STUDY #: NIDA-CTO-0007

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

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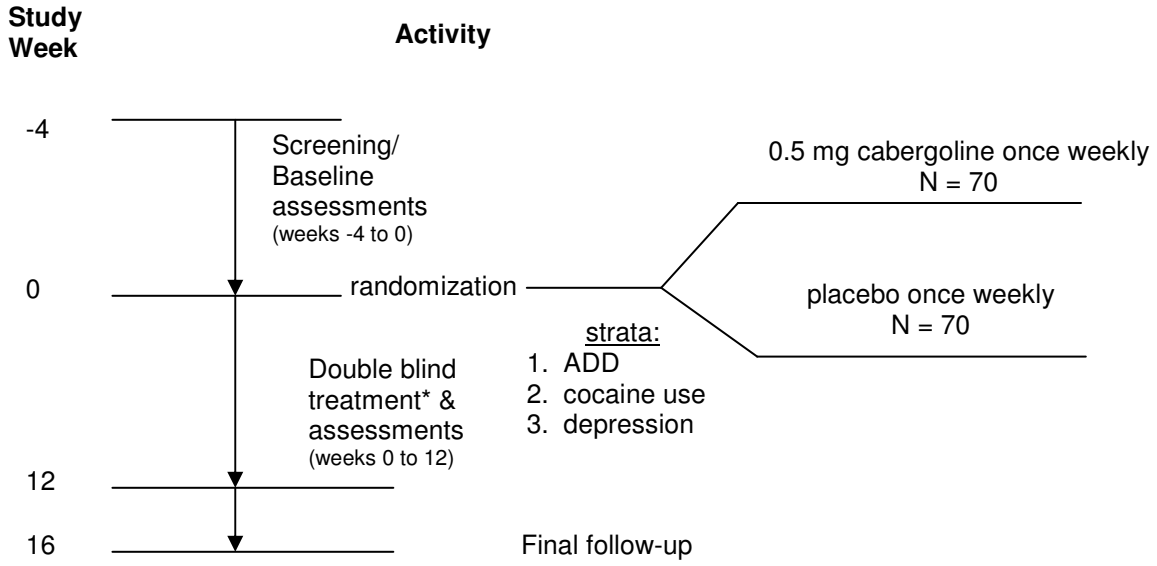
TABLE OF CONTENTS

APPENDICES

1 LIST OF ABBREVIATIONS

Abbreviation	Definition
ADD	attention deficit disorder
AE	adverse event
AIDS	acquired immune deficiency syndrome
ALP	alkaline phosphatase
ALT/SGPT	alanine aminotransferase/serum glutamic pyruvic transaminase
ASI-Lite	Addiction Severity Index-Lite
AST/SGOT	aspartate aminotransferase/serum glutamic oxaloacetic transaminse
BE	benzoylecgonine
BSCS	Brief Substance Craving Scale
BUN	blood urea nitrogen
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
CSSA	Cocaine Selective Severity Assessment
CRF	Case Report Form
CPK	creatine phosphokinase
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders Fourth Edition
DTR&D	Division of Treatment Research and Development
ECG	electrocardiogram
FDA	Food and Drug Administration
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
MAO	monoamine oxidase
mg	milligrams
mL	milliliter
NIDA	National Institute on Drug Abuse
OTC	over-the-counter
RPR	Rapid plasma reagin (test for syphilis)
SAE	serious adverse event
SCID	structured clinical interview for DSM-IV
SUI	substance use inventory

2 STUDY SCHEMA



* Double blind treatment consists of cabergoline (at 0.5 mg dose once per week) or unmatched placebo plus weekly psychotherapy.

3 ABSTRACT

STUDY OBJECTIVES: To assess the efficacy and safety of cabergoline in reducing cocaine use in subjects with cocaine dependence. It is hypothesized that cabergoline 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 period, subjects will be equally randomly assigned to receive either 0.5 mg cabergoline or placebo once per week for 12 weeks with a follow-up assessment 4 weeks after treatment completion. Randomization stratum include diagnosis of attention deficit disorder (ADD), days of cocaine use 30 days prior to screening, and diagnosis of depression. All groups will receive once-weekly manual-guided cognitive behavioral therapy during the 12 weeks of treatment.

STUDY POPULATION: 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). Subjects at least 18 years-of-age, with at least 1 urine BE positive specimen provided within 2-weeks during the baseline period prior to randomization with the ability to understand and provide written informed consent will be included.

TREATMENTS: Subjects will receive either 0.5 mg of cabergoline or placebo once a week for 12 weeks. All subjects will receive manual-guided cognitive behavioral therapy once a week during the initial 12 weeks of treatment.

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 performed during screening or baseline. Vital signs, concomitant medication use, and a urine screen for other substances of abuse will be assessed weekly. A Ham-D and clinical laboratory studies including a pregnancy test, if female, will be performed at weeks 4, 8, and 12. Adverse Events (AEs) will be assessed at each study visit by reviewing a subject diary and recording any AEs on a case report form (CRF). An HIV Risk-Taking Behavior Scale (HRBS) will be used to characterize the population HIV risk behaviors (baseline and week 12). At treatment week 12 and followup week 16, all subjects will have an ECG. Also at treatment week 12 or at the time of study discontinuation, subjects will be evaluated for AEs, vital signs, physical examination, and clinical laboratory studies. A final AE assessment will be performed at final followup (week 16).

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 level at each study visit) 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, and weekly median quantitative urine BE levels. Severity of cocaine dependence will be assessed with the 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). Serum prolactin levels will be assessed to determine if outcomes are associated with serum levels collected at baseline before investigational agent administration, once during weeks 3 to 6, and at week 12 or final visit if patients leaves the study prematurely. The ASI-Lite will be performed at baseline and at the first visit of weeks 4 and 8 and at the end of week 12. The BSCS, CGI-S, and CGI-O will be performed at each week during baseline and at the first visit of each study week. The CCQ-NOW questionnaire is assessed once at baseline and week 12. A Cocaine Selective Severity Assessment (CSSA) will be performed 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 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. The individual effects, if any, of gender, age, race, prior cocaine use, diagnosis of ADD or depression, elevated serum prolactin, and reduced blue cone b wave responses 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 each treatment arm 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 of each type of event.

4 INTRODUCTION

Cocaine as a Major Health Problem. 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.

