavioral Therapy Manual. These sessions will consist of one, 1-hour session of individualized counseling per week. During these sessions, emergency counseling and referral services will be provided. Additional emergency crisis management sessions will be available up to a maximum of four along with visit documentation.

The goal of this behavioral treatment intervention is to increase protocol compliance and educate the subject about his/her dependence and factors associated with drug use, and assist study subjects in achieving abstinence from cocaine without obscuring the impact of the pharmacological treatment. There will be no negative consequences based on urine toxicology results or subject revelations regarding use of illicit substances. The primary purpose of using a manual-guided procedure for therapists is to achieve consistency of theoretical orientation, therapeutic style, and behavioral intervention across subjects and sites. Each therapy session should be audiotaped to monitor drift and assure adherence to manual-guided therapy. Original tapes are to be maintained at the site. The Boston Behavioral Treatment Training Center will select a random proportion of these tapes for review. The psychotherapy manual has the procedure for submission and review of tapes. It is expected that at least one session per month will be rated by the training center.

12 STUDY PROCEDURES

12.1 INFORMED CONSENT

Interested candidates who have been determined by telephone or in person interview to be using cocaine, are seeking treatment, and are available to come to the clinic for at least 19 weeks will meet with a qualified investigative staff member and receive an explanation of the study purpose and requirements. During the initial interview, the interviewer should not ask questions in a manner that reveals the eligibility criteria for study entry. A two-part informed consent process will be used consisting of a single informed consent form but with separate signatures for parts 1 and 2 of the consent process. The difference in the two parts of the consent process is that during part 1, the initial interview and study explanation can be conducted by a qualified study staff member but does not have to be a study physician/ investigator. Part 2 of the consent process is an explanation of the study by a study physician/ investigator. If the study is initially explained to the potential subject by a study staff member that is not a physician/investigator, then part 1 of the form will be signed by the subject and the study staff member. If the study is initially explained to the potential subject by a physician/ investigator, then both of the part 1 and part 2 signature sections will be signed by the potential subject and investigator.

During the initial admission interview potential participants are told the study purpose and procedures. The potential participant will be given a brief questionnaire reviewing the study procedures. Any participant who has difficulty understanding the information contained in the consent form will be rescheduled and the consent process will be repeated. Research staff will work closely with the participant in an effort to help them understand the requirements of their

participation. Persons with literacy problems will be assisted to the extent possible. Any participant who is unable to demonstrate understanding of the information contained in the informed consent will be excluded from study participation and assisted in finding other sources of treatment. Persons who are excluded, or who decline participation, will be given referrals to other resources in the area.

After signing part 1 of the informed consent, participants are given a copy of the signed informed consent form, are assigned a subject identification number, and proceed to the screening/baseline assessments phase of the study. After the subject has completed the screening and baseline assessments and is deemed to be eligible for study participation, an explanation of the study will be provided again, and the candidate will be given an opportunity to review, inquire about, and will be asked to initial the informed consent form to demonstrate that they still willing to go by their decision made at least two weeks earlier. The questionnaire reviewing the study procedures will be given again to make sure that the subject still understands the study procedures.

12.2 SCREENING/BASELINE ASSESSMENTS

Screening assessments will be conducted as shown in Table 1.

Sweat Patch Application. Two sweat patches will be worn by the participants throughout the study:

- One sweat patch (twice weekly) will be applied to the right arm on the Monday visit and replaced on the Friday visit. If the participant misses Monday's visit then the patch may be applied on Tuesday. Similarly, if it is known that the participant will be unable to attend the Friday visit then the patch may be replaced on Thursday.
- Another sweat patch (weekly) will be applied to the left arm once a week, to be removed 7 days later. If the participant misses his or her scheduled visit then the patch will be replaced on the next visit that the participant attends.

The application and removal of sweat patches will be conducted in accordance with the instructions provided by the manufacturers of the PharmCheck™ Sweat Patch. These instructions were written to minimize the possibility for environmental contamination and to detect attempts to tamper with the sweat patch.

12.3 SUBJECT ENROLLMENT

A prospective subject who meets all of the study inclusion and does not meet any of the exclusion criteria (a checklist will be provided in the CRF package) may be enrolled onto the study. The investigator or study coordinator will enter into the computer the Eligibility Checklist, Enrollment, Randomization, and Demographics CRFs to enroll and randomize subjects and obtain a treatment assignment. The data coordinating center will notify the research pharmacist of the subject's treatment assignment. The pharmacist will dispense the investigational agent for the subject within the same day of receiving treatment assignment. The data coordinating center will notify the study coordinator that the pharmacist has been provided with the treatment assignment. The pharmacist will notify the study coordinator as soon as the investigational agent

is prepared. This process should occur in one day to minimize the time between completion of screening and baseline assessments and study start.

12.4 TREATMENT

At the first clinic visit, subjects will be given instructions on how to administer investigational agents and will be given a ten-day supply of investigational agent. Subjects will be scheduled for treatment and assessments three times per week usually on a Monday, Wednesday, and Friday for 12 weeks. Two consecutive days may be scheduled around holidays or other schedule conflicts. Sweat patches will be applied according to the schedule and method described above for baseline procedures. All subjects will be offered an opportunity for HIV testing and counseling and HIV/AIDS education (Appendix II). All subjects will be provided with manual-guided psychosocial therapy once per week during the 13 weeks that they will be receiving study agents. Clinical evaluations are described in detail in section 13.0.

12.5 PREVENTING STUDY DROP-OUTS

Subjects will be encouraged to come for treatment and for the evaluation sessions as described in this protocol. To minimize missed sessions, they will be reimbursed for their transportation and time spent in completing study assessments. It will be emphasized to subjects during screening that even if they have a relapse they should come to all scheduled appointments. They will be discouraged from using cocaine, but there will be no penalty for relapsing or for missed sessions.

12.6 DOSE TAPER AND FOLLOW-UP

At the end of study week 12, subjects will be asked to come to the clinic once at the end of the dose taper (week 13) and 4 weeks later for a final follow-up visit. During the first week of follow-up, subjects receiving reserpine will have the dose reduced to 0.25 mg. Subjects on the placebo arm will receive one placebo tablet. The subject will be asked to provide a urine specimen for BE/creatinine and urine toxicology screen, a self-report for cocaine, alcohol, marijuana, amphetamines, opiates, and barbiturates, and report any AEs or concomitant medications used. At the last study visit, the same assessments and also HAM-D will be performed and the subject will also be asked to provide any current treatments for drug or alcohol abuse and an impression of the study agent. If it is not possible to arrange for the subject to return to the clinic, then the subject should be telephoned and asked to provide a current self-reported cocaine and other drug use, current treatment for drug or alcohol abuse, and an impression of the study agent. If a subject cannot be contacted directly, attempts will be made to reach the individual(s) previously identified by the subject as a contact source.

12.7 MAINTAINING AND BREAKING STUDY BLIND

The decision to break the study blind for an individual subject lies with the site investigator and study principal investigator or with the NIDA medical monitor, but should be resorted to only in cases of life-threatening emergency when knowledge of the treatment arm investigational agent will influence clinical management. The principal investigator must inform NIDA Study Director and NIDA Medical Monitor immediately after breaking the blind.

12.8 SUBJECT REIMBURSEMENT

Subjects will be reimbursed for their transportation, inconvenience, and time. During the screening, enrollment, and transition components they will receive \$10 in retail scrip or vouchers per visit. At the end-of-study evaluation (first visit of week twelve), subjects will receive \$35 in retail scrip or vouchers because they will need to spend a significantly greater amount of time to perform all of the necessary outcome measures. Since this is an intent-to-treat design, efforts will be made to obtain the full 12 weeks of data even for subjects whose attendance or investigational agent compliance is erratic. This remuneration is for time and expenses incurred (e.g., gasoline, public transportation) not for compliance to the protocol.

12.9 STUDY TERMINATION

12.9.1 Subject Termination

An investigator may terminate a subject if s/he deems it clinically appropriate or for any of the following reasons: 1) significant side effects from the investigational agents, 2) serious or unexpected AEs, 3) inability to comply with the study protocol, 4) protocol violation, or 5) serious intercurrent illness.

A subject may withdraw from the study anytime s/he wishes. A subject who is discontinued from receiving the investigational agent, will be allowed to continue the psychosocial-behavioral treatment with the approval of the investigator. Any subject who discontinues prematurely, regardless of the reason, will be requested to return for a final visit to perform the necessary procedures and to obtain data for end of study/early termination.

