IND No.: 45,228

STUDY #: NIDA-CTO-0005

DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF ONDANSETRON FOR THE TREATMENT OF COCAINE DEPENDENCE

Principal Investigator:	**John D. Roache, Ph.D.**
Co-Principal Investigators:	**Bankole A. Johnson, M.D., Ph.D.** **Nassima Ait-Daoud, M.D.** **Richard J. Lamb, Ph.D.** **Martin Javors, Ph.D.** **Thomas Prihoda, Ph.D.** **Joe Harrison, Ph.D.**
Investigator's Address:	Division of Alcohol and Drug Dependence Departments of Psychiatry and Pharmacology University of Texas Health Science Center at San Antonio 7703 Floyd Curl Drive San Antonio, Texas 210/567-5480 (fax: 210/567-5381) **roache@uthscsa.edu**
Research Site:	START Center, 3939 Medical Dr., Suite 100 University of Texas Health Science Center at San Antonio Mailstop 7793 San Antonio, Texas, 78229-3900 210/562-5400 (fax: 210/5625430)
Study Sponsor:	**Bankole A. Johnson, M.D., Ph.D.**
Medical Monitor:	**To be appointed by NIDA**
NIDA Investigators:	**Ahmed Elkashef, M.D.** **Jurij Mojsiak, M.S.** National Institute on Drug Abuse National Institutes of Health 6001 Executive Boulevard Bethesda, MD 20892

NIDA Study Director: **Jurij Mojsiak, M.S.**
National Institute on Drug Abuse
National Institutes of Health
6001 Executive Boulevard
Bethesda, MD 20892

Funding Agency: **Division of Treatment Research and Development**
National Institute on Drug Abuse (NIDA)
National Institutes of Health

Data Coordinating Center: **KAI**
6001 Montrose Road
Rockville, MD 20852-4801
301/770-2730

TABLE OF CONTENTS

APPENDICES

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

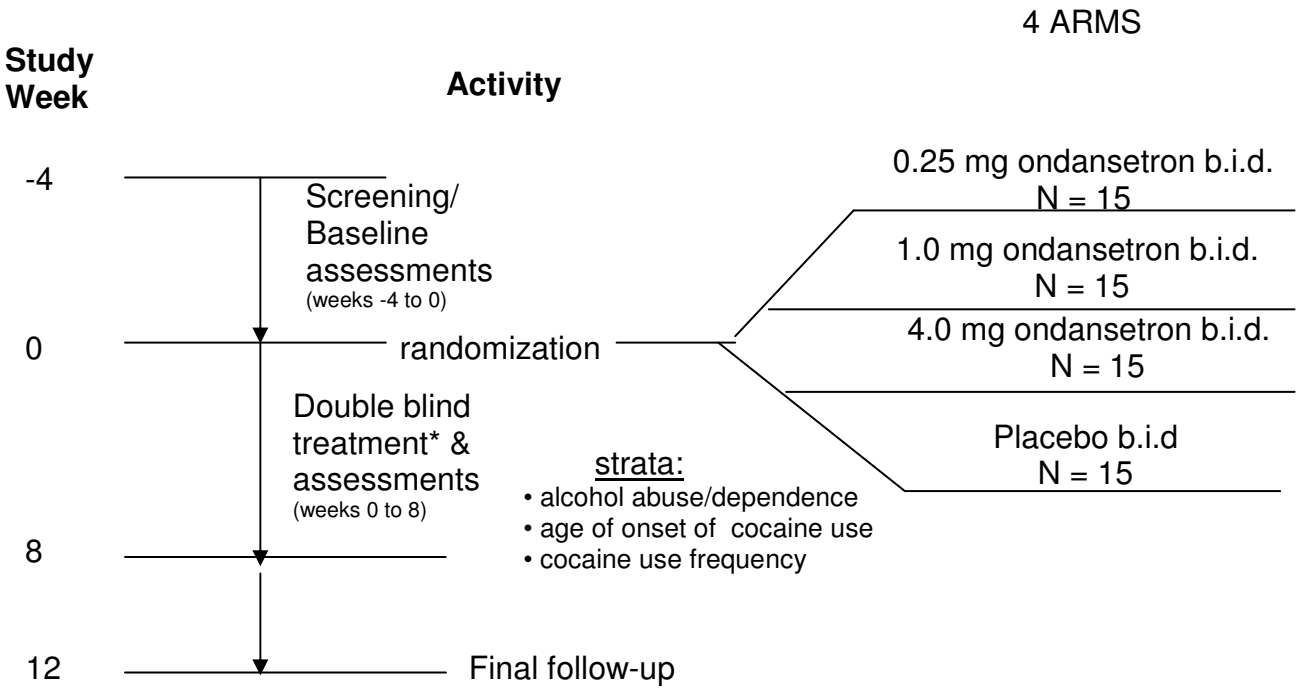
APPENDIX II: HIV/AIDS Education

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

1 LIST OF ABBREVIATIONS

Abbreviation	Definition
ADD	attention deficit disorder
ADHD	attention deficit hyperactivity disorder
AE	adverse event
AIDS	acquired immunodeficiency 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
BIS	Barratt Impulsivity Scale
BUN	blood urea nitrogen
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
CRF	Case Report Form
DA	dopamine
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders Fourth Edition
DTR&D	Division of Treatment Research and Development
ECG	electrocardiogram
ERG	electroretinogram
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
5-HT	serotonin
IRB	Institutional Review Board
LAAM	levomethadyl acetate (L-alpha acetylmethadol)
LDH	lactate dehydrogenase
mg	milligrams
mL	milliliter
NIDA	National Institute on Drug Abuse
OTC	over-the-counter
PRP	platelet rich plasma
RPR	Rapid Plasma Reagin (test for syphilis)
SAE	serious adverse event
SCID	structured clinical interview for DSM-IV
SUI	substance use inventory
SSS	Sensation Seeking Scale
UTHSCSA	University of Texas Health Science Center at San Antonio

2 STUDY SCHEMA



* Double blind treatment consists of daily ondansetron (at either a 0.25 mg, 1.0 mg, or 4.0 mg dose twice a day) or matched placebo plus weekly psychotherapy

3 PROTOCOL SYNOPSIS

STUDY OBJECTIVES. This will be a preliminary assessment of the efficacy and safety of three wide range doses of ondansetron (0.25, 1.0 and 4.0 mg taken orally twice per day) to reduce cocaine use in subjects with cocaine dependence and to determine the optimal dose of ondansetron. It is hypothesized that ondansetron 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) and a decrease in the number of cocaine-positive urine samples. Secondary objectives are to measure a variety of patient biological characteristics that may be associated with treatment response.

STUDY DESIGN: This is a double-blind, placebo-controlled, four-parallel-group design study consisting of a screening and 2-week baseline period in which potential participants will be required to attend the clinic three times per week for assessments and participate in once weekly cognitive behavioral therapy. If an individual meets enrollment criteria, s/he will be randomly assigned to one of four groups: 0.25 mg ondansetron, 1.0 ondansetron, 4.0 mg ondansetron, or placebo given twice a day (b.i.d.) for 8 weeks with a follow-up assessment 4 weeks after treatment completion. Randomization stratum include diagnosis of alcohol abuse/dependence (present vs. absent), age of onset of cocaine use problems (early versus late), and frequency of cocaine use (current high versus low). All groups will receive weekly manual-guided cognitive behavioral therapy during the 8 weeks of treatment.

STUDY POPULATION. 60 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 four treatment groups (15 per group). Subjects will be selected by self-referral and as respondents to media advertising offering free treatment. 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 0.25, 1.0, or 4.0 mg of ondansetron or placebo twice a day for 8-weeks. All subjects will receive manual-guided weekly cognitive behavioral therapy during the 2 weeks of baseline assessments and throughout the initial 8 weeks of treatment.

SAFETY ASSESSMENTS: All candidates for study enrollment will have a physical examination, a 12-lead ECG, clinical laboratory studies (blood chemistry, hematology, urinalysis, and pregnancy test if female), and Hamilton Depression Rating Scale (Ham-D) 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 and 8. AEs will be assessed at each visit and recorded weekly. An HIV Risk-Taking Behavior Scale (HRBS) will be used to characterize the population HIV risk behaviors (baseline and week 8). At treatment week 8 or at the time of study discontinuation, subjects will be evaluated for AEs, vital signs, physical examination, clinical laboratory studies, and electrocardiograph (ECG).

EFFICACY ASSESSMENTS: Three primary outcome measures were selected to determine the success in reduction of cocaine use: 1) weekly mean proportion of cocaine non-use days (self-report confirmed or disproved by urine BE level at each study visit), 2) weekly proportion of cocaine-free urine specimens, and 3) total number of cocaine-free urines over the 8 week study. Secondary outcome measures 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), a Cocaine Selective Severity Assessment (CSSA), Cocaine Craving Questionnaire (CCQ-NOW), and Clinical Global Impression as assessed by the subject (CGI-S) and an observer (CGI-O). An electroretinogram (ERG) will be performed at baseline to evaluate treatment responses in relationship to reduced blue cone b wave responses at baseline ($\leq$ 0.5 microV) and again at week 8 to determine if treatment changed the response. Serum prolactin levels will be assessed to determine if outcomes are associated with serum levels collected at baseline and at weeks 5 and 8. The ASI-Lite is performed at baseline and at the first visit of weeks 4 and 8. The BSCS, CGI-S, and CGI-O are performed twice at baseline and the first visit of each study week. The CSSA is performed three times during baseline and weekly during treatment. The CCQ-NOW questionnaire is assessed at baseline and week 8. Other biological characteristics of the study population include assessments of platelet serotonin function and serotonin receptor genotype. A Barratt Impulsivity Scale (BIS) and Sensation Seeking Scale (SSS) will be obtained at baseline to further characterize the study population.

TREATMENT COMPLIANCE. Treatment compliance will be assessed in two ways. Investigational agent compliance will be determined by documenting the amount of double-blind investigational agent used. Furthermore, ondansetron blood levels will be assessed weekly. Data will remain blinded to the investigators. Participation in cognitive behavioral therapy will be documented by recording the number of counseling sessions attended. High levels of treatment compliance are expected for this study due to the use of a 2-week baseline period used to screen out non-compliant subjects.