Search for Effective Treatments for Cocaine Dependence. Recently, the search for an effective pharmacotherapy for cocaine addiction has focused on dopaminergic agents with direct or indirect agonist activity at dopamine receptors as a replacement strategy (Johanson and Schuster, 1995). Pharmacologically, cocaine is a potent inhibitor of the dopamine transporter, and neuroimaging studies indicate fewer dopamine transporter receptors in the prefrontal cortex of cocaine users (Hitri *et al*., 1994). Cocaine binds at the dopamine transporter and inhibits neurotransmitter reuptake, thus leading to a build-up of extracellular dopamine levels and potentiation of mesolimbocortical pathways (Kuhar *et al*., 1991). Dopamine receptor agonists might be useful in substitution therapy for cocaine which itself is an indirect dopamine agonist, because, in contrast to cocaine, they do not exhibit rewarding (behaviorally reinforcing) properties. Also, by providing continuous dopaminergic tone the dopamine receptor agonists are hypothesized to attenuate the reinforcing effects of acute dopamine overflow triggered by cocaine use. A logical conclusion is that dopamine receptor agonists will relieve the symptoms of cocaine withdrawal and eventually prevent the relapse in cocaine patients.

Rationale for Studying Cabergoline. This study will investigate an ergoline derivative, cabergoline, which is a D2 dopamine receptor agonist. Activation of the mesolimbic dopamine system, which is a major neural substrate for cocaine reinforcement, is known to trigger relapse in animal models of cocaine-seeking behavior. The "priming" effects of cocaine or cocaine-associated cues could be blocked by dopamine receptor antagonists, but these agents can exacerbate cocaine withdrawal symptoms such as anergy, anhedonia and depression (Gawin, 1991).

Bromocriptine, another D2 dopamine receptor agonist, has been shown to reduce craving in cocaine addicts in a double-blind, placebo-controlled study (Dackis *et al.,* 1987). Comparative studies indicate that cabergoline is superior to bromocriptine in efficacy and tolerability and may be regarded as the treatment of choice for hyperprolactinemic disorders, either idiopathic (Webster *et al*., 1993, 1994, 1999) or due to pituitary adenomas (Colao *et al.,* 2000), and in the control of clinical and hormonal features of dopamine-sensitive acromegalic patients (Muratori *et al.,* 1997). In Parkinson's disease patients, cabergoline has been also shown to improve motor functions when used alone or in combination with L-dopa (Inzelbert *et al*., 1995; Steiger *et al*., 1996; Hutton *et al*., 1996; Ahlskog *et al*., 1996). It relieved parkinsonian symptoms in monkeys with MPTP-induced nigrostriatal depletion (Calon *et al*., 2000). Cabergoline proved to be effective in an open clinical trial of idiopathic restless leg syndrome (Stiasny *et al.,* 2000).

Prolactin as a Biological Marker for Dopaminergic Tone. Acute cocaine administration alters secretion of anterior pituitary hormones in experimental animals, and cocaine abuse may compromise neuroendocrine function in humans. Effect of cocaine on prolactin release is consistent with both cocaine-induced activation of dopaminergic systems and central role of dopamine in cocaine abuse and with dopaminergic inhibitory control of prolactin release from the anterior pituitary. D2 dopamine agonists, such as bromocriptine decrease plasma levels of prolactin (Mastronardi *et al.,* 2000). On the other hand, D2 dopamine antagonists, i.e. haloperidol increase plasma levels of prolactin. Also, alpha-methyl-p-tyrosine (inhibitor of tyrosine hydroxylase and thus of dopamine synthesis) increases plasma levels of prolactin (Tohei *et al.,* 2000). Overall, dopamine is believed to act as a prolacting-inhibiting hormone.

Single intranasal administration of cocaine to 12 healthy male volunteers without a history of drug abuse inhibited prolactin secretion (Heesch *et al.,* 1996). Also, in cocaine-dependent men plasma prolactin levels decreased significantly after iv administration of cocaine (Mendelson *et al.,* 1992). However, cocaine's effects on prolactin are biphasic in 10 of 18 animal studies. Thus, prolactin suppression was followed by rebound elevation within 2 hours post-cocaine that exceeded baseline levels by up to and even over 100% (Mello *et al.,* 1990). During chronic cocaine exposure the basal prolactin levels started increasing after 2 months exposure and in 300 days were higher than in drug-free control Rhesus monkeys by 227-350% (Mello *et al.,* 1994). This increase of basal prolactin levels was reversed by dopamine infusion to below the baseline levels confirming well established involvement of dopaminergic system in the effects of cocaine.

The results of animal studies are consistent with clinical reports of hyperprolactinemia in chronic cocaine abusers. Hyperprolactinemia was found in 17 patients hospitalized for cocaine abuse (27.5+/-10.2 ng/ml) and persisted during the course of 4 weeks of hospitalization until discharge (Mendelson *et al.,* 1988). This persistent elevation of plasma prolactin levels after cocaine withdrawal may reflect a chronic cocaine-induced derangement in neural dopaminergic regulatory systems.

In this context, it is worthwhile to evaluate a subset of cocaine-dependent subjects with elevated basal plasma prolactin, which is indicative of long history of abuse, at the study entry. Differences in response, if any, among these subsets of subjects with high and low prolactin levels could useful for pinpointing specific indications (or contraindications) for future clinical use of cabergoline.

Previous Human Experience with Cabergoline for Cocaine Dependence. Cabergoline 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 cabergoline (at a 0.5 mg dose), together with two additional drugs, sinemet and hydergine, against a single placebo (15 subjects per group). Cabergoline showed a statistically significant improvement in observer scored clinical global improvement (CGI-O) at final follow-up when compared to placebo. Spline Generalized Estimating Equation (GEE) regression lines showed a decrease in the mean ln urine BE levels over the course of treatment; however, this difference did not differ significantly from the placebo controls [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)].

Safety of Cabergoline. Receptor binding studies indicate very low affinity of cabergoline to D1 dopamine, apha$_1$- and alpha$_2$-adrenergic, and 5-HT$_1$- and 5-HT$_2$-serotonin receptors. Cabergoline is a selective D2 dopamine agonist; thus, it should not be administered concurrently with D2 antagonists, such as phenothiazines, butyrophenones, thioxanthines, or metoclopramide. The adverse effects of cabergoline are less frequent than those of bromocriptine. In a comparative double-blind trial of 459 women with hyperprolactinemic amenorhea, adverse events were reported in 68% of women taking cabergoline compared to 78% of women taking

bromocriptine (p = 0.03) (Webster *et al.*, 1994). Only 3% discontinued taking cabergoline while 12% discontinued taking bromocritptine (p = 0.001).