Study subjects withdrawn from the protocol secondary to a medical or psychiatric concern will be referred for appropriate treatment. Subjects will be asked to sign a general consent for the release of information to the referred health care. Study staff may request transportation for emergency treatment of a subject if medically appropriate (e.g., for acutely psychotic or suicidal subjects).

All study subjects will be encouraged to carry a wallet card that identifies them as a subject in a clinical research study. The card will provide the name and phone number of the investigator (physician) at the site who can be contacted in the event of an emergency. The card will also instruct the non-study physician rendering emergency care to provide information to the study physician with regards to that care.

12.9.2 Trial Discontinuation

The study sponsor or NIDA has the right to discontinue the investigation at any time.

12.10 CONCOMITANT MEDICATIONS

Any medications (including prescription, over-the-counter, herbal supplements and health store products) to be taken during the study must be approved by the investigator. The following medications should not be used during treatment with reserpine:

- Monoamine oxidase (MAO) inhibitors (furazolidone [e.g., FUROXONE], isocarboxazid [e.g., MARPLAN], phenelzine [e.g., NARDIL], procarbazine [e.g., MATULANE], selegiline [e.g., ELDEPRYL], tranylcypromine [e.g., PARNATE]). Taking a rauwolfia alkaloid while taking or within 2 weeks of taking MAO inhibitors may increase the risk of central nervous system depression or may cause a severe high blood pressure reaction.
- Antihistamines
- Sedatives
- Neuroleptics
- Benzodiazepines
- Hypnotics
- Barbiturates
- Anti-convulsants
- Muscle relaxants
- Anesthetics
- Antihypertensives
- Digitalis glycosides, quinidine
- Tricyclic antidepressants

13 CLINICAL EVALUATIONS

Table 1 provides an overview of the schedule of assessments to be conducted during the study.

13.1 ASSESSMENTS AT SCREENING/BASELINE

After informed consent is signed, subjects will be screened to determine if they meet eligibility requirements, and baseline measures will be obtained. The screening and baseline periods may be conducted simultaneously. In addition, certain baseline assessments that are part of eligibility determinations will also provide physiological, psychological, and disease status information prior to active treatment.

Table 1. Overview of Study Assessments

Assessment	Screening*	Baseline	RANDOMIZATION	Treatment						Follow-up		
				1-3	4	5-7	8	9-11	12	13	17	
Study Week	-4 to 0											
Screening												
Informed Consent	X											
SCID	X				X ^c		X ^c		X ^c			
Psychiatric evaluation	X											
ADD	X											
Medical History	X											
Prior Medications	X											
Infectious disease panel/Syphilis test	X											
HIV test (optional)	X											
Safety/Other												
Physical exam/FEV ₁ ^g	X								X ^b			
Vital Signs		3 X/week for 2 weeks		3 X ^d	X ^a	X ^a	X ^a	X ^a	X ^a	X ^b		
Hematology	X				X ^a		X ^a		X ^b			
Blood Chemistry	X				X ^a		X ^a		X ^b			
Urinalysis	X				X ^a		X ^a		X ^b			
ECG	X				X ^a				X ^b			
Pregnancy test	X				X ^a		X ^a		X ^b			
CSSA		3X		X ^a	X ^a	X ^a	X ^a	X ^a	X ^a	X ^b		
SFQ		Weekly x 2w		X ^a	X ^a	X ^a	X ^a	X ^a	X ^a	X ^b		
CSEQ		Weekly x 2w		X ^a	X ^a	X ^a	X ^a	X ^a	X ^a	X ^b		
HAM-D	X			Once during weeks 1, 2, 4, 6, 8, and 10						X ^b		X
Adverse Events ^c	X	X		3X	3X	3X	3X	3X	3X	3X	X	X
Concomitant medications		Weekly x 2w		X ^a	X ^a	X ^a	X ^a	X ^a	X ^a	X ^b	X	X
Efficacy												
ASI-Lite	X				X ^a		X ^a		X ^b			
Urine BE and creatinine		3 x/week for 2 weeks		3 X	3 X	3 X	3 X	3 X	3 X	3 X	X	X
Sweat Patch ^f		2 x/week for 2 weeks		2X	2X	2X	2X	2X	2X	2X		
SUI		3 x/week for 2 weeks		3 X	3 X	3 X	3 X	3 X	3 X	3 X	X	X
Urine tox screen		Weekly x 2w		X ^a	X ^a	X ^a	X ^a	X ^a	X ^a	X ^b	X	X
HRBS	X								X			
BSCS		Weekly x 2w		X ^a	X ^a	X ^a	X ^a	X ^a	X ^a	X ^b		
CCQ-NOW		X							X ^b			
CGI-S		Weekly x 2w		X ^a	X ^a	X ^a	X ^a	X ^a	X ^a	X ^b		
CGI-O		Weekly x 2w		X ^a	X ^a	X ^a	X ^a	X ^a	X ^a	X ^b		
Treatment Compliance				3 X	3 X	3 X	3 X	3 X	3 X	3 X	X	
Missed visit log				completed as a log only when subject misses visits								
Follow-up questionnaire												X

* - Screening and baseline may be conducted simultaneously; baseline assessments must occur within two consecutive weeks during the screening period; the screening period is completed within four weeks of subject consent.

X^a - Once per week preferably at the first visit of the week.

X^b - At the first visit of week 12 or if the subject discontinues prematurely.

X^c - Assessment for clinical depression only.

X^d - Vital signs are taken at each visit the first two weeks then weekly thereafter

X^e - AEs are assessed at each visit and the AE CRF is completed weekly.

X^f - Sweat patches will be applied once per week to the left arm and twice per week to the right arm.

X^g - FEV₁ is only performed in those subjects suspected of having asthma.

13.1.1 Screening Procedures

1. Informed Consent
2. Complete medical history
3. Physical exam including respiratory function tests (FEV₁) in subjects suspected of having asthma
4. Psychiatric evaluation and SCID evaluation for DSM-IV diagnosis of cocaine dependence and Axis-I disorders
5. ADD interview
6. Prior medications. All medications (including prescription, over-the-counter, herbal supplements and health store products) taken by the subject for the 30 days prior to screening will be documented on a Prior Medication CRF
7. ASI-Lite evaluation
8. HAM-D evaluation
9. Hematology
10. Blood chemistries
11. Urinalysis
12. Pregnancy test (if female)
13. Infectious disease panel
14. Syphilis test
15. Adverse events
16. ECG
17. HRBS
18. HIV test (optional)

13.1.2 Baseline Assessments

Baseline assessments to occur over a two-week period, will include the following:

1. Three-times weekly urine BE plus creatinine measurements for two weeks. Subjects must provide at least 4 urine specimens in a consecutive 2-week period, at least one of which must be positive for urine BE (> 300 ng/mL). Ideally, 3 of the specimens will be obtained in one week and 3 in the next week. No more than 4 of the specimens may be obtained in one week of the two-week baseline and no more than two specimens can be collected on consecutive days in one week.
2. Vital signs at each study visit.
3. Adverse Events (AE) will be assessed at each visit with an AE CRF completed weekly.
4. The following must be obtained weekly for two weeks:
 - a. BSCS
 - b. Urine toxicology screen
 - c. Concomitant Medications
 - d. CGI-S and CGI-O
 - e. SFQ and CSEQ

NOTE: the BSCS, CGI-S, CGI-O, SFQ, and CSEQ scores obtained on the first visit of treatment week 1 before study agent administration will be also included in the baseline mean score calculations.

5. The following must be obtained three times
 - a. CSSA
6. Daily report of use and route of administration of cocaine, alcohol, marijuana, amphetamines, methamphetamines, opiates, barbiturates, benzodiazepines, phencyclidine (PCP), propoxyphene and nicotine will be recorded at each visit on a SUI CRF.
7. A CCQ-NOW will be obtained once during baseline.
8. Sweat patches will be applied twice per week to the right arm and once per week to the left arm. The old patch will be removed when the new one is applied.

13.2 ASSESSMENTS DURING TREATMENT

Over the 12-week period of treatment, subjects will return to the clinic three times per week (ideally on Monday, Wednesday, and Friday). Assessments will be performed as follows:

At each visit:

1. SUI
2. Urine BE and creatinine
3. Treatment compliance
4. AEs (AE CRF completed weekly)
5. Vital signs (first two weeks only then weekly thereafter)

Once/ Twice per week:

1. Sweat patches will be applied twice per week to the right arm and once per week to the left arm. The old patch will be removed when the new one is applied.

