STUDY #: NIDA-CTO-0011

DOUBLE-BLIND, PLACEBO-CONTROLLED, DOSE RESPONSE TRIAL OF ONDANSETRON FOR THE TREATMENT OF METHAMPHETAMINE DEPENDENCE

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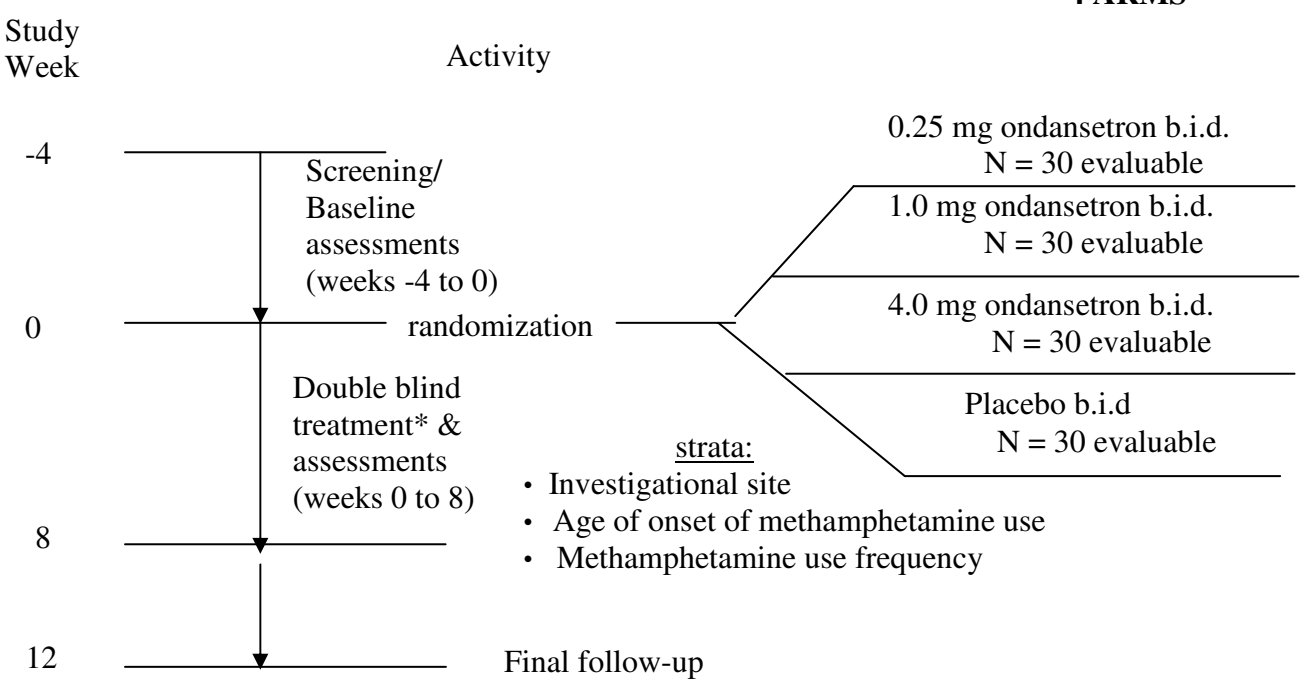
1 LIST OF ABBREVIATIONS

Abbreviation	Definition
ADD	attention deficit disorder
ADHD	attention deficit hyperactivity disorder
AE	adverse event
AIDS	acquired immune deficiency syndrome
ALP	alkaline phosphatase
ASI-Lite	Addiction Severity Index-Lite
ALT/SGPT	alanine aminotransferase/serum glutamate pyruvate transaminase
AST/SGOT	aspartate aminotransferase/serum glutamate oxaloacetate transaminse
BSCS	Brief Substance Craving Scale
BIS	Barratt Impulsivity Scale
BUN	blood urea nitrogen
CBT	cognitive behavioral therapy
CGI-O	Clinical Global Impression Scale – Observer
CGI-S	Clinical Global Impression Scale – Self
CLIA	Clinical Laboratory Improvement Act
CYP	cytochrome P450
DA	dopamine
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders Fourth Edition
ECG	electrocardiogram
eCRF	electronic case report form
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	5-hydroxytryptamine (serotonin)
IRB	Institutional Review Board
IND	Investigational New Drug Application
LAAM	levomethadyl acetate (L-alpha acetylmethadol)
LDH	lactate dehydrogenase
MAWQ	Methamphetamine Withdrawal Questionnaire
mg	milligram
MHA-TP	Microhemagglutination Assay-Treponema pallidum
NIDA	National Institute on Drug Abuse
NDA	New Drug Application
NWT	Northwest Toxicology Laboratories
OTC	over-the-counter
PRP	platelet rich plasma
RVIPT	Rapid Visual Information Processing Task