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 and have at least one clinical assessment. 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 of cocaine use. The individual effects, if any, of ondansetron dose level, prior cocaine use in the last 30 days ($\leq$ 18 and > 18), age of onset of cocaine use [(actual age) or categorical (young versus old)], gender, diagnosis of ADD, baseline severity of depression (HAM-D score $\leq$ 15 and > 15), platelet serotonin function, serotonin transporter polymorphism, reduced blue cone b wave responses ($\leq$ 0.5 microV), elevated prolactin levels (>15 ng/mL) and their first-order interactions 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. The number of missing observations will be compared between treatments. Weekly treatment compliance will be summarized. All adverse events will be reported in tabular form indicating the frequency of each type of event. Dose-response and concentration-response curves will be generated to determine the optimal effective dose with minimal side effects.

4 BACKGROUND AND RATIONALE

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 have been approved by the Food and Drug Administration (FDA) for this indication. Psychosocial and behavioral therapy are currently the treatments of choice for cocaine dependence. Unlike methadone or naltrexone treatment for heroin addiction, disulfiram or naltrexone for alcohol dependence, and nicotine or buproprion for cigarette smoking, there is no pharmacological agent currently approved for the treatment of cocaine dependence. It is the priority of NIDA 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. Several medications are presently under consideration for the treatment of cocaine dependence based on those mechanisms of action.

Rationale for Studying Ondansetron. Ondansetron is a selective serotonin3 (5-hydroxytryptamine3, 5-HT_3) antagonist. Post-synaptic 5-HT_3 receptors are densely located on the terminals of mesocorticolimbic dopamine (DA)-containing neurons where they promote DA release (Kilpatrick *et al.,* 1987; Kilpatrick *et al.,* 1996; Oxford *et al*., 1992). A primary effect of ondansetron is to decrease DA release, especially under suprabasal DA release conditions. Evidence that 5-HT_3 antagonists attenuate behavioral responses to D-amphetamine and cocaine suggests that 5-HT_3 receptors modulate brain dopamine in animals. This action of 5-HT_3 receptor antagonists may reduce the rewarding effects of abused substances as suggested by at least three different animal paradigms. 5-HT_3 receptor antagonists: (1) attenuate hyperlocomotion in the rat induced by intra-accumbens injection of DA or ethanol (Bradbury *et al*., 1985); (2) inhibit DiMe-C7 (a neurokinin) induced hyperlocomotion, an effect also attenuated by the DA antagonist, fluphenazine (Eison *et al.,* 1982; Hagan *et al.,* 1990), and (3) 5-HT_3 receptor antagonists reduce the rewarding effects of a variety of abused drugs including alcohol and amphetamines (Costall *et al.,* 1987; Di Chiara and Imperato, 1988; McBride and Li, 1998; Sellers *et al.,* 1992).

Evidence for antagonistic effects of 5-HT_3 antagonists on the behavioral effects of cocaine have, however, been mixed. 5-HT_3 antagonists have been shown to reduce cocaine-induced extracellular DA release (Kankaanpaa *et al.,* 1996; McNeish *et al.,* 1993) and locomotion (Kankaanpaa *et al*., 1996; McNeish *et al*., 1993; Reith, 1990; Svingos and Hitzemann, 1992) but did not reduce cocaine-induced self-administration (Kankaanpaa *et al*., 1996; Lane *et al*., 1992; McNeish *et al.,*

1993; Peltier and Schenk, 1991; Reith, 1990; Svingos and Hitzemann, 1992) and may (Suzuki *et al.,* 1992) or may not (Cervo *et al*., 1996) reduce conditioned place preference for cocaine.

Ondansetron has been shown to reduce the development of behavioral tolerance and sensitization to cocaine following a period of acute and chronic withdrawal (King *et al.,* 1998, 2000), presumably by down-regulation of 5-HT_3 receptors in the nucleus accumbens (King *et al*., 1999). Further, 5-HT_3 antagonists may reduce discomfort or post-cessation anxiety following psychostimulant withdrawal (Costall *et al*., 1990a; Costall *et al.,* 1990b). These data suggest that ondansetron may play a role in reducing cocaine-mediated reward and ameliorate post-cessation anxiety symptoms following cocaine cessation.

Previous Human Experience with Ondansetron for Pharmacotherapy of Addiction. Drs. Johnson, Roache, and colleagues (Johnson *et al.,* 1999a) have recently completed an analysis of an efficacy trial administering placebo and three dose levels (1, 4, and 16 ug/kg, b.i.d.) of ondansetron to 321 alcohol dependent outpatients receiving group cognitive behavioral therapy. The patients were subtyped, *a priori*, into two groups based upon the age at which they began to experience problem drinking. "Early Onset Alcoholics" were those who experienced problem drinking before the age of 25 years whereas "Late Onset Alcoholics" began after the age of 25 years. The results showed that, relative to placebo, ondansetron reduced alcohol drinking and increased abstinence rates in Early Onset but not in Late Onset Alcoholics who showed similar clinical improvements with both placebo and ondansetron. Early Onset Alcoholics are known to experience greater alcohol related problems, greater craving, have more psychosocial dysfunction, and to have a poorer treatment prognosis (Johnson *et al*., 2000). Recently, there also have been reports that an earlier age of onset (< 21 yrs) for cocaine use was associated with the greater amounts of the same kinds of cocaine-related problems among cocaine dependent populations (Sigmon *et al*., 2000) or increased health-risk behaviors in middle school aged youth (DuRant *et al.,* 1999). For these reasons, the current proposal will examine the ages of onset of regular cocaine use and/or cocaine–related problems in the target population to determine if this impacts treatment outcome.

Effect of ondansetron on biological and behavioral responses to D-amphetamine was examined in 10 healthy human volunteers (Grady *et al.,* 1996). Subjects were pretreated with placebo or ondansetron (0.15 mg/kg) before challenge tests with oral D-methamphetamine (0.5 mg/kg) were performed. Pretreatment with ondansetron attenuated robust activation-euphoria responses to D-amphetamine as well as D-amphetamine-induced increases in plasma levels of cortisol, prolactin, and growth hormone.

There are no studies evaluating the clinical outcome of ondansetron treatment for cocaine dependence. However, Sullivan *et al.,* (1992) did demonstrate that ondansetron doses of 0.25 and 2.0 mg produced dose-related reductions in cocaine-induced subjective effects of intoxication in a human laboratory study of 12 cocaine abusers.

In a previous study (N = 321), ondansetron was safely administered to outpatient alcoholics in oral doses up to 16 ug/kg b.i.d. for 11 weeks (Johnson *et al.,* 1999) with no significant side effects. Currently, a study is in progress in which ondansetron is administered at 64 ug/kg, b.i.d. (i.e., 4.48 mg/70 kg) to the same population.

Pharmacokinetics of Ondansetron. Ondansetron is currently approved as an anti-emetic agent and is commonly used for post-surgical, radiation, and chemotherapy-induced nausea (Tramer *et al.*, 1997). Both intravenous and oral doses of 4-16 mg are common in repeated and sub-acute (4-14 days) dosing regimens. Ondansetron is rapidly absorbed (t_{max} < 2 hrs) with a half-life ($T_{1/2}$) of 5.2 hrs (Roila and Del Favero, 1995). It undergoes hepatic metabolism and has reduced oral bioavailability (<70%) due to first-pass metabolism. Adverse events are uncommon at typical pharmacological dosages. While dose-related headaches are the common adverse event, constipation is experienced with at high doses.

Ondansetron Dose Justification. This is a dose-ranging study because high doses of ondansetron (8 mg 2 or 3 times per day) are recommended and currently used to prevent nausea and vomiting associated with emetogenic chemotherapy, but much lower doses were found effective for the treatment of alcohol dependence. This study will explore three doses of ondansetron 0.25, 1.0, and 4.0 mg, to be taken orally twice per day (b.i.d) for the 8 weeks of treatment.

5 STUDY OBJECTIVES

5.1 PRIMARY OBJECTIVES

The primary objective of this study is to conduct a preliminary assessment of the possible efficacy of ondansetron to reduce cocaine use in outpatients with cocaine dependence. Hypotheses are that ondansetron will increase the weekly mean proportion of cocaine non-use days assessed by self report of use and confirmed by urine assays for BE, that the weekly proportion of BE positive urines will be decreased, and that the total number of cocaine-free urines will be increased in groups treated with ondansetron when compared to placebo controls. The results of this study will be used to design subsequent larger studies to confirm the efficacy of ondansetron. This study is also intended to gather preliminary information on biological or psychosocial characteristics of patients who may show better ondansetron treatment responsiveness. In particular, biological measures reflecting individual differences in serotonergic function are included.

5.2 SECONDARY OBJECTIVES

Secondary objectives include:

1. Determining the safety of ondansetron in the study population.
2. Assessing the efficacy of ondansetron in increasing the proportion of cocaine non-use days as determined by self-report alone.
3. Assessing the efficacy of ondansetron 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 ondansetron in reducing median weekly urine BE levels.
5. Assessing the efficacy of ondansetron in the reduction in the severity of cocaine dependence (assessed by ASI-Lite, CSSA, and self and observer scored CGI) and craving (assessed by BSCS and CCQ-NOW).

6. Assessing the efficacy of ondansetron in increasing the proportion of non-use days of other substances of abuse (alcohol, marijuana, amphetamines, opiates, and benzodiazepines) as determined by self-report and the proportion of negative urine specimens (marijuana, amphetamines, opiates, and benzodiazepines).
7. Using the results of this study to design additional, statistically-powerful studies of fewer doses of ondansetron.
8 Collecting preliminary information on biological or psychosocial characteristics of patients who may show better responsiveness to ondansetron treatment. In particular, biological and psychological measures reflecting individual differences in serotonergic function are included.

6 STUDY SPONSOR

This study will be conducted under IND No.: 45,228. Dr. Johnson is the IND sponsor.

7 STUDY SITE

This will be a single site study conducted at the University of Texas Health Science Center at San Antonio (UTHSCSA).

8 STUDY DESIGN

8.1 EXPERIMENTAL DESIGN

This is a double-blind, placebo-controlled, four arm dose-ranging study comparing three dose levels of ondansetron (0.25, 1.0, and 4.0 mg, b.i.d.) to placebo administered to cocaine dependent outpatients. Over a 10-week period (2 weeks during baseline and 8 weeks during study agent administration), all participants will receive individual cognitive behavioral therapy.

8.2 OUTCOME/RESPONSE MEASURES

Three primary outcome measures were selected to assess the effects of ondansetron on cocaine dependence:

1. the weekly mean proportion of cocaine non-use days as assessed by self-report of use and confirmed by urine BE determination;

2. the weekly proportion of cocaine-free urine specimens over the 8 weeks of treatment; and

3. the total number of cocaine-free urines over the 8 week study.