Once per week, preferably at the first visit each week:

1. Urine toxicology screen
2. BSCS
3. CGI-S
4. CGI-O
5. CSSA
6. SFQ
7. CSEQ
8. Vital signs (see note for each visit above)
9. Concomitant Medications

Once per week the first two weeks then every other week thereafter:

1. HAM-D

At weeks 4 and 12:

1. ECG

Preferably at the first visit of weeks 4 and 8 and mandatory at the first visit of week 12:

1. Hematology
2. Blood chemistries
3. Urinalysis
4. Pregnancy test (if female)
5. ASI-Lite
6. SCID for major depression

In addition a missed visit log will be maintained for each subject and completed if the subject misses a scheduled visit.

13.3 ASSESSMENTS AT END OF TREATMENT (WEEK 12)

All assessments scheduled for study week 12 should be completed at the first visit of the week or if the subjects discontinues prematurely, regardless of the reason (request that the subject return for final assessments).

1. If the subject discontinued prematurely, determine the reason for termination.
2. Physical exam
3. Vital signs
4. SUI
5. Urine BE and creatinine
6. Sweat patches are removed and not replaced
7. AEs
8. Urine toxicology screen
9. BSCS
10. CCQ-NOW
11. CGI-S
12. CGI-O
13. CSSA
14. SFQ
15. CSEQ
16. Hematology
17. Blood chemistries
18. Urinalysis
19. Pregnancy test (if female)
20. ASI-Lite
21. HRBS
22. HAM-D
23. ECG
24. Treatment compliance
25. Concomitant medications

13.4 ASSESSMENTS DURING DOSE TAPER (WEEK 13)

At the end of the dose taper during study week 13, subjects will return to the clinic for the following assessments:

1. Urine BE and creatinine
2. Urine toxicology screen
3. SUI
4. AEs
5. Concomitant medications
6. Treatment compliance (in addition, subjects will be asked to return all unused study agent)

13.5 ASSESSMENTS AT FINAL FOLLOW-UP (WEEK 17)

Subjects will be asked to return to the clinic for one follow-up assessment 4 weeks after completion of treatment. Follow-up assessments include:

1. Urine BE and creatinine
2. Urine toxicology screen
3. SUI
4. AEs
5. Concomitant medications
6. HAM-D

In addition at the last study visit the following will be performed:

Questions regarding current treatment for drug or alcohol abuse, and an impression of the study treatments.

13.6 ASSESSMENT METHODS

13.6.1 Vital Signs

Vital signs to be assessed include oral temperature, sitting blood pressure, pulse rate, respiratory rate, and standing blood pressure and pulse rate (standing 1 minute). If there is a drop in either systolic or diastolic pressure of 10 mm Hg or more, the subject should stand for an additional two minutes and vital signs should be taken again.

13.6.2 Physical Exam and Pulmonary Function Test

A physical exam of the oral cavity, head, eyes, ears nose and throat, cardiovascular system, lungs, abdomen (liver/spleen), extremities, skin, neuropsychiatric mental status and sensory/motor status, musculoskeletal system and general appearance should be performed. Height and weight should be recorded. A forced expiratory volume in 1 second (FEV₁) pulmonary function test should be performed at screening in subjects suspected of having asthma but without a formal diagnosis (an FEV₁ < 70 % will exclude a potential subject from study participation).

13.6.3 Hematology

Blood will be collected in anticoagulant containing evacuated venous blood collection tubes (e.g., Vacutainer™) for hematologic assessments. Complete blood counts (CBC) with differentials and platelet count will be performed. Quantitative analyses for hemoglobin, hematocrit, red blood cells, platelets, total white blood cells, and percentage of neutrophils, lymphocytes, monocytes, eosinophils, and basophils will be performed. Analyses will be performed in the institutions clinical laboratory. The laboratory performing these assessments should be either directly regulated by the College of American Pathologist (CAP) or the Clinical Laboratory Improvement Act of 1988 (CLIA) or indirectly according to CLIA guidelines. The laboratory will need to provide a copy of current certification.

13.6.4 Blood Chemistries

Blood will be collected in serum separation evacuated venous blood collection tubes (e.g., Vacutainer™) and serum separated according to standard procedures. Quantitative analysis will be performed for the following analytes: sodium, potassium, chloride, carbon dioxide, glucose, creatinine, albumin, total protein, calcium, cholesterol, triglycerides, phosphorous, alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), gamma glutamyltranspeptidase (GGT), total bilirubin, lactic dehydrogenase (LDH), creatine phosphokinase (CPK), alkaline phosphatase (ALP), blood urea nitrogen (BUN), uric acid, and iron. The laboratory performing these assessments should be either directly regulated by CAP or CLIA or indirectly according to CLIA guidelines. The laboratory will need to provide a copy of current certification.

13.6.5 Infectious Disease Panel and Syphilis Test

Blood will be collected in a serum separation evacuated venous blood collection tubes (e.g., Vacutainer™) and serum separated according to standard procedures. Qualitative analysis reporting positive/negative results will be performed for the following analytes: Hepatitis B surface antigen, Hepatitis B surface antibody, Hepatitis B core antibody, and Hepatitis C virus antibody. A purified protein derivative (PPD) skin test for tuberculosis will be performed and if positive a chest x-ray is required to assess active tuberculosis. If the subject reports that they have been previously positive for the PPD test, the PPD test will not be performed and only a chest x-ray will be required. A rapid plasma reagin test (RPR) for syphilis will be performed.

13.6.6 HIV Test

All subjects will be offered the opportunity to have an HIV test performed during screening. This test is not requisite for study participation. HIV test informed consent must be obtained before collecting blood for this test. An HIV antibody test will be performed on a serum sample collected from the subject after the HIV informed consent form is signed.

13.6.7 Pregnancy Test

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

13.6.8 HAM-D

The HAM-D is an interviewer administered assessment of the subject's level of depression. The questions for items 1 – 21 were developed by Williams (Williams, 1988). The HAM-D for this study includes three additional questions all associated with cocaine dependence (22. Helplessness, 23. Hopelessness, and 24. Worthlessness).

13.6.9 SCID

A SCID to assess the subject's cocaine-dependence according to DSM-IV criteria, severity of depression, and Axis-I disorders will be conducted during screening. A SCID for major depression will be performed at weeks 4, 8, and 12.

13.6.10 ADD Interview

An interview from the DSM-IV criteria for childhood ADHD has been adapted to diagnose adult ADD. This interview assesses the subject's inattention, hyperactivity, and impulsivity both as the childhood history and as current adult behaviors.

13.6.11 ASI – Lite CF Version

The ASI-Lite CF version will be administered by a research staff member having at least a bachelor's degree in the social sciences or equivalent training and experience as determined by the site's investigator. The ASI-Lite is the interviewer's estimate of the severity of the subject's status in seven areas (medical, employment, drug use, alcohol use, legal, family/social, and psychological). Composite scores will be calculated according to the procedures described by McGahan *et al.* (1982) and Carroll *et al.* (1994). The Lite version is a shorter version of the ASI that still retains all questions used to calculate the ASI composite scores.

13.6.12 Urine Collection and Analyses

Urine will be collected for five types of analyses as follows:

1. Cocaine rapid test
2. BE and creatinine performed at a central laboratory
3. Urine Toxicology Screen (Qualitative Analysis of Substances of Abuse) performed at a central laboratory
4. Urinalysis performed at the local hospital clinical laboratory
5. Pregnancy test performed at the local hospital clinical laboratory

Depending upon the assessment schedule, urine samples will be collected and aliquoted into the appropriate number of specimens. One specimen will be held frozen at the clinical site as a back-up. The others will be frozen (if appropriate – cocaine rapid tests, urinalysis and pregnancy test samples do not need to be frozen) or sent directly to the appropriate laboratory for analysis. Samples to be tested for drugs of abuse and creatinine will be sent to a central laboratory and tested using a validated method. Specimens will be collected and tested as follows:

BE and Creatinine. Urine samples will be collected 3 times a week (generally Monday, Wednesday, and Friday, barring holidays and schedule conflicts). During baseline, three samples will be set aside, one for freezing and one for shipment to a central laboratory for analysis of BE

plus creatinine. In addition a third aliquot will be tested using an on-site test cup for a rapid cocaine test result.

Urine samples collected during treatment and follow-up will be frozen and sent to a central laboratory to be analyzed for BE and creatinine. The back-up sample retained at the site will be stored frozen until the NIDA data coordinating center has notified the site that it can be disposed. Results will not be provided to the site during the study, and the site is prohibited from analyzing samples locally.

Urine Toxicology Screen (Qualitative Analysis of Substances of Abuse). The first sample of each week taken for BE and creatinine analysis will be analyzed additionally for amphetamines, opiates, barbiturates, and benzodiazepines. The frozen sample collected for BE plus creatinine analysis will be tested for these drugs at the central laboratory for analysis.