Abbreviation	Definition
RPR	Rapid Plasma Reagin (test for syphilis)
SAE	serious adverse event
SCID	structured clinical interview for DSM-IV
SERT	serotonin transporter
SUR	substance use report
SSS	Sensation Seeking Scale

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 three times weekly cognitive behavioral therapy

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 methamphetamine use in subjects with methamphetamine dependence and to determine the optimal dose of ondansetron. It is hypothesized that ondansetron treatment, compared to placebo, will be associated with a decrease in methamphetamine use as measured by quantitative urinalysis for methamphetamine.

STUDY DESIGN: This is a double-blind, placebo-controlled, randomized, 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 methamphetamine dependent outpatients. Randomization stratum include investigational site, age of onset of methamphetamine use (early onset, ≤ 17 years of age, versus late onset, > 17 years of age), and frequency of methamphetamine use (current high, > 10 days in the last 30 days, versus low, ≤ 10 days of use in the last 30 days). All subjects will receive a base of standardized, manual-driven cognitive behavioral therapy (CBT) (a 90 minute group session thrice weekly) over 8 weeks of treatment (Huber *et al*., 1997, Rawson *et al*., 1995, Shoptaw *et al.* 1994). A final follow-up assessment will be conducted 4 weeks after completion of treatment.

STUDY POPULATION. Approximately 180 subjects with Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria for methamphetamine dependence determined by structured clinical interview (SCID) will be randomized into one of four treatment groups to obtain 30 evaluable subjects per group for analysis. It is anticipated that 70% of those enrolled will be evaluable based on typical drop-out rates. Subjects will be selected by self-referral and as respondents to media advertising offering free treatment. Subjects must be at least 18 years-of-age and provide at least 1 methamphetamine positive urine specimen within 2-weeks (with an extension to 4 weeks) during the baseline period prior to randomization. All subjects must have the ability to understand and provide written informed consent.

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 CBT three times per week throughout the 8 weeks of treatment.

SAFETY ASSESSMENTS: All candidates for study enrollment will have a physical examination, a 12-lead ECG, and clinical laboratory studies (blood chemistry, hematology, and urinalysis. If the potential participant is female, a pregnancy test will also be performed during screening, at study week 4, and at study termination. Vital signs, concomitant medication use, and a urine screen for other substances of abuse will be assessed weekly during treatment. Clinical laboratory studies will be performed at week 4 and at study termination. AEs will be assessed at each visit. An HIV Risk-Taking Behavior Scale (HRBS) will be used to characterize the population HIV risk behaviors (baseline and at study termination). At study termination (the last assessment visit after treatment completion or if the subject terminates prematurely), subjects

will be evaluated for AEs, vital signs, physical examination, clinical laboratory studies, and electrocardiogram (ECG).

EFFICACY ASSESSMENTS: The primary outcome response measure will be the weekly proportion of methamphetamine-free urines (<300 ng/mL) during the 8 weeks of treatment. Secondary assessments include analyses of other measures of success in the reduction of methamphetamine use including the proportion of successful subjects with 9 consecutive methamphetamine negative urine samples, proportion of methamphetamine non-use days by self report, the largest number of consecutive methamphetamine non-use days, and reductions in use as compared to baseline. Additional measures of treatment effect will include treatment retention, Addiction Severity Index (ASI)-Lite scores, Hamilton Depression Scale (HAM-D) score, Brief Substance Craving Scale (BSCS) score, Clinical Global Impression scores as assessed by the subject (CGI-S) and an observer (CGI-O), and Methamphetamine Withdrawal Questionnaire (MAWQ) score. The ASI-Lite is performed at baseline and at study termination The HAM-D is performed at baseline and at the first visit of week 4 and at study termination. The BSCS, CGI-S, and CGI-O are performed twice at baseline and at the first visit of each study week. The MAWQ is performed at each visit during baseline and the first two weeks of treatment, then weekly thereafter. There will also be a cognitive battery assessed at baseline and at study termination. Another biological characteristic of the study population includes serotonin receptor (SERT) genotyping. This optional blood test will be performed on a baseline blood sample. 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. Participation in CBT will be documented by recording the number of counseling sessions attended.