Adverse reactions were reported by the manufacturer in over 900 subjects with hyperprolactinemia as principally mild or moderate in nature. Adverse events that occurred in at least 5% of subjects included nausea (27%), constipation (10%), abdominal pain (5%), headache (26%), dizziness (15%), asthenia (9%), fatigue (7%), and somnolence (5%). Other psychiatric side effects included depression (3%) and nervousness (2%). In the CREST pilot study of cabergoline treatment of cocaine dependent subjects, all adverse events in the cabergoline arm were reported were mild and moderate in nature. Fatigue, menstrual cramps, and sore throat were reported most frequently (3 or 4 subjects) in the cabergoline arm. Constipation, coryza, myalgia, nasal congestion, neck pain, and weight loss were also reported in the cabergoline arm by two subjects. These side effects were reported in fewer subjects in the placebo arm; however, as the number of subjects in each group was small (n=15), this difference was not significant. A list of the adverse events from this study is provided in Appendix I. Laboratory values that changed after treatment as compared to baseline included increases in total cholesterol (7%), triglycerides (43%), GGT (56%), and neutrophils (21.6%) and decreases in iron (-16%), lymphocytes (-18%), eosinophils (-18%), and basophils (-24%). Only changes in some subject's triglyceride and GGT levels were considered clinically significantly abnormal (Appendix I).

Pharmacokinetics of Cabergoline. Absorption, clearance and metabolism of cabergoline are well studied. The elimination half-life in blood has been reported to be 101 to 110 hours with no difference in fasting or fed volunteers (Persiani *et al.,* 1996). The elimination half-life has also been reported on the basis of urinary data to be 63 to 68 hours (Persiani *et al.,* 1994). Because it has a rather long plasma half-life, its effects are long lasting, and the drug can be administered once or twice a week.

Cabergoline Dose Justification. The recommended dose of cabergoline (Dostinex) is 0.25 mg twice a week or 0.5 mg once a week for the treatment of hyperprolactinemic disorders. Cabergoline has been given safely up to 5 mg per day for the treatment of Parkinson's disease (Webster *et al*., 1993). In the CREST pilot study for the treatment of cocaine dependence, cabergoline was given at a dose of 0.5 mg per week. This current study will explore the same total dose (0.5 mg) given once per week.

5 STUDY OBJECTIVES

5.1 PRIMARY OBJECTIVE

The primary objective of this study is to assess the efficacy of cabergoline in reducing cocaine use in subjects with cocaine dependence (DSM-IV criteria). The hypothesis is that cabergoline will increase the weekly mean proportion of cocaine non-use days over the treatment period as 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 cabergoline in the study population.
2. Assessing the efficacy of cabergoline in reducing the proportion of cocaine use-days as determined by self-report alone.
3. Assessing the efficacy of cabergoline in increasing the proportion of subjects who 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 cabergoline in reducing median weekly urine BE levels.
5. Assessing the efficacy of cabergoline 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 cabergoline in reducing the proportion of use-days of other substances of abuse as determined by self-report, and in reducing the proportion of urines positive for amphetamines, opiates, benzodiazepines, and barbiturates.
7. Determining if serum prolactin levels at baseline correlate with clinical outcomes.

6 STUDY SPONSOR

Steven Shoptaw, Ph.D. is the study sponsor.

7 STUDY SITES

This study will be conducted at two sites, the Torrance Clinic, Torrance, California (affiliation with the UCLA Integrated Substance Abuse Programs, Los Angeles, California) and the Medical University of South Carolina, Institute of Psychiatry, Charleston, SC. Each site will enroll 70 subjects.

8 STUDY DESIGN

8.1 EXPERIMENTAL DESIGN

This is a double-blind, placebo-controlled, two arm study with a parallel-group design. After screening and a 2-week baseline period, subjects will be randomly assigned approximately equally to treatment with either placebo or cabergoline for 12 weeks with a follow-up assessment 4 weeks after treatment completion. All subjects will receive weekly cognitive behavioral therapy throughout the twelve-week treatment phase of the study.

8.2 OUTCOME/RESPONSE MEASURES

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 12-week study 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.

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 level), severity of cocaine dependence (assessed by ASI-Lite and self and observer scored CGI) and craving (assessed by BSCS and CCQ-NOW), and use and non-use days of other substances of abuse as determined by self report, and percentage of negative urines by drug (amphetamines, opiates, benzodiazepines and barbiturates). In addition, an HRBS will be assessed for to describe the population and for other scientific uses. The HRBS will not be a primary or secondary outcome measure. Serum prolactin will be used to assess outcomes in subset populations with high and normal serum prolactin levels.

8.3 BLINDING PLAN

Investigational agents, cabergoline and unmatched placebo, will be supplied by the research pharmacist in pre-coded containers that do not reveal the identity of the investigational agent. The containers 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; and the expiration date. The subject label will include the subject number; subject initials, number of tablets and directions of use. Each subject will receive either one 0.5 mg tablet of cabergoline or one placebo tablet at each dosing. Doses will be administered in clinic by an unblinded study nurse or pharmacist.

8.4 RANDOMIZATION PLAN

Stratified randomization will be used with respect to diagnosis of ADD, historical self-report of cocaine use (< 18 or ≥ 18 days of use in the last 30 days), and severity of depression (Ham-D score ≤ 11 or > 11). The randomization process will be performed by computer at the NIDA data-coordinating center. Treatment assignments will be provided to the study pharmacist for investigational agent preparation.

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 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 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 and 21 days of self-report.

9 SUBJECT SELECTION

140 male and female subjects with cocaine dependence will be enrolled in the study (70/treatment arm). 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. 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 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 of 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 as assessed by SCID
   - organic brain disease
   - dementia
   - any disorder which would require ongoing treatment or which would make study agent compliance difficult
   - history of suicide attempts assessed by SCID and/or current suicidal ideation/plan as assessed by SCID 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)
   - angina
   - active hepatitis or tuberculosis (see note below)
   - clinically significant cardiovascular abnormality (ECG)
   - disease of the gastrointestinal system, liver, or kidneys that could result in altered metabolism or excretion of the study agent
   - history of major gastrointestinal tract surgery (e.g., gastrectomy, gastrostomy, bowel resections)
   - current or historical diagnosis of chronic disease of the gastrointestinal tract (e.g., ulcerative colitis, regional enteritis, or gastrointestinal bleeding).
   - 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. Be anyone who, in the opinion of the investigator, would not be expected to complete the study protocol because of probable incarceration or relocation from the clinic area.

6. Have AIDS (see note below).

7. Have active syphilis that has not been treated or refuse treatment for syphilis (see note below).

8. Have a history of neuroleptic malignant syndrome.

9. Have known or suspected hypersensitivity to cabergoline.

10. Be taking cabergoline for any reason.

11. Have received a drug with known potential for toxicity to a major organ system within 30 days prior to study entry (e.g., isoniazid, methotrexate)

12. Have received medication that could interact adversely with cabergoline, with the time of administration of study agent 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 D2-antagonists, such as:

    - phenothiazines
    - butyrophenones
    - thioxanthines
    - metoclopramide

13. Have participated in any experimental study within 4 weeks, or must not have ever participated on a clinical trial utilizing cabergoline.