Urinalysis. Urine will be collected and analyzed for specific gravity, pH, blood, protein, glucose, ketones, leukocytes, and nitrite. Analysis may be conducted at a local laboratory or by study staff using a qualitative dipstick urinalysis according to the package insert.

13.6.13 Sweat Patches

Sweat patches will be applied once per week to the left arm and twice per week to the right arm of each study subject. Patches will be removed and the absorbent pad placed in a specimen collection bag and sent to a central laboratory for analysis of cocaine and cocaine metabolites using a specific and sensitive assay method.

13.6.14 Substance Use Inventory (SUI)

The SUI measures the subject's report of recent drug use (abuse), with routes of administration, for each day in the study. Self-reported use of cocaine, alcohol, marijuana, amphetamines, methamphetamines, opiates, barbiturates, benzodiazepines, PCP, propoxyphene and nicotine will be recorded on this form at each clinic visit.

13.6.15 BSCS

The BSCS is a self-administered assessment that asks the subject to rate his or her craving for cocaine. The BSCS used for this study is a modification of the State of Feelings and Cravings Questionnaire (Mezinskis *et al.*, 1998). If the subject is unable to self-administer this assessment (e.g. physical handicap, poor reading skills) study personnel can assist by reading the questions out loud to the subject and/or marking the subject's response on the CRF. However, study personnel are not to offer interpretations of the questions.

13.6.16 Cocaine Craving Questionnaire (CCQ-NOW)

The CCQ-NOW is a 45 item self-administered questionnaire that asks the subject to rate his or her craving for cocaine (Tiffany *et al.*, 1992).

13.6.17 Clinical Global Impression-Observer (CGI-O)

The CGI-O requires the physician to rate the global severity of the subject's cocaine dependence symptoms and to rate the improvement of the subject's cocaine dependence since the beginning of the study. The severity of the subject's cocaine dependence is rated according to eight specific problem areas often associated with cocaine dependence. The severity of each of the eight specific problem areas is rated first; the global severity is rated second; and the global improvement is rated last.

13.6.18 Clinical Global Impression-Self (CGI-S)

The CGI-Self is a self-administered assessment that asks the subject to rate the global severity of his or her cocaine dependence symptoms and to rate the improvement of his or her cocaine dependence symptoms since the beginning of the study.

13.6.19 Cocaine Selective Severity Assessment (CSSA)

The CSSA is administered by properly trained personnel. Questions relate to withdrawal symptoms of cocaine dependence. There are a total of 18 questions and subjects report their responses on a scale of 0 to 7 with 0 being no symptoms at all and 7 being the most extreme symptom. In addition, there are two self-administered assessments that ask the subject to rate their cravings over the previous 24 hours.

13.6.20 State of Feelings Questionnaire (SFQ)

The SFQ is a subject-completed questionnaire reporting on feelings associated with anxiety, depression, restlessness, anger, irritability, frustration, impatience, and difficulty concentrating. Subjects rate their feelings on a 5 point scale from none at all to extreme.

13.6.21 Cocaine Subjective Effects Questionnaire (CSEQ)

The CSEQ is a subject-completed questionnaire reporting on the subjective experience (if cocaine was used) of using cocaine including drug effect, rush, good effects, desire, and like the experience. In addition to asking about drug use, the effects are scored on a 7 point scale from none to extreme.

13.6.22 Adverse Events (AEs)

AEs will be assessed at each visit by an investigative staff nurse or physician starting after completion of the informed consent process. If an AE is reported to a nurse that requires medical attention, it should be reported to a study physician immediately. The investigator or study physician will assess subjects for any medical or psychiatric side effects. Either the staff nurse or the physician will assess AEs by asking the participant "How have you been feeling since I saw you last". The type of AE, severity of the AE, and the relationship to the study treatments will be recorded on an AE CRF according to the procedures described in section 14.7.

13.6.23 HIV Risk-Taking Behavior Scale (HRBS)

The HRBS is a brief 12-item interview administered scale that examines the behavior of intravenous drug users in both injecting and sexual behavior.

13.6.24 ECG

Twelve-lead electrocardiograms will be performed according to standard procedures. The results will be reviewed by a board-certified cardiologist for interpretation.

13.6.25 Prior Medications

All medications taken by the subject for the 30 days prior to screening and during the screening baseline period will be documented on a Prior Medication CRF. The reported medications will be reviewed and approved by the principal investigator/study physician.

13.6.26 Concomitant Medications

All medications taken by the subject during the two-week baseline period, while on study, and during follow-up must be pre-approved by the study physician whenever possible to avoid interactions with study drug. All medications will be recorded once per week on a concomitant medications CRF.

13.6.27 Treatment Compliance

At each clinic visit, the subject will be asked to provide a report of the number of tablets taken each day. Compliance with psychosocial therapy will be accounted for by recording the length of time the subject spent in attendance at the weekly therapy session.

13.6.28 Missed Visit Log

A CRF is completed as a log that documents the reason that the subject reports for a missed visit during the treatment phase of the study.

14 REGULATORY AND REPORTING REQUIREMENTS

14.1 FDA FORM 1572

The investigator at each study site will sign a Statement of Investigator (FDA Form 1572) prior to initiating this study.

14.2 IRB APPROVAL

Prior to initiating the study, the investigator at each study site will obtain written IRB approval to conduct the study. Should changes to the study protocol become necessary, protocol amendments will be submitted in writing to the IRB by the investigator for IRB approval prior to implementation. In addition, IRBs will approve all advertising materials used for subject recruitment and any educational materials (e.g., HIV/AIDS Education, Appendix II) given to the subject. Annual reports and progress reports will be submitted to the IRB annually or at a frequency requested by the IRB.

14.3 INFORMED CONSENT

A two-part Informed Consent process consisting of one form with two separate signature parts will be used during this study. Part one of the process will consist of an explanation of the study

by a qualified research staff member. Part two of the process will consist of an explanation of the study by physician investigator and all medical/medication questions will be answered.

All potential candidates for the study will be given a current copy of the two-part Informed Consent Form to read and take home. All aspects of the study will be explained in lay language. After the participant has read the consent form, a short questionnaire will be given to the participant before signing the form. This questionnaire will review all aspects of the study discussed in the consent form. A research staff member will review the answers provided by the participant. Any participant who does not successfully complete the questionnaire will re-read the consent with a research staff member. The participant will retake the questionnaires until s/he shows complete understanding of the information discussed in the consent form before providing consent. Any participant who is unable to demonstrate understanding of the information contained in the informed consent will be excluded from study participation and assisted in finding other sources of treatment. Subjects who refuse to participate or who withdraw from the study will be treated without prejudice.

After determining that the subject is eligible for the study, the study procedures will be reviewed with the subject again, the questionnaire will be given again, and if the subject understands the procedures, the subject will be asked to initial the informed consent form demonstrating their continued willingness to participate in the study.

14.4 DRUG ACCOUNTABILITY

Upon receipt, the investigator/pharmacist is responsible for taking inventory of the investigational agent(s). A record of this inventory must be kept and usage must be documented. Any unused or expired investigational agent(s) shall be returned to the sponsor (or responsible party) unless otherwise instructed.

14.5 OUTSIDE MONITORING

Data and Safety Monitoring Board (DSMB): Safety and efficacy data will be reviewed by a DSMB, which will meet after the first 70 subjects (35 in each arm) have completed/terminated from the study or earlier if deemed necessary. Additional meetings will be held on an *ad hoc* basis. The board will be unblinded to subjects' actual treatment assignments. The DSMB will be responsible for review of data from the interim analysis for re-estimation of sample size.

Medical Monitor: An independent medical monitor will be appointed for the study. The medical monitor will be responsible for establishing concurrence with the investigator on the severity of any SAEs, the relatedness to the study treatments, and for determining if the SAE should be reported to the FDA in a 7 or 15 day expedited report or an annual report. The medical monitor will also be responsible for tracking and assessing trends in the SAEs reported.

Clinical Monitors: All investigators will allow representatives of the sponsor to periodically audit, at mutually convenient times during and after the study, all CRFs and corresponding source documents for each subject. These monitoring visits provide the sponsor with the opportunity to evaluate the progress of the study and to inform the sponsor of potential problems at the study sites. The monitors will assure that submitted data are accurate and in agreement

with source documentation; verify that investigational agents are properly stored and accounted for, verify that subjects' consent for study participation has been properly obtained and documented, confirm that research subjects entered into the study meet inclusion and exclusion criteria, and assure that all essential documentation required by good clinical practices guidelines are appropriately filed.