Secondary outcome measures include assessing the effect of ondansetron on:

1. other measures of the pattern of cocaine use (overall proportion of non-use days, proportion of successful subjects, and weekly median urine BE level);

2. severity of cocaine dependence (assessed by ASI-Lite, CSSA and self and observer scored CGI),

3. cocaine craving (assessed by BSCS and CCQ-NOW);

4. non-use days of other substances of abuse (alcohol, marijuana, amphetamines, opiates, and benzodiazepines) as determined by self report and proportion of negative urines by drug (marijuana, amphetamines, opiates, and benzodiazepines).

In addition, an HRBS, BIS, and SSS assessment will be collected for population descriptive purposes.

8.3 BLINDING PLAN

Investigational agents will be supplied by the UTHSC pharmacy in blister packs that do not reveal the identity of the investigational agent. The data coordinating center will supply the pharmacist with the subject treatment assignment. The research pharmacist will maintain a list of the treatment assignments.

8.4 RANDOMIZATION PLAN

Stratified randomization will be used to balance treatment groups with respect to diagnosis of alcohol abuse/dependence, age of onset of cocaine use [early onset (< 18 years-of-age) versus late onset (≥ 18 years-of-age)], and frequency of cocaine use [current high use (> 18 days of use in the past 30 days) versus current low use (≤ 18 days of use in the past 30 days)]. Alcohol abuse/dependence diagnosis is an important stratum because alcohol abuse is highly comorbid in this population and ondansetron may affect cocaine use indirectly through changes in alcohol use. Age of onset of cocaine abuse was also selected as a stratum as this was an important variable in the previous alcoholism trial (Sigmon *et al.,* 2000). Finally groups will be balanced with respect to the current pattern of use (high use versus low use). 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 matching placebo agent along with cognitive behavioral therapy according to the same schedule at those in the test agent arms.

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, receive the first day's study agent, and complete one clinical assessment. 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

60 male and female subjects with cocaine dependence will be enrolled in the study (15/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 by personal contact, referrals, community flyers, and media (radio/TV/newsprint) advertisements offering free treatment for cocaine dependence. Referrals and advertisement respondents will be screened initially by a brief telephone survey determining basic inclusion/exclusion eligibility and then potentially eligible patients will be invited to the clinic for written informed consent. 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 structured clinical interview (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

Women who are post-menopausal, have had hysterectomies, or have been sterilized may be included without these methods of birth control.

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, caffeine, or marijuana or physiological dependence on alcohol requiring medical detoxification. Although heavy alcohol use and "behavioral" dependence may be included, physiological dependence on alcohol showing signs of withdrawal at zero breath alcohol levels and requiring medical detoxification will cause exclusion.

2. Have neurological or psychiatric disorders, such as:

    - psychosis;
    - bipolar illness;
    - major depression as assessed by SCID;
    - organic brain disease;
    - dementia;
    - seizure disorders
    - 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);
    - serious, 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 or CD4 positive T cell counts < 500 mm^3 (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 ondansetron.

10. Be taking ondansetron 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 concurrent (within two weeks of study participation) pharmacotherapy with psychotropics including, but not limited to antidepressants, anxiolytics, anti-psychotics, anticonvulsants, and psychomotor stimulant-type medications.

13. Have within two weeks used St. Johns Wort, yohimbine, ginko biloba, horehound, or any other central nervous system active herbal preparations.

14. Have received medications or herbal supplements that could interact adversely with ondansetron, with the time of administration of study agent and other medication/herbal supplement 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/herbal supplements that fall into this category include any serotonin-active substances and drugs significantly metabolized by the P-450, such as:

    - serotonin-active substances, i.e., sumitriptan (Imitrex), zolmitriptan (Zomig), cyproheptadine, ketanserin, ritanserin, fluoxetine, paroxetine, sertraline, methysergide, ergotamine, ergonovine;

    - drugs significantly metabolized by the P-450, i.e., cimetidine and phenobarbital;

    - herbals that enhance serotonergic effects, i.e., horehound.

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

16. Be pregnant or lactating.

17. Have any clinically significant abnormal laboratory value (Appendix I).

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

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

20. Have a diagnosis of adult asthma, including those with a history of acute asthma within the past two years, and those with current or recent (past 2 years) treatment with inhaled or oral beta-agonist or steroid therapy (because of potential serious adverse interactions with cocaine).

21. Be actively using albuterol or other beta agonist medications, regardless of formal diagnosis of asthma. (Inhalers are sometimes used by cocaine addicts to enhance cocaine delivery to the lungs.) A subject without respiratory disease who will consent to discontinue agonist use, may be considered for inclusion.

22. For subjects suspect 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), 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, or 5) have an $FEV_1 < 70$ %.

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. Any subjects on any pharmacotherapy for the treatment of AIDS will be excluded.

Prospective subjects who are positive for syphilis by the rapid plasma reagin (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 four 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.

Exclusion criterion 2 will not eliminate potential subjects with unipolar depression secondary to cocaine dependence (i.e., substance induced depression). Furthermore, history of suicide does not refer to lifetime history but to the 30 days prior to baseline screening.

10 INVESTIGATIONAL AGENTS

Ondansetron hydrochloride (Zofran), manufactured by Glaxo Welcome, is a selective antagonist of the 5-HT_3 receptor that has been approved by FDA for the treatment of nausea and vomiting associated with emetogenic chemotherapy. Ondansetron is commercially available as 4 or 8 mg tablets.

Placebo will be supplied as exact match of Ondansetron.

Size 1 opaque gelatin capsules containing placebo, 0.25, 1.0, or 4.0 mg of ondansetron will be prepared by the UTHSC research pharmacist using standard pharmacy compounding practices in the University Hospital Inpatient Pharmacy. Zofran tablets containing 8 mg of ondansetron will be crushed and mixed with cornstarch to fill Size-1 gelatin capsules with the indicated amount of ondansetron. Placebo capsules will be filled with cornstarch only. All doses will be prepared by the Research Pharmacist who has no contact with patients or clinical staff and will maintain the double-blind dose codes for individual patients.

10.1 DISPENSING INVESTIGATIONAL AGENTS

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

Subjects will be instructed to keep the medication stored at room temperature and not in direct sunlight. There are no other medication storage instructions. Subjects will be instructed to consume the morning dose upon awakening from their nighttime sleep period. The evening dose can be taken in the evening with dinner or at a later time, before bed that night. The exact time of the morning and evening doses may vary across patients depending on their schedules, but should be maintained constant for a particular individual.

10.2 PACKAGING AND LABELING

Ondansetron and placebo capsules will be individually packaged in strips of 5 unit dose blister bubbles. Blister packs will be labeled with the subject name, physician name, pharmacy telephone number, subject identification number, week of study, directions for use, and the following statement – Caution: New Drug – limited by federal law to investigational use. A 10-day supply of investigational agents (four strips of 5 blisters) will be banded together and given to the patient in a small bag.

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. On the first clinic visit of each week, subjects will be asked to return the empty blister strips and all unused medication. On each successive clinic visit, unused study agent will be inventoried for discrepancies and discarded. Patients who have not been taking their capsules regularly will be encouraged to do so in the future. New, unused study agent (a 10-day supply) will then be dispensed to that patient.

10.5 SAFETY CONSIDERATIONS

Side effects of ondansetron include angina, angioedema, atrial fibrillation, blurred vision, bronchospasm, constipation, diarrhea, dyspenia, dystonic reaction, elevated hepatic enzymes, headache, hypotension, palpitations, premature ventricular contractions, rash (unspecified), sinus tachycardia, syncope, urticaria, and xerostomia.

Ondansetron is classified as pregnancy category B. Although no adverse events or teratogenic effects have been reported in pregnant women, pregnant women will be excluded from participation and taken off study if they become pregnant.

Subjects will be cautioned not to take concomitant medications, whether prescription, OTC medications, or herbal supplements without consulting the study investigator or physician designee.

11 TREATMENT PLAN

11.1 INVESTIGATIONAL AGENTS

Blinded supplies of ondansetron and/or matched placebo capsules will be dispensed by the research pharmacist weekly for twice daily administration in subjects for 8 weeks. Subjects will be instructed that capsules may be taken without regard to meals and to take two pills daily, one upon awakening in the morning and one in the evening after dinner.

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, to be provided in the study operation manual, is the 2000 version of the Cognitive Behavioral Therapy Manual. These sessions will consist of one, 1-hour session of individualized counseling per week. During these sessions, emergency counseling and referral services will be provided. Additional emergency crisis management sessions will be available up to a maximum of four along with visit documentation.

The goal of this behavioral treatment intervention is to increase protocol compliance and educate the subject about his/her dependence and factors associated with drug use, and assist study subjects in achieving abstinence from cocaine without obscuring the impact of the pharmacological treatment. There will be no negative consequences based on urine toxicology results or 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. A two-part informed consent process will be used consisting of a single informed consent form but with separate signatures for parts 1 and 2 of the consent process. The difference in the two parts of the consent process is that during part 1, the initial interview and study explanation can be conducted by a qualified study staff member but does not have to be a study physician/ investigator. Part 2 of the consent process is an explanation of the study by a study physician/ investigator. If the study is initially explained to the potential subject by a study staff member that is not a physician/investigator, then part 1 of the form will be signed by the subject and the study staff member. If the study is initially explained to the potential subject by a physician/ investigator, then both of the part 1 and part 2 signature sections will be signed by the potential subject and investigator.

During the initial admission interview potential participants are told the study purpose and procedures. Once part-one of the consent form has been signed, the potential participant will be given a brief questionnaire reviewing the study procedures. Any participant who has difficulty understanding the information contained in the consent form will be rescheduled and the consent process will be repeated. Research staff will work closely with the participant in an effort to help them understand the requirements of their participation. Persons with literacy problems will be assisted to the extent possible. Any participant who is unable to demonstrate understanding of the information contained in the informed consent will be excluded from study participation and assisted in finding other sources of treatment. Persons who are excluded, or who decline participation, will be given referrals to other resources in the area.

After signing part 1 of the informed consent, participants are given a copy of the signed informed consent form, are assigned a subject identification number, and proceed to the screening/baseline assessments phase of the study. After the subject has completed the screening and baseline

assessments and is deemed to be eligible for study participation, an explanation of the study will be provided again, and the candidate will be given an opportunity to review, inquire about, and will be asked to initial the informed consent form to demonstrate that they still willing to go by their decision made at least two weeks earlier. The questionnaire reviewing the study procedures will be given again to make sure that the subject still understands the study procedures.