14. Be pregnant or lactating.

15. Have any clinically significant abnormal laboratory value (Appendix II).

16. Have had electroconvulsive therapy within the 3 months preceding screening.

17. Have had any opiate-substitutes (methadone, LAAM, buprenorphine) within 2 months preceding screening.

18. 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 (because of potential serious adverse interactions with cocaine).

19. 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.

20. 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 medication for respiratory problems (e.g., Primatene Mist): a detailed history and physical exam, pulmonary consult, and pulmonary function should be performed prior to including or excluding from the study (an $FEV_1 < 70$ % will exclude a subject from participation).

21. Female using Norplant for birth control with date of Norplant insertion after October 20, 1999 and unable to provide information to document that the Norplant product was not drawn from the lot numbers of failed products.

Notes on inclusion/exclusion criterion: 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 subjects along with HIV education.

Prospective subjects who are positive for syphilis by the RPR test will have a fluorescent treponemal antibody absorbant assay (FTP-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 or current 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

Cabergoline:

Cabergoline, a D2 dompamine receptor agonist, has been approved by the FDA under the trade name DOSTINEX (NDC 0013-7001-12) for the treatment of hyperprolactinemic disorders.

Cabergoline tablets, for oral administration, contain 0.5 mg of cabergoline. Inactive ingredients consist of leucine, USP, and lactose, NF. Each tablet is white, scored on one side and has the letter P and the letter U on ether side of the breakline. The other side of the tablet is engraved with the number 700. Cabergoline is available in bottles of 8 tablets.

Cabergoline is manufactured

for: Pharmacia Corporation

by: Pharmacia Corporation S.p.A., Milan, Italy

Placebo: Unmatched placebo will be supplied by Pharmacia Corporation.

10.1 DISPENSING INVESTIGATIONAL AGENTS

Investigational agents will be distributed by the research pharmacist either to the designated 'unblinded' study pharmacist or 'unblinded' study nurse of each site for subject dosing during clinic visits. Subjects must swallow the investigational agent in the clinic during clinic visits; investigational agent may not be taken out of the clinic.

Subjects randomized to receive cabergoline will receive one 0.5 mg tablet at the beginning of each week. Subjects randomized to receive placebo will receive one placebo tablet at the beginning of each week. Subjects may not be dosed more frequently than every four days (doses must be four days apart.)

10.2 LABELING

Investigational agents will be packaged in light protected polyethylene vials. The vials will be labeled with a product label and a subject label. The product label will include the protocol number; following statement – Caution:– Limited by federal law to investigational use; expiration date. The subject label will include the subject number; subjects initials; number of tablets and directions for use.

10.3 STORAGE

Investigational agents will be stored at controlled room temperature 20° to 25° C (68° to 77° F) 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

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 sites pending instructions for disposition by the Sponsor at the end of the study.

10.6 SAFETY CONSIDERATIONS

The most common side effects of cabergoline in order of frequency include nausea, headache, dizziness, constipation, asthenia, abdominal pain, fatigue, and somnolence. Other psychiatric side effects include depression and nervousness. Cabergoline is contraindicated in subjects with severe renal or hepatic impairment. Drug-drug interactions include symptomatic hypotension when administered with antihypertensives and decreased efficacy when administered with dopamine antagonists.

Subjects will be cautioned not to take concomitant medications, whether prescription, over-the-counter, herbal supplements and health store products, without consulting the study investigator or physician designee.

11 TREATMENT PLAN

11.1 INVESTIGATIONAL AGENTS

Depending upon treatment arm assignment, subjects will receive either one tablet of 0.5 mg of cabergoline or one placebo tablet at the beginning of each week for a total of 12 weeks of treatment. Subjects will be given investigational agents at clinic visits.

11.2 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 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 patient 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 interview to have diagnostic criteria for cocaine dependence, 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 telephone interview, the interviewer should not ask questions in a manner that reveals the eligibility criteria for study entry.

The initial interview and reading of the consent form can be conducted by a qualified study staff member. 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.

If the candidate is still interested in participating in the study, he/she will sign the consent form with the investigator. 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 determined to be eligible for study participation, 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.

12.2 SCREENING/BASELINE ASSESSMENTS

Screening and baseline assessments will be conducted as shown in Table 1.

12.3 SUBJECT ENROLLMENT

Once the patient has passed all inclusion and exclusion criteria, and the screening and baseline data have been entered into computer, site staff may enter the required randomization information into the randomization module and the subject will be given a randomization number. The research pharmacist will dispense the investigational agent to the clinic within the same day of receiving the treatment assignment.

12.4 TREATMENT PHASE

On the first day that dosing is scheduled and before dosing occurs, a blood specimen may be drawn for serum prolactin level (if prolactin levels were not obtained during baseline). Urine will

be collected for BE and creatinine testing and the subject will then be given the first dose of investigational agent.

Subjects will be scheduled for 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. All subjects will be offered an opportunity for HIV testing and counseling and HIV/AIDS education (Appendix III). All subjects will be provided with manual-guided psychosocial therapy once per week during the 12 weeks of treatment. 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 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 FOLLOWUP

Four weeks after the end of treatment, subjects will be asked to come to the clinic for a final followup visit. The subject will be asked to provide a urine specimen for BE/creatinine and urine toxicology screen, provide self-report for cocaine, alcohol, marijuana, amphetamines, opiates, and barbiturates use, report any AEs, and be given an ECG. The subject will be asked to list any current treatments for drug or alcohol abuse and to give an overall impression of the study agent. If it is not possible to arrange for the subject to return to the clinic, the subject will 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 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 Project Officer and NIDA Medical Monitor immediately after breaking the blind.

12.8 SUBJECT REIMBURSEMENT

Subjects will be reimbursed for travel expenses, for providing data, and for time contributed to this research study. Subjects will receive $20 in retail scrip or vouchers for each of the visits in which blood is drawn for prolactin levels. Subjects will receive $5 in retail scrip or vouchers for each visit during the 12 weeks of treatment to be paid at the end of treatment. Subjects will be paid $10 in retail scrip or vouchers for the week 16 follow-up assessment. The maximum payment is $300. Subjects will be compensated regardless of whether they continue to receive

the investigational agent. 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 reason, including the following:

1) significant side effects from the investigational agents
2) serious or unexpected AEs
3) inability to comply with the study protocol
4) protocol violation
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 cognitive behavioral therapy 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).

Every study subject will be encouraged to carry a wallet card that identifies him or her as a subject in a clinical research study. The card will provide the 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. Cabergoline should not be administered concurrently with D_2-antagonists, such as phenothiazines, butyrophenones, thioxanthines, or metoclopramide.