Monitors will conduct a site initiation visit prior to the start of the study. At this visit, they will assure that proper study-related documentation exists, assist in training investigators and other site personnel in study procedures and good clinical practice's guidelines, confirm receipt of study supplies, and assure that acceptable facilities are available to conduct the study.

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

14.6 ADVERSE EVENTS REPORTING

In accordance with FDA reporting requirements, all AEs occurring during the course of the clinical trial will be collected, documented, and reported by the study investigators or study physicians according to the specific instructions detailed in this section of the protocol and Appendix III. The occurrence of AEs will be assessed at each visit starting the completion of the informed consent process and an AE CRF completed weekly.

An AE is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial, whether or not the event is considered related to the investigational agent or clinically significant. For this study, AEs will include events reported by the subject, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant clinical laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. Stable chronic conditions, such as arthritis, which are present prior to clinical trial entry and do not worsen are not considered AEs. All AEs must be recorded on the AE CRF. The AE CRF is also used to record follow-up information for unresolved events reported on previous visits.

Each week, a study investigator must review the AE CRF completed for the previous week for any events that were reported as continuing. All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed by study investigators until satisfactory resolution. AEs should be reported up to 4 weeks following completion of treatment.

14.7 SERIOUS ADVERSE EVENTS

Each adverse event or reaction will be classified by the study investigator as serious or non-serious. Based on the seriousness of the adverse event or reaction appropriate reporting procedures will be followed. The International Conference on Harmonization (ICH) Guideline for Industry: Clinical Safety Data Management: Definitions and Standards for Expedited

Reporting, ICH-E2A March 1995, as implemented by the U.S. Food and Drug Administration defines serious adverse event (SAE) or reaction as any untoward medical occurrence that at any dose:

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

An unexpected event is one that is not described with respect to nature, severity, or frequency in the current Investigator's Brochure or product package insert.

Any SAEs due to any cause, that occur during the course of this investigation, whether or not related to the investigational agent, must be reported within 24-hours by telephone to: the Study Medical Monitor, the NIDA Study Director, and the sponsor- investigator. The telephone report is to be followed by submission of a completed SAE Form with demographic information and a narrative explanation of the event. Attached to the SAE Form should be photocopies of the AE Form, the Concomitant Medication Form, and the Medical History Form from the subject's CRFs. Any serious medical events are also to be reported to the responsible IRB according to local regulatory requirements. All participating investigators will be notified of any serious and unexpected AE requiring submission to the FDA in an IND safety report from the sponsor-investigator.

Any fatal or life-threatening SAE that is investigational agent related and unexpected must be reported by the sponsor-investigator initially to the FDA within 7 calendar days via telephone, facsimile or e-mail. A follow-up written report must be submitted in 8 days to the FDA. All AEs that are both serious and unexpected but not life-threatening or lethal must be reported to the FDA, in writing, within 15 calendar days of notification of the sponsor-investigator of the SAE. All other SAEs will be reported in an annual report or more frequently as necessary. Any additional clinical information that is obtained must be reported to the FDA, as it becomes available in the form of an information amendment. The sponsor-investigator will inform NIDA of all SAEs that occur during the study.

There can be serious consequences including ultimately, criminal and/or civil penalties for sponsors who fail to comply with FDA regulations governing the reporting of SAEs to FDA. The study investigators in this study have the responsibility of promptly reporting all SAEs to NIDA and the sponsor- investigator in order that the sponsor- investigator can comply with these regulations.

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

15 ANALYTICAL PLAN

15.1 STATISTICAL HYPOTHESES

The primary objective of this randomized controlled trial is the assessment of the efficacy of reserpine in reducing cocaine use in subjects with cocaine dependence (DSM-IV criteria). It is hypothesized that reserpine will reduce the weekly mean proportion of non-use days relative to placebo as determined by self-report of cocaine use confirmed with urine assays for BE.

Secondary objectives include assessing the efficacy of reserpine in increasing the overall proportion of cocaine non-use days (weeks 2 – 12 combined) and the proportion of subjects that achieve measured reductions in cocaine and other drug use (non-use days on treatment compared to non-use days at baseline), the reduction in the severity of cocaine dependence and craving (ASI-Lite, BSCS, CCQ-NOW, CGI-S, and CGI-O), and the relative safety of reserpine (AEs, laboratory data, physical exams, HAM-D, and vital signs) in the study population.

There is no generally accepted definition of clinically significant improvement in the treatment of cocaine dependency. The primary and secondary outcome variables are intended to explore various aspects of response to therapy and to help define a clinically meaningful response. The primary outcome has been chosen for its ability to indicate activity of the test product. Some of the secondary outcome variables add a measure of clinical relevance to the reduction of use by requiring either sustained abstinence or a predetermined, substantial overall reduction in use days. Other secondary outcome variables explore the need for laboratory confirmation of the self-report of use. Still others explore the effect of therapy on psychosocial aspects of cocaine dependency.

The primary outcome measure was selected based on a recommendation resulting from a meeting of the College on Problems of Drug Dependence (CPDD) on April 28 – 29, 1999. The consensus from this meeting was as follows:

“The consensus of the group was that the best overall outcome measure was a composite index of abstinence derived from a combination of confidential subjects self-report and objective biological testing (typically urinalysis testing). The recommendation was that this composite index of abstinence be used to classify each day as abstinent or non-abstinent and that the primary outcome analysis be based on these classifications.”

Data will be collected in this study for scientific use and not as primary or secondary outcome measures. These include the HRBS, CSSA, SFQ, CSEQ, and the sweat patch data.

15.2 OUTCOME MEASURES

15.2.1 Primary Outcome Measure

The primary outcome variable is the weekly mean proportion of cocaine non-use days. Cocaine use and non-use days will be defined by subject self-report of use, confirmed or disproved by quantification of urine BE. For the primary efficacy response, each day of the 11-week treatment (weeks 2 through 12) period will be coded as either a use or a non-use day based on the self-reports and on the urine BE data. Three urine collection days are scheduled per calendar week. The first day of week 2 and the last day of week 12 that the subject receives the investigational agent will not be scored as use or non-use days because of the scoring rules. Thus, each subject has a maximum of 75 study days over the twelve weeks of the study.

Because of the pharmacokinetics of cocaine and BE, carryover from previous cocaine use may be difficult to distinguish from new use. The rules enunciated by Preston *et al.* (1997), modified to meet the conditions of this study, (Rules 1-5 below) will facilitate classification of each assessment day as use or no-use.

The following will indicate “new use”:

RULE 0: Subject reports new use.

The subject self report claims no new use but any of the following applies:

RULE 1: An increase in cocaine metabolite concentration over concentration of preceding urine specimen to any value over 300 ng/ml.

RULE 2: Both of the following occur: 1) cocaine metabolite concentration is greater than 300 ng/mL and 2) cocaine metabolite concentration is greater than one-half of the concentration measured in the preceding urine specimen.

RULE 3: Cocaine metabolite is greater than 300 ng/ml in the first urine specimen collected in the study.

RULE 4: If the previous urine specimen was collected more than 2 calendar days before, urine specimen with cocaine metabolite greater than 300 ng/ml.

RULE 5: Creatinine less than 20 mg/dl and cocaine metabolite/creatinine ratio is increased compared to that of previous specimen. (Cocaine metabolite does not have to be above 300 ng/ml).

Assessment days may be less than 48 hours apart in this study, but must be 24 hours apart. For this reason, the Preston rules were modified to delete reference to previous urine specimen collected at least 48 hours earlier.

Self-report gives preliminary determination of each day as a use or non-use day. Non-use days are confirmed or disproved by the urine BE data as follows:

1. Subject reports no new use since last urine BE or within the preceding 72 hours (whichever is the shorter time frame) but urine BE shows new use, then score the preceding day as a use day.
2. Self report days of non-use will be considered as missing if not followed by a urine BE assessment within 7 days. In the case of obtaining urine within 7 days, data will also be considered as missing if the concordance rate between self report and urine BE for the individual is < 70 %.
3. Self report of use are accepted in all cases.

Percentage non-concordance between self-report of use and urine BE data will be calculated for each study subject as the percentage of the number of days that were scored as use days based on urine BE data overruling self-report (according to criteria in #1 immediately above) divided by the total number of urine samples analyzed, as follows:

$\% \text{ non-concordant} = \# \text{ non-concordant use days} / \text{total urine samples analyzed} * 100\%$, thus

$\% \text{ concordant} = 100 - \% \text{ non-concordant}$.

The concordance rate of < 70% was established based on a survey of data sets from recently completed NIDA studies that showed that mean concordance rates ranged from 70-90%.