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 and receive the first day's study agent. The evaluable population is defined as the subjects who are randomized, meet the inclusion and exclusion criteria and who contribute at least four (4) usable on-study urine samples and 21 days of self report of methamphetamine use/non-use reported on a substance use report (SUR). The individual effects, if any, of ondansetron dose level, age of onset of methamphetamine use (early onset, ≤17 years of age, versus late onset, > 17 years of age), frequency of methamphetamine use (current high, > 10 days versus low, ≤ 10 days of use in the last 30 days determined by timeline followback during screening), gender, diagnosis of ADD, alcohol use (average number of drinks per day in the last 30 days determined by timeline followback during screening), 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

4.1 METHAMPHETAMINE

Methamphetamine (Methedrine, "speed", "ice") is used and misused as a central nervous system stimulant. Methamphetamine (N-methylamphetamine) is a non-cathecholamine phenylisopropanolamine that belongs to ephedrine family of sympathomimetic drugs. It readily enters the central nervous system and has a marked stimulant effect on mood and alertness and a depressant effect on appetite. Methamphetamine acts primarily by increasing release of stored catecholamines - dopamine, epinephrine and norepinephrine. It is also a weak inhibitor of monoamine oxidase (MAO), an action that would increase its cathecholaminergic activity. Amphetamines affect serotonergic systems as well. Thus, D-amphetamine releases serotonin and may act as a direct agonist of serotonin receptors (Weiner, 1985; Kuczenski, 1983). It also increases serotonergic neurotransmission by inducing the firing rate of serotonergic cells in the raphe nucleus of brain stem (Groves and Tepper, 1983). Neurotoxicological studies have established that certain dose regimens of methamphetamine evoke the degeneration of dopaminergic and serotonergic fibers in the brains of many animal species, including monkeys (Wrona *et al.,* 1994). Pharmacokinetics of methamphetamine are similar to those of ephedrine: it has high bioavailability, a long duration of action, and a significant fraction of methamphetamine is excreted unchanged in the urine. Methamphetamine abuse has a typical pattern of withdrawal manifested by signs and symptoms opposite to those produced by the drug. Users become sleepy, have a ravenous appetite, are exhausted, and may suffer from mental depression. This syndrome may last for several days after the drug is withdrawn. Tolerance develops quickly, so that abusers may take huge doses compared with those used medically, e.g., as anorexiants.

4.2 METHAMPHETAMINE AS A MAJOR HEATH PROBLEM

Methamphetamine has become a major drug of abuse in this country (NEDTAC, 1998) for nearly a decade. High rates of methamphetamine dependence are also registered in Great Britain (Klee, 1992; 1997a), Japan (Suwaki, 1991; 1997), Australia (Hando and Hall, 1994; 1997; Makai and McAllister, 1993), and in many other countries (Klee, 1997b). In Great Britain, the methamphetamine problem is considered of greater public health consequence than cocaine, especially in relation to HIV. In Australia, amphetamines are the second most frequently used drugs, after cannabis.

In the United States, methamphetamine abuse is particularly a problem in the western states and it has more recently become a substantial concern in other sections of the country. The National Household Survey on Drug Abuse (1997) reported a 28% increase from 1994 to 1996 in the number of individuals who have tried methamphetamine in their lives (3.8 million in 1994

compared to 4.9 million in 1996). The rate of use among high school seniors was approximately 2.3% in 1996 with 4.4% reporting lifetime use (Monitoring the Future, 1997). Increased methamphetamine availability and production are being reported in diverse areas of the country, particularly rural areas, prompting concern about widespread use (ONDCP, 1998) and the problems associated with its use are also growing.