13 CLINICAL EVALUATIONS

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

13.1 ASSESSMENTS AT SCREENING/BASELINE

Prior to enrollment on the study, subjects will be screened to determine if they meet eligibility requirements. 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		Treatment						Follow-up
Study Week	-4 to 0*			1-3	4	5-7	8	9 -11	12	16
Screening										
Informed consent	X									
SCID	X									
Psychiatric evaluation	X									
ADD evaluation	X									
Medical history	X		R							
Prior medications	X		A							
Infectious disease panel/ syphilis test	X		N							
HIV Test (optional)	X		D							
Safety			O							
Physical exam/FEV_1[d]	X		M						X^c	
Vital signs	X		I	X^b	X^b	X^b	X^b	X^b	X^c	
Hematology	X		Z		X^b		X^b		X^c	
Blood chemistries	X		A		X^b		X^b		X^c	
Ham-D	X		T		X^b		X^b		X^c	
CSSA		3X	I	X^b	X^b	X^b	X^b	X^b	X^c	
Urinalysis	X		O		X^b		X^b		X^c	
Pregnancy test	X		N		X^b		X^b		X^c	
ECG	X								X^c	X
Adverse events	X	X		3X	3X	3X	3X	3X	3X	X
Concomitant medications		Weekly x 2 weeks		X^b	X^b	X^b	X^b	X^b	X^b	X
Efficacy										
ASI-Lite	X				X^b		X^b		X^c	
HRBS	X								X^c	
BSCS		Weekly x 2 weeks		X^b	X^b	X^b	X^b	X^b	X^b	
CCQ-NOW		X							X^b	
CGI-S		Weekly x 2 weeks		X^b	X^b	X^b	X^b	X^b	X^b	
CGI-O		Weekly x 2 weeks		X^b	X^b	X^b	X^b	X^b	X^b	
SUI		3 X/week for 2 weeks		3 X	3 X	3 X	3 X	3 X	3 X	X
Urine BE and creatinine		3 X/week for 2 weeks		3 X	3 X	3 X	3 X	3 X	3 X	X
Urine tox screen		Weekly x 2 weeks		X^b	X^b	X^b	X^b	X^b	X^b	X
Serum prolactin		X^a		X^a	X^a				X^c	
Treatment compliance				3 X	3 X	3 X	3 X	3 X	3 X	
Follow-up interview										X

*Baseline assessments must occur within 2 weeks during the screening period. The screening period is within 4 weeks of subject enrollment. Baseline and screening period may occur simultaneously.

X^a – Blood is collected in fasted state at least once (preferably twice) before investigational agent administration, once during weeks 3-6, and once at week 12 or at final visit if subject discontinues prematurely. The two specimens prior to investigational agent may be drawn during baseline, or one may be drawn during baseline and one on study day 1 prior to administration of first dose of investigational agent.

X^b - Once during the week preferably at the first visit of the week.

X^c - At the final scheduled study visit (last visit of week 12) or if the subjects discontinues prematurely.

X^d - FEV_1 is only performed in those subjects suspected of having asthma.

13.1.1 Screening Procedures:

1. Informed consent
2. Complete medical history, physical exam including a respiratory function test (FEV_1) in subjects suspected of having asthma, and vital signs
3. Psychiatric evaluation and SCID evaluation for DSM-IV diagnosis of cocaine dependence, and Axis-I disorders
4. ADD interview
5. 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 the screening period will be documented on a Prior Medication CRF.
6. ASI-Lite evaluation
7. Ham-D evaluation
8. Hematology
9. Blood chemistries
10. Urinalysis
11. Pregnancy test (if female)
12. Adverse Events
13. Infectious disease panel
14. Syphilis test
15. HRBS
16. ECG
17. 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.

2. The following must be obtained weekly for two weeks:
   a. BSCS
   b. CGI-S
   c. CGI-O
   d. Urine toxicology screen
   e. Concomitant medications
   f. Adverse events

3. The following must be obtained 3 times:
   a. CSSA

4. A CCQ-NOW will be obtained once during baseline.

5. Serum prolactin level determination will be done at least once, preferably twice during baseline.

6. Daily report of cocaine, alcohol, amphetamines, marijuana, opiates, and barbiturates use will be recorded at each visit on a SUI CRF.

13.2 ASSESSMENTS DURING TREATMENT

Once during weeks 3-6, subjects should come to the clinic in the fasted state and have blood drawn for serum prolactin determination.

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. AEs
4. Treatment compliance
5. Concomitant medications

Once per week at the first visit each week:
1. Urine toxicology screen
2. BSCS
3. CGI-S
4. CGI-O
5. Vital signs
6. CSSA

At the first visit of weeks 4, 8, and last visit of week 12:
1. Hematology
2. Blood chemistries
3. Urinalysis
4. Pregnancy test (if female)
5. Ham-D
6. ASI-Lite

13.3 ASSESSMENTS AT END OF STUDY TREATMENT (WEEK12)

At the final scheduled study treatment visit (week 12) or if the subject discontinues prematurely, regardless of the reason (request that the subject return for final assessments), the following assessments will be performed:

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. AEs
7. Urine toxicology screen
8. BSCS
9. CCQ-NOW
10. CGI-S
11. CGI-O
12. Hematology
13. Blood chemistries
14. Serum prolactin (fasting)
15. Urinalysis
16. Pregnancy test (if female)
17. ASI-Lite
18. HRBS
19. HAM-D
20. CSSA
21. ECG
22. Treatment compliance
23. Concomitant medications

13.4 ASSESSMENTS AT FINAL FOLLOW-UP (WEEK 16)

Subjects will undergo the following assessments 4 weeks after completion of treatment:

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

In addition, the following will be performed:

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

13.5 ASSESSMENT METHODS

13.5.1 Vital Signs

Vital signs to be assessed include oral temperature, sitting blood pressure, pulse rate and respiratory rate.

13.5.2 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 (FEV_1) pulmonary function test should be performed during screening on any subject that is suspected of having asthma but without a formal diagnosis (an $FEV_1 < 70$ % will exclude a potential subject from study participation).

13.5.3 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.

13.5.4 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 dehyrdrogenase (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.

13.5.5 Serum Prolactin

Subjects will be scheduled to come to the clinic in the fasted state and having not smoked, drunk caffeine, or used cocaine. Blood will be collected in serum separation vacutainer tubes and serum separated according to standard procedures. Quantitative analysis will be performed for prolactin by a central laboratory. Normal ranges for serum prolactin at this laboratory are 3.1-16.5 ng/ml for adult males and 3.6 - 18.9 ng/ml for nonpregnant females. Levels of prolactin are known to be increased in humans during stress (Fujikawa *et al.,* 2000). Thus, stress can confound the data, so the blood should be collected in a non-stressful environment after the subject has been resting quietly for 15-30 minutes.

13.5.6 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.

13.5.7 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.

13.5.8 Pregnancy Test

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

13.5.9 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).