In addition, the primary outcome measure, the cocaine non-use day, was defined using an additional modification of the Preston rules as demonstrated in Appendix IV. This alternative primary outcome measure will be compared between treatment groups using the same methods as used for the main primary outcome measure but as a separate exploratory analysis.

15.2.2 Secondary Outcome Measures

Measured reductions in cocaine and other drug use

- A.** The proportion of successful subjects. A successful subject is one who reduces the overall proportion of cocaine use days to 75% or less of his/her baseline rate.
- B.** The proportion of successful subjects. A successful subject is one who reduces the overall proportion of cocaine use days to 50% or less of his/her baseline rate.
- C.** The proportion of successful subjects. A successful subject is one who reduces use days to 75% of his/her baseline level according to subject self report without regard to BE levels.
- D.** The proportion of successful subjects. A successful subject is one who achieves 3 consecutive weeks of abstinence – self report confirmed by urine BE.
- E.** Weekly mean proportion of non-use days according to subject self report without regard to BE levels.

- F.** Weekly mean proportion of non-use days of other drug use, by other drug according to self-report.
- G.** Proportion of negative urines for other drug use (the denominator is the total possible urines to be collected while the subject was on study, i.e., 12 if the subject completes treatment, 8 if the subject completed 8 weeks of treatment, etc.).
- H.** Weekly mean ln urine BE level.
- I.** Overall proportion of cocaine non-use days during the 11 week treatment period (weeks 2 through 12, non-use days divided by non-missing study days).
- J.** The maximum number of consecutive cocaine non-use days.

Reduction in the severity of cocaine dependence and craving

- K.** CGI-O scores.
- L.** CGI-S scores.
- M.** ASI-Lite scores.
- N.** BSCS scores.
- O.** Change in CCQ-NOW score over baseline.

Safety of Reserpine

- P.** AEs, laboratory data, physical exams, HAM-D, and vital signs.

15.3 INTENT-TO-TREAT AND EVALUABLE SUBJECT POPULATIONS

The intent-to-treat population is defined as the subjects who are randomized to treatment and who receive the first day's study agents. The evaluable population is defined as the subjects who are randomized and properly qualified to participate in the study in accordance with the inclusion and exclusion criteria, and who contribute at least four (4) usable on-study urine samples and 21 days of self report, and who do not receive adjusted doses of reserpine due to side effects.

15.4 ANALYSIS PLAN

15.4.1 Efficacy Assessments

Each primary and secondary efficacy outcome measure will be analyzed for the intent-to-treat and for the evaluable population. Major differences in the results, if any, will be further explored. While there is every intent to be complete in describing the analyses to be performed, it is not possible to anticipate every contingency and some adjustments may be required to meet constraints posed by the structure of the data.

All statistical tests will be two-sided at a 5% Type I error rate. Confidence intervals will be two-sided with a 95% confidence coefficient.

Primary Efficacy Outcome

The primary outcome variable for each subject is the weekly mean proportion of cocaine non-use days during treatment (weeks 2 through 12). Each subject's weekly mean proportion is equal to the number of his/her cocaine non-use days divided by the number of his/her non-missing study days during that week. There is interest in attempting to estimate the actual number of cocaine "use" or "non-use" days by combining the self-reported patterns of use confirmed or disproved by the presence of urinary BE. For this outcome measure, each day of treatment (weeks 2 through 12) will be coded as either a use or non-use day based on the self-reports and on the urine BE data. Three urine collections are scheduled per calendar week. The first day of week 2 and the last day of week 12 will not be scored as use or non-use days because of the scoring rules. Thus there would be a maximum of 75 days over 11 weeks of the study treatment for each subject.

The weekly mean proportion of cocaine non-use days on study will be compared between treatment groups using Generalized Estimating Equations (GEE). GEE provide a model-based regression methodology applicable for the analysis of the correlated data that will result from this repeated measures longitudinal study. The GEE procedure proposed by Liang and Zeger (1986) and Zeger and Liang (1986) model the population average and has several useful features:

1. It can be used to analyze different types of outcomes such as continuous, binary, or count.
2. It can be used to analyze an unbalanced design caused by either differing numbers of observations per person or by observations taken at different times.
3. The parameter estimates are consistent even if assumptions about the variance structure are not completely accurate.

As a secondary analysis, prior use in the last 30 days before screening (≤ 18 and > 18 days of cocaine use), site, gender, diagnosis of ADD, and their first-order interactions with treatment will also be included in the model. Presentation will include the full model with all terms and a reduced model containing only significant terms.

Secondary Efficacy Outcomes

Unless the primary response analysis implies the need for a more elaborate model, between group comparisons of the secondary outcomes will be performed as follows:

1. Proportion of successful subjects, measures A, B, C, and D will be assessed by Chi-square tests.

2. Weekly mean proportion of cocaine non-use days, other drug non-use days, and ln BE levels measures E, F, and H by GEE.
3. The proportion of negative urines for other drug use, proportion of cocaine non-use days on study, the maximum number of consecutive cocaine non-use days, the change in the CCQ-NOW score over baseline, measures G, I, J, and O, will be assessed by t-test.
4. Weekly CGI-S, CGI-O, BSCS scores and monthly ASI-Lite score, measures K, L, M, and N will be assessed by GEE (the BSCS, CGI-S, and CGI-O scores obtained on the first visit of treatment week one before study agent administration will be also included in the baseline mean score calculations).
5. Adverse events, laboratory data, physical exams, and vital signs will be reported in tabular form. AEs will be listed indicating the frequency of each type of event by various demographic characteristics such as gender, ethnicity, age, duration of addiction, other medical problems both related to and independent of the addiction, and combinations of these characteristics. The frequencies of adverse events by type will be compared between study arms using Chi-square analyses.

15.4.2 Descriptive Statistics

Summaries of the characteristics of the subject population in both treatment arms at baseline will be prepared for both the intent-to-treat and evaluable subjects. A summary will be prepared to show dropouts/retention over time in each treatment group and for major subgroups. The number of missing observations will be compared between treatments and for major subgroups. Weekly treatment compliance of each group will be summarized. All adverse events will be reported in tabular form indicating the frequency and severity of each type of event.

15.4.3 Sweat Patch Data Analysis

The analyses performed on the sweat patch data will include the following:

1. Cocaine use by the reserpine and placebo groups will be compared using the quantitative results from the twice-weekly patches.
2. Cocaine use by the reserpine and placebo groups will be compared using the qualitative results from the twice-weekly patches.
3. The quantitative and qualitative results from a subgroup of the weekly patches will be compared to the twice-weekly patch results to confirm that the results yielded from these two sets of patches are highly correlated.
4. The completeness of the dataset yielded by thrice-weekly urine toxicology and twice weekly and weekly sweat patches will be compared following the guidelines used by Winhusen *et al.* (2001).
5. The reliability and validity of three potential sweat patch measures, derived from the twice

weekly patch, will be evaluated following the analyses used by Winhusen *et al.* (2001). The three measures will consist of qualitative results based on the limit of quantification (LOQ) of the assay method used, quantitative results, and qualitative results based on optimizing the sweat patch cutoff. The optimization procedure is based on maximizing classification accuracy (CA).

6. The relationship between twice-weekly sweat patch results and self-report of use will be explored and compared with the corresponding relationship between the urine BE levels and self-report. The analysis might include formulating rules for defining a “new use” based on self-report confirmed or disproved by sweat patch data.

15.5 SAMPLE SIZE CALCULATION

The primary outcome measure is the weekly mean proportion of cocaine non-use days. Cocaine use and non-use days will be defined by subject self-report of use, confirmed or disproved by quantification of urine BE. Power analyses were based on the following assumptions: normal distribution of the data, an equal correlation between observations at any two times is 40% (i.e., exchangeable working correlation) and a scale estimator of 26. These assumptions were based on results from a recent eight-week pilot clinical study conducted in which 0.5 mg of reserpine was compared to placebo in cocaine dependent subjects. An additional assumption is that a 12% increase in the proportion of cocaine non-use days within the reserpine group compared to the placebo group would be considered clinically significant. Based on GEE methods for sample size calculations proposed by Liu and Liang (1997), then 34 subjects will be required in each treatment group to detect this clinically meaningful difference with a power of 80% at a 5% Type I error rate. Historically, the retention rates in NIDA funded clinical trials with cocaine dependent subjects is approximately 50% after 11 weeks; therefore, at least 70 subjects should be randomized into each treatment group to ensure an adequate sample size at the end of the trial. The sample size for this clinical trial will be 140 subjects.