12.2 SCREENING/BASELINE ASSESSMENTS

Screening assessments will be conducted as shown in Table 1.

Outpatient studies of cocaine dependence often are plagued by protocol non-compliance and high dropout rates. Additionally, studies of anti-hedonic medications to reduce cocaine use require a minimal amount of cocaine use at baseline in order to demonstrate medication-induced reductions in use. For these reasons, the current study proposes to use a 2-week baseline phase in order to prospectively observe whether prospective patients are likely to be protocol compliant and whether they in fact have used or are using cocaine recently prior to treatment. All volunteers (1) providing written informed consent, (2) reporting cocaine use at least once per week during the past 30 days, and (3) expressing a desire for treatment will be included into this 2-week baseline phase of the study. Concurrently, screening measures will continue to be collected in several brief visits over several days, and patients will receive an "orientation and educational" session with a therapist as the normal prelude to psychotherapy. This procedure will: (1) spread the time commitment for screening over several shorter visits; (2) identify patients who are likely to be protocol compliant so that drop-outs can be identified early before double-blind randomization; (3) identify patients who are continuing to use cocaine, and therefore, are in greater need of pharmacotherapy and exposure to its attendant risks; and (4) begin the process of counseling and therapy, even during the screening and inclusion process.

12.3 SUBJECT ENROLLMENT

A subject who meets all of the study inclusion and does not meet any of the exclusion criteria (a checklist will be provided in the CRF package) may be enrolled onto the study. Investigators or study coordinators will enter into a computer the Eligibility Checklist, Enrollment, Randomization, and Demographics data for each subject's randomization and enrollment. The data-coordinating center will notify the research pharmacist of the subject's treatment assignment. The pharmacist will prepare the weekly blister packs of investigational agent for the subject as soon as possible after receiving the treatment assignment. The data-coordinating center will notify the investigator that the pharmacist has been provided with the treatment assignment. The pharmacist will notify the investigator as soon as the investigational agent is prepared. This process should occur in one day to minimize the time between completion of screening and baseline assessments and study start.

12.4 TREATMENT PHASE

Depending on the treatment arm to which subjects were assigned, subjects will receive 0.25, 1.0 or 4.0 mg ondansetron or matched placebo twice a day.

Subjects will be scheduled for assessments three times per week usually on a Monday, Wednesday, and Friday for 8 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 II). All subjects will be provided with manual-guided cognitive behavioral therapy once per week during the 8 weeks of treatment. Clinical evaluations are described in detail in section 13.0.

12.5 PREVENTION OF 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.

Subjects will be encouraged to complete study visits, assessments, and cognitive behavioral therapy sessions, even if they are unable to tolerate the study medication. If a subject decides to drop out of the study prior to week 8, s/he will be asked to complete all final assessments (termination) at the time of drop out. If a subject wishes to stop taking the study agent but to continue to participate in and cognitive behavioral therapy sessions, s/he will continue to have all scheduled assessments according to the protocol and will complete the study at week 8. In this case, all study measures will be completed per protocol with the exception of those strictly related to the study agent.

Of course, as with any research protocol, subjects are free to discontinue the study and to refuse to participate in any of the procedures. If a subject drops out without making their intentions known, staff will attempt to contact them by telephone or written correspondence. Once the subject has been contacted and made their desire to withdraw consent known, they will not be bothered by research staff again.

12.6 FOLLOW-UP (WEEK 12)

At the end of treatment week 8, subjects will asked to come to the clinic for one final follow-up assessment four weeks later. The subject will be asked to provide a urine specimen for BE/creatinine and urine toxicology screen, provide self-report for alcohol, marijuana, amphetamines, opiates, and benzodiazepine use, a time-line follow back for cocaine use, and report any AEs. At the final visit, 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 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.

12.8 EMERGENCY PROCEDURES

Patients are given a 24-hr number to call in the event of an emergency. This number reaches an answering service who will record the patient name and telephone number for recontact. Then the answering service will call the homes and/or pagers of investigator-doctors on a predetermined call schedule until one of the responsible parties is reached. That investigator will then be responsible to recontact the patient to determine the nature of the emergency and provide reassurance, advice, or treatment referrals as appropriate.

The study agent label also contains the telephone number of the 24 hour Inpatient Pharmacy. Third party, emergency medical personnel can call that number to get drug information in the event of an emergency.

12.9 SUBJECT REIMBURSEMENT

Subjects will be reimbursed for travel expenses, for providing data, and for time contributed to this research study as follows.

1. $5 for each urine sample provided;
2. an extra $5 on the first weekly visit if the subject provided three samples in the previous week;
3. $25 for the final followup visit assessment.
4. $50 for participation in the ERG assessments because of the additional time and discomfort associated with the corneal lens procedure; and
5. an additional $15 for the inconvenience of the morning prolactin blood sample on double-blind visit #5.

All of these payments are for costs, inconvenience and participation only. None depend upon the outcome; i.e., there is no financial contingency on the urine results or assessment responses themselves.

12.10 STUDY TERMINATION

12.10.1 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 investigational agents;
2) serious or unexpected AEs;
3) inability to comply with the study protocol;
4) protocol violation;
5) serious intercurrent illness; or
6) for HIV positive subjects a worsening of the disease state that requires pharmacotherapy for HIV or any related condition.

A subject may withdraw from the study anytime s/he wishes. A subject who is discontinued from receiving the investigational agent, will be allowed to continue the 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 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.

12.10.2 Trial Discontinuation

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

12.11 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. Ondansetron should not be administered concurrently with serotonin-active substances (agonists, antagonists, reuptake inhibitors, i.e., sumitriptan (Imitrex), zolmitriptan (Zomig), cyproheptadine, ketanserin, ritanserin, fluoxetine, paroxetine, sertraline, methysergide, ergotamine, ergonovine) and drugs significantly metabolized by the P-450, such as cimetidine and phenobarbital, or serotinergic enhancing hebal supplements such as horehound.

13 CLINICAL EVALUATIONS

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

13.1 SCREENING ASSESSMENTS

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.

1. Informed consent
2. Complete medical history

Table 1. Overview of Study Assessments

Assessment	Screening	Baseline		Treatment								Follow-up
Study Week	-4 to 0			1	2	3	4	5	6	7	8	12
Screening/Subject Characteristics												
Informed consent	X											
SCID – Axis I disorders	X											
ADD evaluation	X											
Medical history	X											
Prior medications	X											
Infectious disease panel/RPR	X											
HRBS	X										X[b]	
HIV test (optional)	X											
Alcohol Breathalyzer	X											
Quantity Frequency Interview	X											
SSS		X										
BIS		X										
Cocaine use: time-line follow back		X										X
Safety												
Physical exam/FEV_1[c]	X										X[b]	
Vital signs	X			X	X	X	X	X	X	X	X[b]	
Hematology	X						X				X[b]	
Blood chemistries	X						X				X[b]	
Urinalysis	X						X				X[b]	
Pregnancy test	X						X				X[b]	
ECG	X										X[b]	
Adverse events	X	X		X	X	X	X	X	X	X	X[b]	X
Concomitant medications		2X		X	X	X	X	X	X	X	X[b]	X
Efficacy												
ASI-Lite	X						X				X[b]	
Ham-D	X						X				X[b]	
BSCS		2X		X	X	X	X	X	X	X	X[b]	
CCQ-NOW		X									X[b]	
CGI-S		2X		X	X	X	X	X	X	X	X[b]	
CGI-O		2X		X	X	X	X	X	X	X	X[b]	
CSSA		3X		X	X	X	X	X	X	X	X[b]	
SUI		3 X/week for 2 weeks		3X	3X	3X	3X	3X	3X	3X	3X	X
Urine BE and creatinine		3 X/week for 2 weeks		3X	3X	3X	3X	3X	3X	3X	3X	X
Urine toxicology screen		2X		X	X	X	X	X	X	X	X[b]	X
Platelet serotonin function		X[a]										
Serotonin Receptor genotype		X[a]										
Serum Prolactin		X[a]						X			X[b]	
ERG		X[a]									X[b]	
Treatment compliance - drug				X	X	X	X	X	X	X	X[b]	
Treatment compliance – therapy		2X		X	X	X	X	X	X	X	X[b]	
Ondansetron blood levels				X	X	X	X	X	X	X	X	
Follow-up interview												X

RANDOMIZATION

X[a] - At the last clinic visit.

X[b]- At the final scheduled study visit (last visit of week 8) of if the subject discontinues prematurely.

FEV_1[c] - Performed only in subjects suspected of asthma and in the discretion of the investigator.

3. Physical exam including respiratory function tests (FEV_1) in subjects who have a history of, or show symptoms of asthma or respiratory problems. The decision to perform this test is made according to the judgment of the principal investigator and/or study physician
4. 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 (prior 30 days)
6. ASI-Lite evaluation
7. Ham-D evaluation
8. Hematology
9. Blood chemistries
10. Alcohol breathalyzer
11. Urinalysis
12. Pregnancy test (if female)
13. Adverse events
14. Infectious disease panel
15. Syphilis test
16. HRBS
17. ECG
18. HIV test (optional)

13.2 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 during baseline:
   a. CSSA

4. The following must be obtained once during baseline:
   a. SSS
   b. BIS

c. Quantity Frequency Interview
d. Cocaine use timeline follow-back

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

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

7. At the last baseline visit, all subjects will be given an ERG and blood will be drawn for serum prolactin levels, platelet serotonin function, and serotonin transporter polymorphism analysis. Subjects should be instructed to come to the clinic before breakfast. After 5-30 minutes of rest, blood will be drawn and then the ERG will be performed.

13.3 ASSESSMENTS DURING TREATMENT

Over the 8-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 (AE CRF completed weekly)
4. Treatment compliance

Once per week at the first visit each week:
1. Urine toxicology screen
2. BSCS
3. Vital signs
4. CSSA
5. Plasma ondansetron level
6. Concomitant medications

Once per week at the cognitive behavioral therapy visit:
1. CGI-S
2. CGI-O

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

At the first visit of weeks 5 and 8:
1. Serum prolactin levels.