13.5.10 SCID

A SCID (Helzer, *et al*., 1981) to assess the subject's cocaine-dependence according to DSM-IV criteria, severity of depression, and Axis-I disorders will be conducted during screening.

13.5.11 ADD Interview

An interview from the DSM-IV criteria for childhood attention deficit hyperactivity disorder 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.

13.5.12 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.

13.5.13 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.

13.5.14 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, benzodiazepines, and barbiturates. 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.

13.5.15 Substance Use Inventory (SUI)

The SUI measures the subject's report of days of recent drug use and routes of administration. The use of cocaine, alcohol, marijuana, amphetamines, opiates, and barbiturates will be recorded on this form at each clinic visit.

13.5.16 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. At the first screening visit, the SUI will cover the subject's report of drug use and routes of administration for the prior 30 days.

13.5.17 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).

13.5.18 Clinical Global Impression-Observer (CGI-O)

The CGI-O requires the physician to rate the global severity of the subjects'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 to be rated first; the global severity is rated second; and the global improvement is rated last.

13.5.19 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.

13.5.20 Adverse Events (AEs)

Subjects will be given a diary in which to record symptoms starting as soon as the informed consent process is completed. Subjects will be instructed to be particularly cognizant of any unusual symptoms that occur during cocaine use. The subject's diary will be reviewed at each clinic visit by an investigative staff nurse or physician to make a determination if an AE occurred. 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 once per week. 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 14.6.

13.5.21 HIV Risk-Taking Behavior Scale (HRBS)

The HRBS is a brief 11-item interview administered scale which examines the behavior of intravenous drug users in both injecting and sexual behavior.

13.5.22 ECG

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

13.5.23 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 site principal investigator/study physician.

13.5.24 Concomitant Medications

All medications taken by the subject during the two-week baseline period, while on study, and during followup 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.

13.5.25 Treatment Compliance

Treatment compliance will account for the amount of investigational agents taken by each subject at each treatment. Compliance with psychosocial therapy will be accounted for by recording the length of time the subject spent in attendance at the weekly therapy session.

14 REGULATORY AND REPORTING REQUIREMENTS

14.1 FDA FORM 1572

The investigator 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 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 III) 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

The informed consent process will consist of an explanation of the study by a qualified research staff member. The investigator will sign with the patient and answer all study questions. The patient will have the opportunity to ask all medical/medication study questions with the study physician during the consent process prior to commencing screening and baseline procedures.

All potential candidates for the study will be given a current copy of the 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 agents(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: Safety and efficacy data will be reviewed by a data and safety monitoring board that will meet after the first 70 (35 subjects in each arm) have completed/terminated from the study or earlier if deemed necessary. Additional meetings after that 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. 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 IV. The occurrence of AEs will be assessed starting as soon as the informed consent process is completed and at each study visit by reviewing the subject's diary and asking about the subject's heath status. An AE CRF will be 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 must be reported up to 4 weeks following completion of, or termination from 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 patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.)*
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity; or
- is a congenital anomaly/birth defect.

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 within 3-days 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. All serious medical events are also to be reported to the responsible institutional review board 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 followup 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 PRIMARY OBJECTIVE

The primary objective of this randomized controlled trial is the assessment of the efficacy of cabergoline in reducing cocaine use in subjects with cocaine dependence (DSM-IV criteria).

15.2 SECONDARY OBJECTIVES

Secondary objectives include:

1. Determining the safety of cabergoline in the study population.
2. Assessing the efficacy of cabergoline in reducing the proportion of cocaine use-days as determined by self-report alone.
3. Assessing the efficacy of cabergoline 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).
4. Assessing the efficacy of cabergoline in reducing the weekly median urine BE levels.
5. Assessing the efficacy of cabergoline 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 cabergoline in reducing the proportion of use-days of other substances of abuse as determined by self-report, and in reducing the proportion of urines positive for amphetamines, opiates, benzodiazepines, and barbiturates.
7. Determining if serum prolactin levels at baseline correlate with clinical outcomes and if cabergoline modulates serum prolactin levels.

15.3 OUTCOME MEASURES

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 patients 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. Data from the HRBS and serum prolactin levels are included in this category. This data is being collected in order to build a database of risk behaviors associated with cocaine use and assess cabergoline effects on biological markers (prolactin levels) to further characterize the study population.

15.3.1 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 12-week study 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 1 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 82 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 in the laboratory 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 more than 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:

% non-concordant = # non-concordant use days/total urine samples analyzed * 100%, thus

% concordant = 100 - % 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%.

15.3.2 Secondary Outcome Measures

Measured reductions in cocaine and other drug use over the twelve week treatment period

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 SUR.

G. Proportion of negative urines for other drug use (missing samples are considered positive).

H. Weekly median ln urine BE level.

I. Overall proportion of cocaine non-use days during the 12 week treatment period (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 scores over baseline.

Safety of Cabergoline

P. AEs, laboratory data, physical exams, Ham-D scores, and vital signs.

15.4 STATISTICAL HYPOTHESES

15.4.1 Primary Efficacy Outcome

It is hypothesized that cabergoline will increase the weekly mean proportion of cocaine non-use days relative to placebo as determined by self-report of cocaine use confirmed with urine assays for BE.

15.4.2 Secondary Efficacy Outcomes

It is hypothesized that cabergoline as compared to placebo will increase the proportion of successful subjects, the weekly mean proportion of cocaine non-use days according to self-report alone, the weekly mean proportion of other drug non-use days according to self-report and proportion of negative urines for other drugs use, and decrease the weekly mean ln urine BE level. It is further hypothesized that cabergoline will reduce the severity of cocaine dependence and craving and depression as assessed by ASI-Lite, BSCS, CCQ-NOW, CGI-S, and CGI-O.

15.4.3 Other Hypotheses

Subjects with elevated baseline serum prolactin levels (> 15 ng/ml), may represent a population with a long history of cocaine abuse at the study entry. Elevated prolactin levels will be used as covariates in the main analysis. Separate subset analyses of these populations may be of interest depending upon the results of the primary analysis.

15.5 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 per protocol 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.

15.6 ANALYSIS PLAN

15.6.1 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. 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 (a maximum of 6 days for week 1 and 12 and 7 days for weeks 2 through 11). 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 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 1 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 82 days over 12 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, site, prior use in the last 30 days (≤ 18 and > 18), gender, diagnosis of ADD, baseline severity of depression (Ham-D score ≤ 15 and > 15), and elevated serum prolactin levels (≥ 15 ng/ml), 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 urine 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, and the change in CCQ-NOW scores over baseline, measures G, I, J, and P will be assessed by t-test.

4. Weekly CGI-S, CGI-O, and BSCS, and monthly ASI-Lite scores, measures K, L, M, and N will be assessed by GEE.

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.