15.6 CONTROL OF BIAS

Stratified randomization will be performed to balance treatment arms with respect to gender and historical self-report of cocaine use for the last 30 days at the time that informed consent is given (≥ 18 days of use and < 18 days of use). The randomization process will be performed by computer at the data coordinating center. The investigative pharmacist will be provided with the treatment assignments. Investigative staff and subjects will remain blind to treatment assignment. Study agents will be prepared in a matched configuration.

15.7 INTERIM ANALYSIS

An interim analysis is planned when one-half of the subjects have been enrolled and follow-up is complete. The interim analysis will be conducted unblinded to treatment arm assignment. The purpose of the interim analysis is to determine if the sample size needs to be adjusted because of the uncertainties associated with the expected treatment effect and variance of the outcome measures. The procedures published by Cui *et al.* (1999) will be used to re-estimate the sample size.

15.8 POST HOC ANALYSES

Data will be collected in this study for scientific use and not as primary or secondary outcome measures. Analyses of data from the HRBS interview is included in this category. This data are being collected to build a database that will help characterize the study population. Additional post hoc analysis may be performed to evaluate other confounding factors on outcomes such as HAM-D scores or patterns of cocaine use at baseline and after treatment.

16 DATA MANAGEMENT AND CASE REPORT FORMS (CRF)

Data management activities and statistical analytical support will be coordinated through the NIDA data coordinating center.

16.1 DATA COLLECTION

Data will be collected at the study sites on source documents which will be entered at the site into electronic case report forms (eCRFs). The eCRFs will be supplied by the NIDA data coordinating center. eCRFs are to be completed on an ongoing basis during the study. The medical chart and the source documents are the source of verification of data. eCRFs should be completed according to the instructions in the study operations manual. The principal investigator is responsible for maintaining accurate, complete and up-to-date records for each subject. The principal investigator is also responsible for maintaining any source documentation related to the study, including any films, tracings, computer discs or tapes.

16.2 DATA EDITING AND CONTROL

Data are edited for out-of-range values, internal consistency and data entry errors as they are entered into the computer and resolved at the site by the coordinator/PI. Prior to her visit, the monitor will review the eCRF, identify any obvious inconsistencies, and request changes be made at the site prior to her visit. At the monitoring visit, any inconsistencies between source and eCRF will be resolved by the coordinator. If any data problems are found in the data analysis process, the site will be notified and will respond by modifying the eCRF or annotating it electronically to explain the discrepancy. NIDA/DTR&D and the participating sites will receive reports at least monthly regarding the quality and quantity of data submitted to the data coordinating center.

The principal investigator agrees to routine data audits by the staff of the NIDA data coordinating center and by NIDA's programmatic staff. The study monitors will routinely visit the study site to assure that data submitted on the appropriate forms are in agreement with source documents. They will also verify that the investigational agents have been properly stored and accounted for, subject informed consent for study participation has been obtained and documented, all essential documents required by Good Clinical Practice regulations are on file, and sites are conducting the study according to the research protocol. Any inconsistencies will be resolved, and any changes to the data forms will be made using the data coordinating center procedures.

16.3 DATA ENTRY, PROCESSING AND ANALYSES

Data will be collected at the study sites on source documents which will be entered into eCRFs. When the study is completed and all data have been entered into the clinical database and the database has been checked by Quality Assurance and is locked, statistical analysis of the data will be performed by the data coordinating center's statisticians in accordance with the analytical plan section of this protocol. Periodically, during the investigation, data sets will be submitted to the NIDA DTR&D central data repository according to procedures specified in the study operations manual.

16.4 STUDY DOCUMENTATION AND RECORDS RETENTION

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

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Accordingly, source documents include, but are not limited to, laboratory reports, ECG tracings, X-rays, radiologist reports, subject diaries, biopsy reports, ultrasound photographs, subject progress notes, hospital charts or pharmacy records and any other similar reports or records of any procedure performed in accordance with the protocol.

Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original document.

Government agency regulations and directives require that the investigator must retain all study documentation pertaining to the conduct of a clinical trial. These documents must be kept for a minimum of two years after discontinuation of the IND or 2 years after the approval of an NDA.

16.5 CONFIDENTIALITY

16.5.1 Confidentiality of Data

Particular attention is drawn to the regulations promulgated by the Food and Drug Administration (FDA) under the Freedom of Information Act providing, in part, that proprietary information furnished to clinical investigators and IRBs will be kept confidential by the FDA only if maintained in confidence by the clinical investigator and IRB.

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

16.5.2 Confidentiality of Subject Records

To maintain subject confidentiality, all laboratory specimens, CRFs, reports and other records will be identified by a coded study subject number only. Research and clinical records will be stored in a locked cabinet. Only research staff and NIDA program officials will have access to the records. Subject information will not be released without written permission, except as necessary for monitoring by the FDA, the NIDA monitoring contractor, or NIDA. Upon approval of the study by an IRB, an application will be filed with NIDA for a certificate of confidentiality.

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

17 PUBLICATIONS OF THE STUDY RESULTS

NIDA and the investigative group agree that clinical database will be made available to individual investigators to encourage other publications, either by a group or by an individual investigator provided that: manuscripts based on the use of reserpine for the treatment for cocaine dependence may not be submitted for publication until the main findings of the study have been published and this study has been accepted by the FDA for filing to the IND or NDA. Review of manuscripts resulting from this study or from data generated during this study must occur according to the NIDA DTR&D Publications Policy prior to submission for publication. Authorship shall be consistent with NIDA and DTR&D policies.

18 SIGNATURES

NIDA REPRESENTATIVES

Typed Name	Signature	Date
<u>Ann Montgomery, R.N.</u> Study Director	_____	_____
<u>Jurij Mojsiak, M.S.</u> Project Officer	_____	_____
<u>Ahmed Elkashef, M.D.</u> CMB Branch Chief	_____	_____

INVESTIGATOR (S)

I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol; deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment with the IRB approval. I also agree to report all information or data in accordance with the protocol, and in particular I agree to report any serious adverse experiences as defined in section 14.7 of this protocol.

Typed Name	Signature	Date
<u>Eugene Somoza, M.D., Ph.D.</u> Principal Investigator	_____	_____
<u>R. Jeffery Goldsmith, M.D.</u> Subinvestigator	_____	_____
<u>Judy Harrer, Ph.D.</u> Subinvestigator	_____	_____
<u>Theresa Winhusen, Ph.D.</u> Subinvestigator	_____	_____
<u>Florence Coleman, M.D.</u> Subinvestigator	_____	_____
<u>Domenic Ciraulo, M.D.</u> Subinvestigator	_____	_____

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APPENDIX II: HIV/AIDS Education

Education should be performed by trained staff and should include the following topics:

- Modes of transmission
- High risk behaviors
- Prevention behaviors
 - stop drug use
 - don't share needles
 - clean "works" before using
 - use of condoms
- HIV Testing
 - What test is for
 - Confidential vs anonymous
 - Optional
 - What +/- test results mean
 - Anxiety related to waiting for results
- Demonstration of:
 - Use of alcohol swipes
 - Use of bleach kits
- Subject wishes to be tested?
 - If yes, talk through the consent
 - Obtain signature
 - Offer outside referrals

APPENDIX III: Instructions For Evaluating and Reporting Adverse Events and Serious Adverse Events

A. GENERAL INSTRUCTIONS

1. Adverse Events (AE) must be assessed at each visit, and the AE CRF completed weekly.
2. The patient must be seen by study physician weekly to assess AEs.
3. AEs will be reported as soon as the subject signs the informed consent.
4. Report the severity of the event following the guidance in section B below.
5. Report the relatedness of the event to the study agent administration according to the guidance in section C.

B. DEFINITIONS – SEVERITY OF EVENTS

Mild: Awareness of symptom, but easily tolerated.

Moderate: Discomfort enough to cause interference with usual activity.

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

C. DEFINITIONS – RELATEDNESS OF EVENTS

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

- **Exposure:** Is there evidence that the subject was actually exposed to the drug/placebo?
- **Timing of the study drug/placebo:** Did the AE/SAE follow in a reasonable temporal sequence from administration of the drug test?
- **Consistency with study drug profile:** Known pharmacology and toxicology of the study drug in animals and man; reaction of similar nature having been previously described with the study drug.
- **Alternative explanations** for the adverse event such as concomitant medications, concurrent illness, non-medicinal therapies, diagnostic tests, procedures or other confounding findings.
- **Response to discontinuation** of the study drug/placebo.