13.4 ASSESSMENTS AT END OF STUDY TREATMENT (WEEK 8)

At the final scheduled study treatment visit (week 8) 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 [without FEV_1]
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. Urinalysis
15. Pregnancy test (if female)
16. ASI-Lite
17. HRBS
18. HAM-D
19. CSSA
20. ECG
21. ERG
22. Plasma ondansetron level
23. Treatment compliance
24. Concomitant medications

13.5 ASSESSMENTS AT FINAL FOLLOW-UP

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

1. Urine BE and creatinine
2. Urine toxicology screen
3. Cocaine use time-line follow back
4. SUI
5. AEs
6. Concomitant medications

In addition, the following will be performed:

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

13.6 ASSESSMENT METHODS

13.6.1 Vital Signs

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

13.6.2 Physical Exam and Pulmonary Function Test

A physical exam of the oral cavity, head, eyes, ears nose and throat, cardiovascular system, lungs, abdomen (liver/spleen), extremities, skin, neuropsychiatric mental status and sensory/motor status, musculoskeletal system and general appearance should be performed. Height and weight should be recorded. A forced expiratory volume in 1 second (FEV_1) pulmonary function test will be performed as part of the physical exam on individuals who have a history of, or show symptoms of asthma or respiratory problems. The decision to perform this test is made according to the judgment of the Principal Investigator and/or Study Physician (an $FEV_1 < 70$ % will exclude a potential subject from study participation).

13.6.3 Hematology

Blood will be collected in anticoagulant containing evacuated venous blood collection tubes (e.g., Vacutainer™) for hematologic assessments. Complete blood counts (CBC) with differentials and platelet count along with CD4 T cell counts will be performed. Quantitative analyses for hemoglobin, hematocrit, red blood cells, platelets, total white blood cells, total CD4 positive T cells and percentage of neutrophils, eosinophils, basophils lymphocytes, and monocytes will be performed. Analyses will be performed in the institutions clinical laboratory. The laboratory performing these assessments should be either directly regulated by the College of American Pathologist (CAP) or the Clinical Laboratory Improvement Act of 1988 (CLIA) or indirectly according to CLIA guidelines. The laboratory will need to provide a copy of current certification.

13.6.4 Blood Chemistries

Blood will be collected in serum separation evacuated venous blood collection tubes (e.g., Vacutainer™) and serum separated according to standard procedures. Quantitative analysis will be performed for the following analytes: sodium, potassium, chloride, carbon dioxide, glucose, creatinine, albumin, total protein, calcium, cholesterol, triglycerides, phosphorus, alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), gamma glutamyltranspeptidase (GGT), total bilirubin, lactate 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.

13.6.5 Infectious Disease Panel/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 a chest x-ray will be required. A rapid plasma reagin test (RPR) for syphilis will be performed.

13.6.6 HIV Test

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

13.6.7 Pregnancy Test

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

13.6.8 HAM-D

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

13.6.9 SCID

A SCID (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.

13.6.10 ADD Interview

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

13.6.11 Cocaine Use Time-Line Follow Back

Detailed histories of cocaine use over the past 30 days will be obtained using the timeline follow-back method (Maisto *et al*., 1979).

13.6.12 Quantity Frequency Interview

Drug use histories will be determined by a structured interview with the Quantity and Frequency Interview (QFI) which quantifies drug use during the past year and lifetime for each major category of drug.

13.6.13 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.

13.6.14 Cocaine Selective Severity Assessment (CSSA)

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

13.6.15 Electroretinogram (ERG)

Previous research has shown that a reduced blue cone b-wave amplitude of the ERG is associated with cocaine use (Roy, *et al.,* 1996, 1997). An ERG will be recorded using standard methods (Roy, *et al.,* 1996). Briefly, the cornea is anesthetized, the pupil is dilated to a diameter of at least 8 mm, and the ERG is recorded from one eye with a bipolar Burian-Allen-Lawwill contact lens electrode. The subject continuously views a full-field bright white adapting light (17,000 trolands retinal illuminance). ERGs are produced by chromatically filtered full-field strobe flashes flickering at 5.1/s and superimposed on the background field. ERGs will be produced by short (blue), middle (green), and long (red) wavelength flashes by interposing broad band chromatic filters in the strobe flash path. The blue cone b-wave amplitude produced by blue flashes is measured conventionally as the secondary b-wave riding on early b-wave from the trough of the preceding negative a-wave. Cone ERGs produced by blue flashes are averaged over 1000 flash trials giving a sensitivity of 0.1 uV.

13.6.16 URINE COLLECTION AND ANALYSES

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

1. Cocaine rapid test
2. BE and Creatinine performed locally at UTHSCSA
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 collected. Two will be frozen (one for a retention sample and one for local laboratory analysis of BE plus creatinine). The 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 in two aliquots and one aliquot will be analyzed locally for BE and creatinine. The frozen back-up aliquot will be stored until the NIDA data-coordinating center has notified the site that it can be disposed.

All urine results will be transmitted to the NIDA data-coordinating center. Results will not be provided to the investigator or staff during the study.

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 marijuana, amphetamines, opiates, and benzodiazepines. The frozen sample collected for BE plus creatinine analysis will be tested for these drugs at the local laboratory.

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

13.6.17 SUBSTANCE USE INVENTORY (SUI)

The SUI includes the subject's report of use of cocaine, alcohol, marijuana, amphetamines, opiates, and benzodiazepines for each day of the week. The subject is asked to report any use on days since the last clinic visit and the current visit. The day that the subject is reporting use is not scored until the subsequent visit as use may occur later in the day.

13.6.18 BSCS

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

13.6.19 Cocaine Craving Questionnaire (CCQ-NOW)

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

13.6.20 Clinical Global Impression-Observer (CGI-O)

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

13.6.21 Clinical Global Impression-Self (CGI-S)

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

13.6.22 Prior Medications

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

13.6.23 Concomitant Medications

All medications taken by the subject during the two-week baseline period, while on study, and at the final followup assessment will be recorded once per week on a concomitant medications CRF. The reported medications will be reviewed by the principal investigator/study physician for possible drug interactions.

13.6.24 Adverse Events (AEs)

AEs will be assessed starting after the informed consent process and at each study visit by an investigative staff nurse or physician. If an AE that required medical attention is reported to a nurse, it should be reported to a study physician immediately. A study physician will meet with the subject once a week to review the AEs recorded by the nurse and to assess for any additional AEs. The investigator or study physician will assess subjects for any medical or psychiatric side effects. Both the research assistant and physician will assess AEs by asking the subject, “How have you been feeling since I saw you last?” Once a week, the type of AE, severity of the AE, and the relationship to the study treatments will be recorded on an AE CRF according to the procedures described in section 14.7.

13.6.25 HIV Risk-Taking Behavior Scale (HRBS)

The HRBS is a self-administered assessment of the subject's engagement in activities that increase the likelihood of contracting HIV. If the subject is unable to self-administer this assessment (e.g. physical handicap, poor reading skills) study personnel can assist by reading the

questions out loud to the subject and/or marking the subject's response on the CRF. However, study personnel are not to offer interpretations of the questions.

13.6.26 ECG

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

13.6.27 Blood Ondansetron Levels

At the first study visit (before investigational agent administration) of each week during the treatment phase, 5 ml of blood will be withdrawn in purple-top vacutainer tubes. The tubes will be centrifuged at 10,000 g for 10 minutes to separate the plasma. Plasma samples will be stored in 500 ul polypropylene tubes and frozen for later assay of ondansetron levels. Assays will be conducted by a central laboratory in a way that keeps the laboratory blinded as to dosage group assignment of the subject and the study site investigators blinded as to the results of the assay.

13.6.28 Analysis of Platelet Serotonin Function

At the last baseline visit, 120 ml of blood will be withdrawn from an arm vein to conduct *in vitro* assays of cocaine and benzoylecgonine (BE) plasma levels (performed at a central laboratory) and platelet serotonin content and function. These data will be used to experimentally describe possible high or low serotonin function subgroups of subjects who may differentially respond to ondansetron.

Platelet Membrane Preparation. 50 ml of whole blood is drawn by standard procedures into EDTA containing Vacutainer^{TM} tubes. PRP (platelet rich plasma) is prepared by centrifugation of whole blood at 150 *g* for 20 min at 23^{o}C in a Beckman TJ-6 centrifuge. The PRP is then centrifuged at 10,000 *g* for 10 min at 4^{o}C to obtain a platelet pellet. Each pellet is washed twice in 8 ml of washing buffer (50 mM Tris-HCl, 150 mM NaCl, 20 mM EDTA, pH 7.4) and sonicated with two 5 second bursts (10% max) in 8 ml of lysis buffer (5 mM Tris-HCl, 5 mM EDTA, pH 7.4). The final pellet is suspended in 2 ml of incubation buffer (50 mM Tris-HCl, 3 mM KCl, 120 mM NaCl, pH 7.4) and kept at -80^{o}C until analysis.

[^{3}H]-Paroxetine Binding. [^{3}H]-paroxetine binding is performed according to Arranz *et al.* (1999). Platelet membrane homogenates are incubated at 6 concentrations of [^{3}H]-paroxetine (0.015 to 0.5 nM) in incubation buffer in a total volume of 1.6 ml. Non-specific binding is determined in the presence of 100 µM 5-HT. After incubation for 60 min at 25^{o}C, 6 ml of ice cold Tris-HCl incubation buffer is added to each tube, then the samples are filtered through Whatman GF/C filters using a Brandel Cell Harvester. The filters are washed with two 6 ml of ice cold incubation buffer, air dried, then placed in scintillation vials with 8 ml of Beckman Redi-Solv scintillation fluid for counting. Samples are analyzed in duplicate. Binding accounts for less than 10% of total radioactivity ([^{3}H]-paroxetine) added. The amount of membrane protein is determined using the BioRad protein assay. Specific [^{3}H]-paroxetine binding is calculated by subtracting non-specific binding from total binding and is expressed as fmoles/mg protein. K_d and B_{max} of [^{3}H]-paroxetine binding is determined using Prism 3 software by GraphPad. K_d is expressed as nM.

5-HT content. Platelet 5-HT concentration is measured using HPLC with colorimetric detection according to Javors *et al.* (2000). PRP is prepared as described above, then stored at –80°C. On the day of analysis, samples are thawed on ice, then sonicated on ice with 3 short bursts of 5 sec duration. Fifty µl of a 3.4 M solution of perchloric acid and 10 µl of a 1 µg/ml solution of N-methylserotonin (internal standard) are added to each 250 µl sample. The samples are vortexed and centrifuged, then aliquots of the supernatants are transferred to autosampler tubes for the injection of 100 µl into the HPLC. The flow rate of the HPLC pump is 1.2 ml/min. The mobile phase is 8% (v/v) HPLC grade acetonitrile and 92% (v/v) of a solution containing 48.7 mg of octylsulfonic acid and 93.7 mM phosphoric acid, pH 2.55. The HPLC system is a Waters model 510 pump, a Waters model 717 sample injector, an ESA coulometric detector with a 5011 cell (detector 1 at 350 millivolts), and a Spherisorb C18 column (3 micron, 4.5 mm ID x 15 cm length). Platelet 5-HT content is expressed as nmol 5-HT per mg whole platelet protein. An aliquot of the platelet suspension is used to determine whole platelet protein using the Bio Rad protein assay.