15.6.2 Descriptive Statistics

Summaries of the characteristics of the subject population in both study 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 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.

15.7 SAMPLE SIZE CALCULATION

The proposed 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 are based on the following assumptions: normal distribution of the data, an equal correlation between observations at any two times is 56% (i.e., exchangeable working correlation) and a scale estimator of 28. These assumptions are based on results from a recent eight-week pilot clinical study conducted in which 1 mg of cabergoline was compared to placebo in cocaine dependent subjects. An additional assumption is that a 15% increase in the proportion of cocaine non-use days within the cabergoline 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 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 12 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.

15.8 CONTROL OF BIAS

The treatment groups will be stratified based on a diagnosis of ADD, historical self-report of cocaine use for the last 30 days at the time that informed consent is given (balanced for ≥18 days of use and < 18 days of use), and severity of depression determined by Ham-D score (balanced for scores ≥11 and <11)]. The randomization process will be performed by computer at the NIDA data coordinating center.

15.9 INTERIM ANALYSIS

An interim analysis is planned when one-half of the subjects (approximately 35 in each arm) have been enrolled and follow-up is complete. The interim analysis will be conducted unblinded to treatment arm assignment and reported to the DSMB for review. 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.

15.10 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, and serum prolactin levels are included in this category. Additional *post hoc* analysis may be performed to evaluate other confounding factors on outcomes such as depression 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 site principal investigator is responsible for maintaining accurate, complete and up-to-date records for each subject. The site 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 site 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 sites 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 that 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 case report forms, 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 under the Freedom of Information Act providing, in part, that proprietary information furnished to clinical investigators and Institutional Review Boards will be kept confidential by the Food and Drug Administration only if maintained in confidence by the clinical investigator and Institutional Review Board.

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 Institutional Review Board, 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 Patient Records

To maintain subject confidentiality, all laboratory specimens, CRFs, reports and other records will only be identified by a coded study subject number. 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 data 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 cabergoline 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
Ann Montgomery, R.N. Study Director	_____	_____
Jurij Mojsiak, M.S. Project Officer	_____	_____
Ahmed Elkashef, M.D. CMB Acting 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
Steven Shoptaw, Ph.D. Project Principal -Investigator	_____	_____
Thomas Newton, M.D. Co-Principal -Investigator	_____	_____
Richard Rawson, Ph.D. Investigator	_____	_____
Walter Ling, M.D. Investigator	_____	_____
Donnie Watson, Ph.D. Site Principal Investigator	_____	_____
Jonathan Harry, M.D. Site Co-Principal Investigator	_____	_____
Robert Malcolm, M.D. Site Principal Investigator	_____	_____

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APPENDIX I: Summary of Adverse Events from Pilot CREST Study of Cabergoline for Cocaine Dependence

Table 1. Frequency of Adverse Events By Treatment Group and Severity

	Cabergoline Group					Placebo Group					
Severity Grade:[1] / Event:	1	2	3	4	Total	1	2	3	4	Total	GRAND TOTAL
ABDOMINAL CRAMPS		1			1			1		1	2
ACNE					0		1			1	1
APPETITE DECREASED					0	1				1	1
APPETITE INCREASED					0	1*				1	1
BLACK STOOLS		1			1					0	1
BLISTER, LEFT FOOT					0		1			1	1
BRONCHITIS					0	1				1	1
BURNS, FOREARM					0		1			1	1
CALLOUS, RIGHT FOOT					0		1			1	1
CERVICAL LYMPHOD		1			1					0	1
CONJUNCTIVA INJECTED, LEFT		1			1					0	1
CONSTIPATION	2				2					0	2
CORYZA	2				2					0	2
COUGH	1	1			2		2			2	4
CP ON INSPIRATION	1	1			2					0	2
CRAMP, HAND					0	1				1	1
DARK STOOLS	1				1					0	1
DIARRHEA					0	1	1			2	2
DIZZINESS					0	1	2			3	3
DROWSINESS	2				2	2	1			3	5
DRY MOUTH	1				1					0	1
DYSPEPSIA					0	1				1	1
EAR ACHE					0	1				1	1
EAR PAIN, LEFT	1				1					0	1
ENLARGED CERVICAL LYMPH NODE		1			1					0	1
EUMOSIS, LEFT ARM		1			1					0	1
FATIGUE	2	2			4		2			2	6
FEELS ILL	1*				1	1*				1	2
FEVER					0			1		1	1
FLATULENCE	1				1		1	1		2	3
FLU	1				1					0	1
HARD STOOLS	1				1					0	1
HEAD COLD		1			1					0	1
HEADACHE		2			2	2	5			7	9
HEADACHE, FRONTAL					0		1			1	1
HEMORRHOID					0		1			1	1
INDIGESTION					0	1				1	1
INSOMNIA					0	1		1		2	2

Table 1. Frequency of Adverse Events By Treatment Group and Severity											
	Cabergoline Group					Placebo Group					GRAND TOTAL
Severity Grade:[1] / Event:	1	2	3	4	Total	1	2	3	4	Total	
LEU EUKMOSIS	1				1					0	1
LIP SWOLLEN, LOWER	1				1					0	1
MENSTRUAL CRAMPS		2			2					0	2
NASAL BLEEDING					0	1				1	1
MYALGIA		2			2					0	2
NASAL CONGESTION	1	1			2	1				1	3
NAUSEA		2			2	3	1			4	6
PAIN, ABDOMEN	1				1	1	1			2	3
PAIN, ANKLE		1			1					0	1
PAIN, BACK					0		1			1	1
PAIN, CHEST	1				1	1				1	2
PAIN, HEAD		1			1					0	1
PAIN, JOINT					0	1				1	1
PAIN, LEFT FLANK	1				1					0	1
PAIN, LEGS					0		1			1	1
PAIN, LOW BACK					0		1			1	1
PAIN, NECK	1	1			2		1			1	3
PAIN, ORAL					0	1				1	1
PAIN, SHOULDER & NECK		1			1					0	1
PALPITATIONS					0	1				1	1
PRURITIS					0		1			1	1
RASH					0	1				1	1
RELAXED	1				1					0	1
SHAVED LOWER BACK					0		1			1	1
SICK					0	1				1	1
SINUS PAIN	1				1					0	1
SLEEPINESS					0	1	1	1		3	3
SORE THROAT	2	1			3	1		1		2	5
SPLINTER		1			1					0	1
SPRAIN, SHOULDER					0		1			1	1
STIFF NECK	1				1					0	1
STOMACH ACHE	1				1	1				1	2
STRAIN, LEFT ANKLE		1			1					0	1
STRAIN, LOWER BACK					0		1			1	1
TIGHTNESS IN CHEST	1				1	1				1	2
TIGHTNESS IN JAW					0		1			1	1
TIGHTNESS IN STOMACH	1				1					0	1
TIREDNESS					0	1				1	1
TWISTED LEFT ANKLE		1			1					0	1
UPPER RESPIRATORY INFECTION					0	2	1			3	3
URINARY TRACT INFECTION		1			1					0	1