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

- ***Unrelated:***
The subject did not receive the test drug, the temporal sequence of the AE/SAE onset relative to administration of the test drug is not reasonable, or there is another obvious cause of the AE/SAE.
- ***Unlikely to be Related:***
There is evidence of exposure to the test drug or there is another more likely cause of the AE/SAE.
- ***Possibly Related:***
There is evidence of exposure to the test drug, the temporal sequence of the AE/SAE onset relative to administration of the test drug is reasonable, but the AE/SAE could have been due to another equally likely cause.
- ***Probably Related:***
There is evidence of exposure to the test drug, the temporal sequence of the AE/SAE onset relative to administration of the test drug is reasonable, and the AE/SAE is more likely explained by the test drug than by any other cause.
- ***Definitely Related:***
There is evidence of exposure to the test drug, the temporal sequence of the AE/SAE onset relative to administration of the test drug is reasonable, the AE/SAE is more likely explained by the test drug than by any other cause, and the AE/SAE shows a pattern consistent with previous knowledge of the test drug or test drug class.

D. SPECIFIC INSTRUCTIONS – LABORATORY/ECG ADVERSE EVENT

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

All laboratory AEs should be specified as an increased or decreased test result (e.g. “increased glucose”, “decreased potassium”) or as a term that implies an abnormality (e.g., hypercalcemia, azotemia).

E. SERIOUS ADVERSE EVENT AND UNEXPECTED ADVERSE EVENT REPORTING

24 hour Reporting Requirements

Any serious adverse event, including death due to any cause, which occurs to any subject from the time of admission through discharge whether or not related to the study drug/placebo, must be reported ***within 24 hours*** to the NIDA Medical Monitor, the NIDA Study Director, and the principal investigator (IND sponsor).

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

- Name of person reporting the SAE/unexpected AE
- Subject's I.D. number
- Name of the principal investigator and institution
- Description of the SAE/unexpected AE
- Date and time of Onset
- Date/time of administration of last dose of study agent/placebo prior to the SAE/unexpected AE
- Severity of the SAE/unexpected AE
- Investigator's assessment of the relationship of the SAE/unexpected AE to study drug (related, possibly related, probably related, unlikely related, not related)
- Any action taken with the study drug, alteration to protocol defined schedule, diagnostics, and treatments secondary to the SAE/unexpected AE.

3-day Supporting Documentation Requirements

Written documentation for all SAEs/unexpected AEs must be received by the NIDA Medical Monitor/Alternate and the IND sponsor within 3 days of reporting the event. Required documents that must be submitted include the following:

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

Follow-Up of All Adverse Events/Serious Adverse Events

All adverse medical events must be followed until they are resolved, or until all attempts to determine the resolution of the AE/SAE are exhausted. This may require an extended inpatient period or a change in status from outpatient to inpatient. All treatments, outcomes and information regarding whether or not the subject was referred to their Primary Care Provider for additional follow-up must be recorded in the source document. All serious and unexpected

adverse events occurring 30 days after administration of the last dose of study drug/placebo must be reported.

The investigator is required to provide the Medical Monitor/Alternate and the IND sponsor with all relevant follow-up information necessary to facilitate a thorough understanding of the event and judgment regarding the relationship to the study drug/placebo.

Reporting to the FDA

The principal investigator, who is the IND sponsor, is required to report SAEs to the FDA:

- in 7 days if the SAE is unexpected (or, if expected, unusually serious or rarely seen), life-threatening or lethal, and at least possibly related to the study agent, with a follow-up written report in 8 days;
- in 15 days if the SAE is unexpected (or, if expected, unusually serious or rarely seen), but not immediately life-threatening; and
- in an annual report in all other cases.

APPENDIX IV: ALTERNATIVE DEFINITION OF PRIMARY OUTCOME MEASURE FOR EXPLORATORY ANALYSIS

Primary Outcome Measure

The primary outcome variable is the weekly mean proportion of cocaine non-use days. As defined in section 3, a subject's weekly mean proportion is equal to the number of his/her cocaine non-use days divided by the number of his/her non-missing study days during that week. Cocaine use and non-use days will be defined by subject self-report of use, confirmed or disproved by quantification of urine BE. For the primary efficacy response, each day of the 11-week treatment (weeks 2 through 12) period will be coded as either a use or a non-use day (or as an unknown day) based on the self-reports and on the urine BE data. Three urine collection days are scheduled per calendar week. The first day of week 2 and the last day of week 11 that the subject receives the investigational agent will not be scored as use or non-use days. Thus, each subject has a maximum of 75 study days over the twelve weeks of the study.

Because of the pharmacokinetics of cocaine and BE, carryover from previous cocaine use may be difficult to distinguish from new use. The rules enunciated by Preston *et al.* (1997), modified to meet the conditions of this study, (Rules 1-5 below) will facilitate classification of each assessment day as use or no-use.

The following will indicate "new use":

RULE 0: Subject reports new use.

The subject self report claims no new use but any of the following applies:

RULE 1: An increase in cocaine metabolite concentration over concentration of preceding urine specimen to any value over 300 ng/ml.

RULE 2: Both of the following occur: 1) cocaine metabolite concentration is greater than 300 ng/mL and 2) cocaine metabolite concentration is greater than 1/N of the concentration measured in the preceding urine specimen, where N depends as follows on the number of days that have elapsed since the last specimen.

Number of Days Elapsed	N
1	2
2	4
3	8

Note that this is a revision of RULE 2 as it is found in Section 15.2.1 of this document.

RULE 3: Cocaine metabolite is greater than 300 ng/ml in the first urine specimen collected in the study.

RULE 4: This version of this rule as it is found in Section 15.2.1 of this document has been superseded by RULE 2 above.

RULE 5: Creatinine less than 20 mg/dl and cocaine metabolite/creatinine ratio is increased compared to that of previous specimen. (Cocaine metabolite does not have to be above 300 ng/ml).

Cocaine use for each day is determined via two mechanisms. The first is self-report; the second utilizes urine BE levels as described below. Any day for which one or both of the two mechanisms indicates use is considered to be a use day. Any day for which both of the two mechanisms indicate non-use is considered to be a non-use day. Any day for which both mechanisms indicate that use is unknown, or one indicates unknown and one indicates non-use, is considered to be an unknown day. This algorithm is summarized in the following table:

		Self Report of Use		
		Use	Non-Use	Unknown
Urine BE Levels	Use	Use	Use	Use
	Non-Use	Use	Non-Use	Unknown
	Unknown	Use	Unknown	Unknown

BE levels from urine collected on a given day are used to determine the use/non-use/unknown status for any previous days for which a status has not already been determined via BE level results. A BE-based status value is determined as follows:

- 1) If all of the appropriate rules (excluding Rule 0, which is only used for self report) indicate that no new use has occurred, mark up to three previous days (those not already marked) as Non-Use. Mark any still-unmarked previous days (more than three days ago) as Unknown.
- 2) If any appropriate rule (excluding Rule 0) indicates that a new use has occurred, mark the previous day as a Use day, and mark any other previous days for which a BE status has not been entered as Unknown.

Percentage non-concordance between self-report of use and urine BE data will be calculated for each study subject as the percentage of the number of days that were scored as use days based on urine BE data overruling self-report (according to criteria in (2) immediately above) divided by the total number of urine samples analyzed, as follows:

$\% \text{ non-concordant} = \# \text{ non-concordant use days} / \text{total urine samples analyzed} * 100\%$, thus

$\% \text{ concordant} = 100 - \% \text{ non-concordant}$.

The false negative percentage will also be calculated as the number of days that were scored as use days based on self-report overruling urine BE data, divided by the total number of urine samples analyzed.

Examples of Scoring Use/Non-Use Days

Example I: Subject reports no new use over 12 days, all urine BE data are available and two urine BE's suggest new use. Using the procedure described above, 2 use days are scored, 7 non-use days are scored, and 3 unknown days are scored.

Day	M	T	W	T	F	S	S	M	T	W	T	F
SUI	0	0	0	0	0	0	0	0	0	0	0	0
BE	0		1		0			0		0	1	
Score	U	1	0	0	0	0	0	0	0	1	U	U

0 = No use or no new use; 1 = use or new use, M = missing, U=unknown; SUI = self report of use; BE = urine BE results 0 = no new use, 1 = new use; Score = assignment of use or non-use day.

Example II: Subject reports no new use over 12 days; 8 days elapse between urine samples, and the next two urine samples after the missing samples show new use. Using the procedure described above, 2 use days are scored, and 10 Unknown days are scored.

Day	M	T	W	T	F	S	S	M	T	W	T	F
SUI	0	0	0	0	0	0	0	0	0	0	0	0
BE	0		M		M			M		1		1
Score	U	U	U	U	U	U	U	U	1	U	1	U