Platelet [^{3}H]-5HT Uptake. Platelet suspensions are prepared as described in Javors *et al*. (1990). Blood is drawn from an arm vein with a Butterfly infusion set (21 gauge, 3/4 inch needle) into 60 ml polypropylene syringes containing 10 ml of Acid-Citrate-Dextrose (ACD) buffer and 120 units of heparin for every 50 ml blood. ACD buffer contains 85 mM sodium citrate, 62.2 mM citric acid, and 110 mM dextrose, pH 4.9. The blood is then placed in polystyrene test tubes and centrifuged at 150 g for 20 min at 23°C in a Beckman TJ-6 using a swinging bucket rotor. With a polypropylene Pasteur pipette, the PRP is aspirated, carefully avoiding the buffy coat, PGI-2 (300 ng/ml) is added to prevent loss of platelets during centrifugation, then the PRP is centrifuged at 850 g for 10 min at 23°C to pellet the platelets. The platelet poor plasma is discarded and the platelet pellet carefully resuspended in platelet buffer (137 mM sodium chloride, 2 mM potassium chloride, 1 mM magnesium chloride, 5.5 mM glucose, 5.0 mM HEPES, pH 7.4), then the platelet suspension is incubated at 37°C until it has the characteristic pearlescent appearance of discoid, unactivated platelets in suspension. Tthe platelet count in this sample is determined with a Coulter Counter (model S-plus VI) and the concentration is adjusted to 2 x 10^8 platelets/ml with the addition of platelet buffer.

[^{3}H]5-HT uptake is performed according to Javors *et al.* (2000). Aliquots of a platelet suspension (2 x 10^8 platelets/ml) are incubated with [^{3}H]5-HT (specific activity 28.2 Ci/mmol) at several concentrations (0.5, 1, 2, 4, 8, 16, 32, 64, 125, 250, 500, and 1000 nM) at 37°C. A second set of tubes is incubated at 0°C, then identically processed and analyzed so that total and non-specific 5HT uptake may be determined. The uptake is initiated with the addition of [^{3}H]5-HT, the incubation proceeds for 2 min, then the uptake is quenched by the addition of 5 ml of platelet buffer containing 300 ng/ml of PGI-2 and immediate filtration through Whatman GF/B filters using a Brandel Cell Harvester. Assay tubes and filters are washed with an additional 5 ml of cold platelet buffer with PGI-2. The filters are air dried, placed in 8 ml Beckman Ready-Solv HP scintillation counting solution, and counted for [^{3}H]5-HT. Specific platelet [^{3}H]5-HT uptake is calculated by subtracting non-specific from total uptake and is expressed as picomoles 5-HT/10^8 platelets/min. K_m and V_{max} values for specific [^{3}H]5-HT uptake is calculated using Prism 3 software by GraphPad. (Javors *et al.,* 1990) Characterization of the effect of the adenosine agonist cyclohexyladenosine on PAF-induced increases in $[Ca^{2+}]_i$ in human platelets

in vitro. Platelet serotonin uptake is higher in early onset than late onset alcoholics (Javors *et al., Alcohol and Alcoholism*, in press).

13.6.29 Tests for Serotonin Transporter Polymorphic Variation

It has been hypothesized that ondansetron responsiveness may be associated with polymorphic variation in the serotonin transporter (Johnson *et al.,* 2000). According to the hypothesis, individuals with the homozygous LL-type (or long form) of the transporter may respond to ondansetron whereas patients with the dominant short form allele (SS or SL allelic forms) may not.

DNA will be collected from a 30 ml blood sample using standard techniques and will be tested for the allelic composition of the L and S forms of the serotonin transporter. Blood samples will be coded by subject number only for the genetics lab to conduct the analyses.

Thirty ml of blood is collected into standard EST tubes. The white blood cells (WBC) are centrifuged and separated from the plasma. WBC are resuspended and lysed in a phenol/chloroform/aqueous mixture. The DNA separates into the aqueous phase and is purified through two phenol/chloroform/aqueous extractions and overnight exposure to proteinase K. The DNA is precipitated by suspension in ethanol and then is resuspended in TE-buffer wherein it can be stored indefinitely. DNA samples will be amplified by standard PCR techniques in the promoter region of the serotonin transporter. After amplification, the samples are denatured and run on an electrophoresis gel along with commercially-available internal standards. The genotypes will be blindly scored by two experienced genetics technicians using Genescan genotyping software.

13.6.30 Serum Prolactin

Subjects will be scheduled to come to the clinic in the fasted state. 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, and the blood should be collected in a non-stressful (relaxing) environment during the blood draw procedure.

13.6.31 Treatment Compliance

Treatment compliance will be monitored by recording the amount of investigational agents taken by each subject at each treatment and by measuring blood ondansetron levels. Compliance with cognitive behavioral therapy will be monitored 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

A two-part Informed Consent process consisting of one form with two separate signature parts will be used during this study. Part one of the process will consist of an explanation of the study by a qualified research staff member. Part two of the process will consist of an explanation of the study by physician investigator and all medical/medication questions will be answered.

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

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

14.4 DRUG ACCOUNTABILITY

The research pharmacist is responsible for maintaining an 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 disposed of properly.

14.5 OUTSIDE MONITORING

Data and Safety Monitoring Board (DSMB): Safety and efficacy data will be reviewed by a DSMB that will meet after the first 30 subjects 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.

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 investigator or sub-investigators according to the specific instructions detailed in this section of the protocol and Appendix III. The occurrence of AEs will be assessed starting after the informed consent process is complete and at each study visit and an AE CRF completed weekly.

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

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

Each week, a study investigator must review the AE CRF completed for the previous week for any events that were reported as continuing. All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed by study investigators until satisfactory resolution. AEs 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 Project Officer, and the sponsor-investigator. The telephone report is to be followed by submission of a completed SAE Form with demographic information and a narrative explanation of the event. Attached to the SAE Form should be photocopies of the AE Form, the Concomitant Medication Form, and the Medical History Form from the subject's CRFs. All serious medical events are also to be reported to the responsibleIRB 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 OUTCOME MEASURES

There is no generally accepted definition of clinically significant improvement in the treatment of cocaine dependency. The primary and secondary outcome measures are intended to explore various aspects of response to therapy and to help define a clinically meaningful response. Three primary outcomes measures have been chosen as indications of the efficacy of the test product in reducing cocaine use in cocaine dependent subjects and include: 1) the weekly mean proportion of cocaine non-use days as determined by self-report of use and confirmed by urine BE analysis, 2) the weekly proportion of cocaine-free urine specimens over the 8 week study, and 3) the number of cocaine-free urine specimens provided over the 8 week study. 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.

Data will be collected in this study for scientific use and not as primary or secondary outcome measures. Data from the HRBS, BIS, and SSS are included in this category. This data is being

collected in order to build a database of risk behaviors associated with cocaine use and to further characterize the study population.

15.2 PRIMARY OUTCOME MEASURES

Three primary outcome measures were selected to test the efficacy of various doses of ondansetron in reducing cocaine use as follows:

1. The weekly mean proportion of cocaine non-use days as assessed by self-report of use and confirmed by urine BE determination.

2. Weekly proportion of cocaine-free urine specimens over the 8 weeks of treatment.

3. The number of cocaine-free urine specimens provided over the 8 weeks of treatment.

15.2.1 Cocaine Non-Use Days

Cocaine non-use days was selected as a primary outcome measure 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."

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 8-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 8 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 54 study days over the 8 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. 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-concordance = # non-concordant use days/total urine samples analyzed * 100%,

% 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%.

15.2.2 Weekly Proportion of Cocaine-Free Urines

The second primary outcome variable for each subject is the weekly proportion of cocaine–free urine samples. The cocaine-free urine sample is defined if urine benzoylegonine (BE) level is less then 300 ng/ml. Three urine collection days are scheduled per calendar week. The weekly cocaine-free sample is recorded as '0' if all three urine BE level in the week were less than 300 ng/ml. The weekly cocaine-free sample is recorded as '1' if the proportion of weekly cocaine-free samples is between 0.67 and 0.75, inclusive. The weekly cocaine-free sample is recorded as '2' if the proportion of weekly cocaine-free samples is between 0.33 and 0.5, inclusive. The weekly cocaine-free sample is recorded as '3' if the proportion of weekly cocaine-free samples is 0.

15.2.3 Number of Cocaine-free Urine Specimens

The total number of cocaine-free urine specimens (BE less then 300 ng/ml) provided over the 8 week study will be tabulated.

15.2.4 Secondary Outcomes

Measured reductions in cocaine and other drug use over the eight 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 SUI.

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 8 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. CSSA score.

O. BSCS scores.

P. Change in CCQ-NOW score over baseline.

Safety of Ondansetron

Q. AEs, laboratory data, physical exams, HAM-D scores, and vital signs.

15.3 STATISTICAL HYPOTHESES

15.3.1 Primary Efficacy Outcomes

It is hypothesized that ondansetron 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. It is further hypothesized that ondansetron will decrease the weekly proportion of BE positive urine specimens over the treatment period and increase the total number of cocaine-free urine specimens.

15.3.2 Secondary Efficacy Outcomes

It is hypothesized that ondansetron 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 ondansetron will reduce the severity of cocaine dependence and craving and depression as assessed by ASI-Lite, BSCS, CCQ-NOW, CSSA, CGI-S, and CGI-O.

15.3.3 Other Hypotheses

We hypothesize that responsiveness to ondansetron may be associated with serotonin transporter polymorphism and that ondansetron may be more effective in the subgroup of subjects with homozygous LL-type of serotonin transporter than in that with SS or SL allelic forms. Also, measurement of platelet serotonin function in tandem with psychosocial assessment of baseline characteristics related to serotoninergic functioning of subjects (i.e. impulsivity) will identify subgroups with high and low serotonin function that may differentially respond to ondansetron.

Literature data indicate that cocaine-dependent subjects exhibit reduced blue cone b-wave ERG responses (Roy *et al.*,1996; Smelson *et al.*1998). It is postulated that this is most likely due to alteration of dopaminergic neurotransmission (dopamine is found in high concentrations in the retina). Importantly, the cocaine-dependent subjects with a blunted ERG blue cone b-wave response (≤ 0.5 microV) showed significantly greater increases in craving following cue-exposure than subjects without the blunted ERG blue cone response. Thus, it is hypothesized that subjects with a blunted ERG response may represent a subgroup more vulnerable to cocaine craving and relapse. It is further hypothesized that ondansetron may normalize blue cone b-wave ERG responses in the subset of subjects with reduced responses.