Table 1. Frequency of Adverse Events By Treatment Group and Severity											
	Cabergoline Group					Placebo Group					GRAND TOTAL
Severity Grade:[1] / Event:	1	2	3	4	Total	1	2	3	4	Total	
WEIGHT GAIN		1			1					0	1
WEIGHT LOSS	1	1			2					0	2
Total:	**33**	**31**	**0**	**0**	**64**	**34**	**33**	**6**	**0**	**73**	**137**
[1]severity rating scale: 1=mild, 2=moderate, 3=severe, 4=life-threatening											
*missing data (1 case each, no severity ratings available)											

Table 2: Laboratory Values at Baseline and Termination, Including Percent Change from Baseline, with Lower and Upper Limits of Normal for Patients Treated with Cabergoline

Analyte	Blood Levels										% change from BL	Clinically Significant AB Lab Values	
	BASELINE					FOLLOW-UP							
	n	Mean	Std.Dev.	Min.	Max.	n	Mean	Std.Dev.	Min.	Max.			
Sodium (mEe/L)	15	142.40	2.16	140	146	7	143.00	2.00	140	145	0.4%	<135	>145
Potassium (mEq/L)	15	4.61	0.65	4	6	7	4.33	0.38	4	5	-6.1%	<3.4	>5.4
Chloride (mEq/L)	15	106.40	3.58	100	111	7	103.43	5.16	94	108	-2.8%	<94	>112
Glucose (mg/dL)	15	96.87	18.11	64	124	7	99.29	20.83	62	131	2.5%	>2 std dev	
Creatinine (mg/dL)	15	1.03	0.16	1	2	7	1.07	0.13	1	1	3.9%	>2	
Albumin (g/dL)	15	4.38	0.22	4	5	7	4.33	0.18	4	5	-1.1%	<3.2	>5.4
Total protein (g/dL)	15	7.31	0.38	7	8	7	7.59	0.49	7	8	3.8%	<4.1	>8.3
Calcium (mg/dL)	15	9.49	0.36	9	10	7	9.41	0.53	9	10	-0.8%	<8.4	>10.3
Cholesterol (mg/dL)	15	164.67	22.47	124	197	7	176.29	23.34	148	202	7.1%	<93	>260
Triglycerides (mg/dL)	15	132.13	56.14	73	233	7	188.57	115.95	65	387	42.7%	<24	>240
Phosphorus (mg/dL)	15	3.38	0.56	3	5	7	3.79	0.64	3	5	12.1%	<2.4	>7.7
SGOT/AST (U/L)	15	27.80	29.05	11	128	7	28.71	21.51	14	62	3.3%		>150
SGPT/ALT (U/L)	15	20.73	17.44	5	60	7	36.00	39.23	7	95	73.7%		>180
GGT (U/L)	15	33.40	56.59	8	235	7	52.14	81.08	6	234	56.1%	<2	>90
Total bilirubin (mg/dL)	15	0.67	0.50	0	2	7	0.61	0.29	0	1	-9.0%	>1.5	
LDH (U/L)	15	169.67	63.05	119	391	7	152.00	23.04	127	194	-10.4%	<100	>395
Alkaline phosphatase (U/L)	15	63.27	12.67	35	82	7	67.43	15.69	36	85	6.6%	>1170	
BUN (mg/dL)	15	14.13	3.96	9	21	7	13.64	1.70	11	16	-3.5%	<10	>28
Uric acid (mg/dL)	15	4.53	1.31	3	7	7	4.91	1.16	3	6	8.4%	<1.8	>8.6
Iron (mcg/dL)	15	109.53	46.22	50	193	7	92.14	35.70	56	143	-15.9%	<40	>180
Hemoglobin (g/dL)	15	14.60	0.73	14	16	7	14.63	0.87	14	16	0.2%	<10.2	>20.2
Hematocrit (%)	15	43.00	1.84	39	45	7	42.70	1.56	40	45	-0.7%	<30.8	>61.5
RBC (M/mm^3)	15	4.81	0.34	4	6	7	4.71	0.18	4	5	-2.1%	<3.55	>6.35
Platelet Count (K/mm^3)	15	227.60	42.76	165	300	7	228.86	28.61	192	270	0.6%	<150	>400
WBC (K/mm^3)	15	6.77	1.27	5	9	7	6.41	0.93	5	7	-5.3%	<3.9	>28.1
Neutrophils (%)	15	49.47	15.31	5	71	7	60.14	5.67	56	71	21.6%	<18	>80
Lymphocytes (%)	15	34.07	7.69	25	52	7	27.86	5.40	18	34	-18.2%	<12	>71
Monocytes (%)	15	8.20	2.88	3	13	7	8.00	1.53	6	10	-2.4%	>13	
Eosinophils (%)	15	4.00	2.14	1	9	7	3.29	1.60	1	6	-17.8%	>10	
Basophils (%)	15	0.93	0.96	0	3	7	0.71	0.49	0	1	-23.7%	>5	

APPENDIX II: Criteria for Identifying Laboratory Values as Clinically Significantly Outside Normal Limits

Blood Chemistry and Hematology

Analyte	Values	
Glucose (mg/dL)	<40	>140
AST (SGOT)		> 2.5X ULN*
ALT (SGPT)		> 2.5X ULN
Alkaline Phosphatase		> 2.5X ULN
Lactate Dehydrogenase		> 2.5X ULN
Gamma Glutamyltranspeptidase		> 2.5X ULN
Creatinine (mg/dL)		>1.7
Bilirubin (total) (mg/dL)		>1.5
Hemoglobin (g/dL)		
Male	<11.0	
Female	< 9.5	
Red Blood Cells (mill/mm^3)	<3.5	
White Blood Cells (per mm^3)	<2,800	> 16,000
Neutrophils (%)	<35	>80
Eosinophils (%)		> 10
Basophils (%)		>5
Lymphocytes (%)	<10	>50
Monocytes (%)		>15
Platelet Count (per mm^3)	<75,000	>700,000

*ULN = upper limit of normal

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

A. GENERAL INSTRUCTIONS

1. The Adverse Event (AE) CRF must be completed for each visit and reviewed weekly by a study physician.

2. Record AEs as soon as the informed consent process is completed.

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

4. 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:

- ***Unknown:***
  Use this category only if the cause of the AE/SAE is not possible to determine

- ***Definitely Not Related:***
  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.

- ***Remotely 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, the NIDA Study Director, 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, the NIDA Study Director, 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 followup 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.