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. It is hypothesized that subjects with elevated serum prolactin levels may represent a subset of subjects with poorer responses to treatment.

Thus, serotonin/serotonin transporter function and polymorphism, blue cone b wave ERG response amplitude, and elevated serum prolactin levels will be used as covariates in the main analysis. Separate subset analysis of these populations may be of interest depending upon the results of the primary analysis.

15.4 INTENT-TO-TREAT AND EVALUABLE SUBJECT POPULATIONS

The intent-to-treat population is defined as the subjects who are randomized to treatment, receive the first day's study agents, and complete at least one-assessment visit after receipt of the study agent. The evaluable population is defined as the subjects who are 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.

15.5 ANALYSIS PLAN

15.5.1 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.

15.5.1.1 Primary Efficacy Outcomes

15.5.1.1.1 Cocaine Non-Use Days

Each subject's weekly mean proportion of non-use days 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 weeks 1 and 8 and 7 days for weeks 2 through 7. Thus, the total number of study days is 54.

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.

15.5.1.1.2 Weekly Proportion Cocaine-Free Urines

The weekly mean proportion of cocaine-free urines on study will be compared between treatment groups using GEE for ordinal categorical response (Lipsitz *et al.,* 1994).

15.5.1.1.3 Total Cocaine-Free Urines

The total number of cocaine-free urine specimens will be compared between treatment groups using ANOVA.

15.5.1.2 Secondary Analyses

As a secondary analysis, ondansetron dose level, prior use in the last 30 days (≤ 18 and > 18), age of onset [(actual age) or categorical (young versus old) value], gender, diagnosis of ADD, baseline severity of depression (HAM-D score ≤ 15 and > 15), platelet 5-HT_3 function, serotonin transporter polymorphism, reduced blue cone b wave responses ($\leq$ 0.5 microV), level of serotonin function, elevated 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. The investigators may conduct other secondary and more exploratory analyses.

15.5.1.3 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 ANOVA and individual treatment group comparisons by Dunett's test.

4. Weekly CGI-S, CGI-O, CSSA, and BSCS, and monthly ASI-Lite scores, measures K, L, M, N, and O 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. The frequencies of adverse events by type will be compared between study arms using Chi-square analyses.

15.5.2 Dose Response Analysis

Dose response curves will be generated using the slope of the GEE for both of the primary outcome measures. The frequency and severity of adverse events will be presented for each dose. The shape and the location of the population (group) average dose response will be evaluated for positive outcomes and adverse events to select the best dose for larger phase 2 studies.

15.5.3 Descriptive Statistics

Summaries of the characteristics of the subject population in each of the four treatment arms at baseline will be prepared for both the intent-to-treat and evaluable subjects. A summary will be prepared to show dropouts/retention over time in each treatment group. The number of missing observations will be compared between treatments. 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.

15.6 SAMPLE SIZE CALCULATION

As this is a dose finding pilot study and there is no data to determine what type of effect ondansetron will have on the study population, no formal power analysis was performed. Rather, the number of subjects in each group, 15, is hypothesized to provide an indication of the safety and efficacy of each dose ondansetron in the study population.

15.7 CONTROL OF BIAS

The treatment groups will be stratified based on a diagnosis alcohol abuse/dependence (present versus absent), age of onset of cocaine use problems (early versus late), and frequency of cocaine use (current high versus low). The randomization process will be performed by computer at the NIDA data coordinating center.

15.8 POST HOC ANALYSES

Data will be collected in this study for scientific use and not as primary or secondary outcome measures. This includes serotonin receptor function and genotype, blue cone b-wave responses

by ERG, serum prolactin levels, and HRBS, BIS, and SSS assessments. 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 principal investigator is responsible for maintaining accurate, complete and up-to-date records for each subject. The principal investigator is also responsible for maintaining any source documentation related to the study, including any films, tracings, computer discs or tapes.

16.2 DATA EDITING AND CONTROL

When data are received at the NIDA data coordinating center, it will be reviewed and if incomplete or inaccurate data are found a data clarification request will be forwarded to the clinical site for a response. The site will resolve data inconsistencies and errors prior to returning data to the data coordinating center. All corrections and changes to the data will be reviewed prior to being entered into the main study database. 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.

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

16.3 DATA ENTRY, PROCESSING AND ANALYSES

Data will be collected at the study sites on source documents which will be enetered 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, patient diaries, biopsy reports, ultrasound photographs, patient 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 the NDA.

16.5 CONFIDENTIALITY

16.5.1 Confidentiality of Data

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

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

16.5.2 Confidentiality of Patient Records

To maintain subject confidentiality, all laboratory specimens, CRFs, reports and other records will be identified by a coded study subject number only. Research and clinical records will be stored in a locked cabinet. Only research staff and NIDA program officials will have access to the records. Subject information will not be released without written permission, except as

necessary for monitoring by the FDA, the NIDA monitoring contractor, or NIDA. Upon approval of the study by an IRB, an application will be filed with NIDA for a certificate of confidentiality.

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

17 PUBLICATIONS OF THE STUDY RESULTS

NIDA and the investigative group agree that 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 ondansetron 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 REPRESENTATIVE

Typed Name	Signature	Date
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
John D. Roache, Ph.D. Principal -Investigator	_____	_____
Bankole A. Johnson, M.D., Ph.D. Co-Principal -Investigator	_____	_____
Nassima Ait-Daoud, M.D. Co-Principal -Investigator	_____	_____
Richard J. Lamb, Ph.D. Co-Principal -Investigator	_____	_____
Martin Javors, Ph.D. Co-Principal -Investigator	_____	_____
Thomas Prihoda, Ph.D. Co-Principal -Investigator	_____	_____
Joe Harrison, Ph.D. Co-Principal –Investigator	_____	_____

19 REFERENCES

Arranz, *et al.* (1999) Platelet serotonergic binding sites in alcohol-dependent patients. *Alcohol and Alcoholism* 34, 726-732.

Bradbury, A. J. *et al*. (1985) Biochemical correlates of motor changes caused by the manipulation of dopamine function in the substantia nigra of the mouse. *Neuropharmacology* **24**, 1155-1161.

Beatty WW, Katzung VM, Moreland VJ, Nixon SJ. Neuropsychological performance of recently abstinent alcoholics and cocaine abusers. *Drug Alcohol Depend* 1995; 37:247-253.

Berry J, van Gorp WG, Herzberg DS, Hinkin C, Boone K, Steinman L, Wilkins JN. Neuropsychological deficits in abstinent cocaine abusers: preliminary findings after two weeks of abstinence. *Drug Alcohol Depend* 1993; 32:231-7.

Carroll KM, Rounsaville BJ, Gordon LT, *et al.* Psychotherapy and pharmacotherapy for ambulatory cocaine abusers. *Arch Gen Psychiatry* 1994; 51:177-187.

Cervo, L., Pozzi, L. and Samanin, R. (1996) 5-HT3 receptor antagonists do not modify cocaine place conditioning or the rise in extracellular dopamine in the nucleus accumbens of rats. *Pharmacology, Biochemistry & Behavior* **55**, 33-7.

Costall, B., Domeney, A. M., Naylor, R. J. and Tyers, M. B. (1987) Effects of the 5-HT3 receptor antagonist, GR38032F, on raised dopaminergic activity in the mesolimbic system of the rat and marmoset brain. *British J Pharm* **92**, 881-94.

Costall, B., Jones, B. J., Kelly, M. E., Naylor, R. J., Onaivi, E. S. and Tyers, M. B. (1990a) Ondansetron inhibits a behavioural consequence of withdrawing from drugs of abuse. *Pharmacology, Biochemistry & Behavior* **36**, 339-44.

Costall, B., Jones, B. J., Kelly, M. E., Naylor, R. J., Onaivi, E. S. and Tyers, M. B. (1990b) Sites of action of ondansetron to inhibit withdrawal from drugs of abuse. *Pharmacology, Biochemistry & Behavior* **36**, 97-104.

DuRant, R.H., Smith, J.A., Kreiter, S.R., and Krowchuk, D.P. (1999) The relationship between early age of onset of initial substance use and engaging in multiple health risk behaviors among young adolescents. *Archives of Pediatrics & Adolescent Medicine **153**, 286-291.*

Di Chiara, G. and Imperato, A. (1988) Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic dopamine system. *Proc Nat Acad Sci* **85**, 5274-5278.

Easton C, Bauer LO. Neuropsychological correlates of urine toxicology results. *Prog Neuropsychopharmacol Biol Psychiatry* 1996; 20:969-982.

Eison, A. S., Iversen, S. D., Sandberg, B. E., Watson, S. P., Hanley, M. R. and Iversen, L. L. (1982) Substance P analog, DiMe-C7: evidence for stability in rat brain and prolonged central actions. *Science* **215**, 188-90.

Fujikawa K, Fukuoka H, Alam KS, Yoshizato H, Higashimoto S, Soya H, Tanaka M, Nakashima K. Subcutaneously administered prolactin and 20K hGH, but not rGH or 22K hGH, prevent restraint strain-induced gastric ulcers in rats. Endocr 2000; 47:S49-S52.

Greenberg, B. D., Tolliver, T. J., Huang, S. J., Li, Q., Bengel, D. and Murphy, D. L. (1999) Genetic variation in the serotonin transporter promoter region affects serotonin uptake in human blood platelets. *American Journal of Medical Genetics* **88**, 83-7.

Hagan, R. M., Jones, B. J., Jordan, C. C. and Tyers, M. B. (1990) Effect of 5-HT3 receptor antagonists on responses to selective activation of mesolimbic dopaminergic pathways in the rat. *British J Pharm* **99**, 227-32.

Hallikainen, T., Saito, T., Lachman, H. M., Volavka, J., Pohjalainen, T., Ryynanen, O. P., Kauhanen, J., Syvalahti, E., Hietala, J. and Tiihonen, J. (1999) Association between low activity serotonin transporter promoter genotype and early onset alcoholism with habitual impulsive violent behavior. *Mol Psychiatry* **4**, 385-8.

Heinz, A., Jones, D., Mazzanti, C., Goldman, D., Ragan, P., Hommer, D., Linnoila, M. and Weinberger, D. (1999) A relationship between serotonin transporter genotype and in vivo protein expression and alcohol neurotoxicity. *Biological Psychiatry (In Press)*.

Helzer J, Croughton J, Robins L, Ratcliff K. National Institute of Mental Health Diagnostic Interview Schedule: Its history, characteristics, and validity. *Arch Gen Psychiatry* 1981; 38:381-389.

Ishiguro, T., Saito, S., Akazawa, H., Mitushio, H., Tada, K., Enomoto, H., Mifune, M., Toru, M., Shibuya, H. and Arinami, T. (1999) Association between drinking-related antisocial behavior and a polymorphism in the serotonin transporter gene in a Japanese population. *1999* **23**, 1281-1284.

Javors, M. et al., (1990) Characterization of the effect of the adenosine agonist cyclohexyladenosine on PAF-induced increases in $[Ca^{2+}]_i$ in human platelets *in vitro*. *Cell Calcium* **11**, 647-653.

Javors, M. et al., (2000) Reduction of platelet serotonin content in depressed patients treated with either paroxetine or desipramine. *Int J Neuropsychopharmacology*, Submitted.

Johnson, B. and Ait-Daoud, N. (2000, in press) Neuropharmacological treatments for alcoholism: scientific basis and clinical findings. *Psychopharmacology*.

Johnson, B. A., Cloninger, C. R., Roache, J. D., Bordnick, P. S. and Ruiz, P. (2000) Age of onset as a discriminator between alcoholic subtypes in a treatment-seeking outpatient population. *Amer J Addictions* **In press, 2000**.

Johnson, B. A., Roache, J., Javors, M., Di Clemente, C., Cloniger, R., Prihoda, T., Bordnick, P., Ait-Daoud, N. and Hensler, J. (1999a) Ondansetron reduces the drinking of biologically predisposed alcoholics: implications for mechanistic processes at 5-HT3 receptors. *J Amer Med Assoc* **(submitted)**.

Johnson, B. A., Roache, J. D., Javors, M., C., D., Cloninger, R., Prihoda, T. J., Bordnick, P. S. and Ait-Daoud, N. (1999b) Ondansetron reduces the drinking of biologically predisposed alcoholics: Implications for mechanistic processes at 5-HT3 receptors. *Submitted*.

Kankaanpaa, A., Lillsunde, P., Ruotsalainen, M., Ahtee, L. and Seppala, T. (1996) 5-HT3 receptor antagonist MDL 72222 dose-dependently attenuates cocaine- and amphetamine-induced elevations of extracellular dopamine in the nucleus accumbens and the dorsal striatum. *Pharmacol Toxicol* **78**, 317-21.

Kilpatrick, G., Jones, B. and Tyers, M. (1987) Identification and distribution of 5-HT3 receptors in rat brain using radioligand binding. *Nature* **330**, 746-748.

Kilpatrick, G. J., Hagan, R. M. and Gale, J. D. (1996) 5-HT3 and 5-HT4 receptors in terminal regions of the mesolimbic system. *Behavioral Brain Research* **73**, 11-3.

King, G. R., Xiong, Z. and Ellinwood, E. H., Jr. (1998) Blockade of the expression of sensitization and tolerance by ondansetron, a 5-HT3 receptor antagonist, administered during withdrawal from intermittent and continuous cocaine. *Psychopharmacology (Berl)* **135**, 263-9.

King, G. R., Xiong, Z. and Ellinwood, E. H. (1999) Blockade of accumbens 5-HT3 receptor down-regulation by ondansetron administered during continuous cocaine administration. *Eur J Pharmacol* **364**, 79-87.

Lane, J. D., Pickering, C. L., Hooper, M. L., Fagan, K., Tyers, M. B. and Emmett-Oglesby, M. W. (1992) Failure of ondansetron to block the discriminative or reinforcing stimulus effects of cocaine in the rat. *Drug & Alcohol Dependence* **30**, 151-62.

LeMarquand, D., Pihl, R. O. and Benkelfat, C. (1994) Serotonin and alcohol intake, abuse, and dependence: clinical evidence. *Biological Psychiatry* **36**, 326-37.

Lipsitz SR, Kim K, Zhao L. Analysis of repeated categorical data using generalized estimating equations. Stat Med. 1994; 15:1149-1163.

Little, K., Kirkman, J., Carroll, F., Breese, G. and Duncan, G. (1993) [125I]RTI-55 binding to cocaine-sensitive dopaminergic and serotonergic uptake sites in the human brain. *J Neurochem* **61**, 1996-2006.

McBride, W. J. and Li, T. K. (1998) Animal models of alcoholism: neurobiology of high alcohol-drinking behavior in rodents. *Critical Reviews in Neurobiology* **12**, 339-69.

McGahan PL, Griffith JA, Parante R, McLellan AT. Composite scores from the Addiction Severity Index. Washington, DC: National Institute on Drug Abuse Project DA02554 and the Veterans Administration, 1982.

McNeish, C. S., Svingos, A. L., Hitzemann, R. and Strecker, R. E. (1993) The 5-HT3 antagonist zacopride attenuates cocaine-induced increases in extracellular dopamine in rat nucleus accumbens. *Pharmacology, Biochemistry & Behavior* **45**, 759-63.

Mezinskis J, Dryenforth S, Goldsmith R, Cohen, Somoza E. Craving and withdrawal symptoms for various drugs of abuse. *Psychiatric Annals* 1998; 28.10:577-583.

O'Malley S, Adamse M, Heaton RK, Gawin FH. Neuropsychological impairment in chronic cocaine abusers. *Am J Drug Alcohol Abuse* 1992;18:131-44.

Oxford, A. W., Bell, J. A., Kilpatrick, G. J., Ireland, S. J. and Tyers, M. B. (1992) Ondansetron and related 5-HT3 antagonists: recent advances. *Progress in Medicinal Chemistry* **29**, 239-70.

Peltier, R. and Schenk, S. (1991) GR38032F, a serotonin 5-HT3 antagonist, fails to alter cocaine self-administration in rats. *Pharmacology, Biochemistry & Behavior* **39**, 133-6.

Pirker, W., Asenbaum, S., Kasper, S., Walter, H., Angelberger, P., Koch, G., Pozzera, A., Deecke, L., Podreka, I. and Brucke, T. (1995) beta-CIT SPECT demonstrates blockade of 5HT-uptake sites by citalopram in the human brain in vivo. *J Neural Transmission - General Section* **100**, 247-56.

Preston, KL, Silverman K, Schuster CR, Cove EJ. Use of quantitative urinalysis in monitoring cocaine use. Medication Development for the Treatment of Cocaine Dependence: Issues in Clinical Efficacy Trials; NIDA Research Monograph 175: 253-263, 1997.

Reith, M. E. (1990) 5-HT3 receptor antagonists attenuate cocaine-induced locomotion in mice. *Eur J Pharm* **186**, 327-30.

Roberts LA, Bauer LO. Reaction time during cocaine versus alcohol withdrawal: longitudinal measures of visual and auditory suppression. *Psychiatry Res* 1993; 46:229-37.

Rosselli M, Ardila A. Cognitive effects of cocaine and polydrug abuse. *J Clin Exp Neuropsychol* 1996;18:122-35.

Roy, et al., (1996, 1997) Reduced Blue Cone Electroretinogram in Cocaine-Withdrawn Patients. *Arch Gen Psychiatry*, 54, 153-156.

Schuckit, M. A., Mazzanti, C., Smith, T. L., Ahmed, U., Radel, M., Iwata, N. and Goldman, D. (1999) Selective genotyping for the role of 5-HT2A, 5-HT2C, and GABA alpha 6 receptors and the serotonin transporter in the level of response to alcohol: a pilot study. *Biological Psychiatry* **45**, 647-51.

Sellers, E. M., Higgins, G. and Sobell, M. B. (1992) 5-HT and alcohol abuse. *Trends in the Pharmacological Sciences* **13**, 69-75.

Sigmon, S. C., Higgins, S. T. and Badger, G. J. (2000) Relation of age of cocaine initiation to drug use severity and treatment outcome. In *Problems of Drug Dependence*, Vol. NIDA Research Monograph, Harris, L. S. ed. U.S. Government Printing Office, Washington, D.C.

Strickland TL, Mena I, Villanueva-Meyer J,. *et al.* Cerebral perfusion and neuropsychological consequences of chronic cocaine use *J Neuropsychiatry Clin Neurosci* 1993; 5:419-27.

Suzuki, T., Shiozaki, Y., Masukawa, Y. and Misawa, M. (1992) 5-HT3 receptor antagonists block cocaine- and methamphetamine-induced place preference. *Yakubutsu, Seishin, Kodo [Japanese Journal of Psychopharmacology]* **12**, 33-8.

Svingos, A. L. and Hitzemann, R. (1992) 5-HT3 receptor antagonists block cocaine-induced locomotion via a PCPA-sensitive mechanism. *Pharmacology, Biochemistry & Behavior* **43**, 871-9.

Tiffany ST, Singleton E, Haertzen CA, Henningfield JE. The development of a cocaine craving questionnaire. Drug Alcohol Depend. 1993; 34:19-28.

Williams JB. A structured interview guide for the Hamilton Depression Rating Scale. *Arch Gen Psychiatry* 1988; 45: 742-747.

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

Analyte **Abnormal Values**

Blood Chemistry and Hematology

Analyte	**Values**	
Glucose (mg/dL)	<40	>140
AST (SGOT)		> 4 X ULN*
ALT (SGPT)		> 4 X ULN
Alkaline Phosphatase		> 4 X ULN
Lactate Dehydrogenase		> 4 X ULN
Gamma Glutamyltranspeptidase		> 4 X 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 II: HIV/AIDS Education

Discuss with the Subject:

- Modes of transmission
- High risk behaviors
- Prevention behaviors
  - stop drug use
  - don't share needles
  - clean "works" before using
  - use of condoms

- HIV Testing
  - What test is for
  - Confidential vs anonymous
  - Optional
  - What +/- test results mean
  - Anxiety related to waiting for results

- Demonstration of:
  - Use of alcohol swipes
  - Use of bleach kits

- Subject wishes to be tested?
  - If yes, talk through the consent
  - Obtain signature
  - Offer outside referrals

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

A. GENERAL INSTRUCTIONS

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

2. AEs will be reported as soon as the subject signs the informed consent.

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

4. Report the relatedness of the event to the study 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 Project Officer, and the principal investigator (IND sponsor).

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

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

3-day Supporting Documentation Requirements

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

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

Follow-Up of All Adverse Events/Serious Adverse Events

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

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

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

Reporting to the FDA

The co-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.