Methamphetamine-related visits to emergency rooms nationwide remain high (SAMHSA, 1997); methamphetamine-related deaths increased 217% between 1992 and 1995 (DAWN, 1998); and the amount of methamphetamine seized in California in the past three years increased 518% (ONDCP, 1998). Violence associated with methamphetamine (users under the influence, users who commit violent acts to obtain methamphetamine, and/or distributor-trafficker violence) is also a concern (DEA, 1996). Moreover, a generation of new users is engaging in highly risky sexual activities under the influence of methamphetamine, which raises the possibilities for a new wave of HIV transmission

The problem is particularly acute in California, where methamphetamine has been a significant concern for 30 years. Methamphetamine-related hospital admissions have increased 366% between 1984 and 1993 (Cunningham and Thielemeir, 1996). Recently, methamphetamine has been the primary drug problem for those admitted for drug treatment in the state; and the increase in admissions has been particularly noticeable among Latino methamphetamine abusers (NEDTAC, 1998). The lack of effective treatment for methamphetamine users has far reaching health ramifications both in terms of the consequences from continued drug use and from the potential for increased HIV transmission. As a result, the development of effective treatments for methamphetamine dependence has become a pressing concern for the national and global drug abuse treatment community.

4.3 SEARCH FOR EFFECTIVE TREATMENTS FOR METHAMPHETAMINE DEPENDENCE

Despite a decade of intensive research, an effective pharmacotherapy for stimulant dependence remains elusive with a noted lack of controlled clinical trials in pharmacotherapy for methamphetamine abuse in particular (King and Ellinwood, 1995; Ling and Shoptaw, 1997). To date, the bulk of the research in the field is oriented toward treatment of cocaine dependence and many of the suggestions on pharmacotherapies for methamphetamine abuse is based upon clinicians' experiences with treating cocaine abuse. The idea of applicability of cocaine treatment strategies for pharmacotherapy of methamphetamine dependence is based on the similarity of their pharmacological actions, i.e. cross-behavioral sensitization and tolerance between these psychostimulants in animal studies (Akimoto *et al*., 1990; Johnson *et al*., 1998; Peltier *et al*., 1996). The concept of building on knowledge from cocaine dependence studies and applying this knowledge to methamphetamine studies was endorsed by the recent Methamphetamine Addiction Treatment Think Tank (MATTT) consultants meeting convened at NIDA on 12 January 2000.

One conceptual approach for cocaine pharmacotherapies has been to evaluate medications that have antidepressant properties to treat the anhedonia and depressive symptoms in early withdrawal [e.g., desipramine, and selective serotonin reuptake inhibitors (SSRIs)]. Medications

that alleviate anhedonia have a direct effect on improving the patient's depressive mood and are believed to reduce the "fantasy urges" that often trigger use (King and Ellinwood, 1997). Another strategy has been to target the dopaminergic neurotransmitter system involved in the reward mechanism to interrupt the reinforcing action of these psychostimulants and thus reduce their use and prevent relapse (Hyman and Nestler, 1995; Ling and Shoptaw, 1997; Mendelson and Mello, 1996).

4.4 RATIONALE FOR STUDYING ONDANSETRON

Ondansetron is a selective serotonin3 (5-hydroxytryptamine3, 5-HT_3) receptor 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 methamphetamine 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).

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.

4.5 PREVIOUS HUMAN EXPERIENCE WITH ONDANSETRON FOR PHARMACOTHERAPY OF ADDICTION

Johnson *et al.,* (2000) 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. Ondansetron was tolerated well in these subjects. Early Onset Alcoholics are known to experience greater alcohol related problems, greater craving, have more psychosocial dysfunction, and 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 study will examine the ages of onset of regular methamphetamine use in the target population to determine if this impacts treatment outcome.

4.6 SAFETY OF ONDANSETRON

Ondansetron's Approved Use. Ondansetron is currently approved as an antiemetic agent and is safe and effective for the prevention of nausea and vomiting in postoperative patients and in patients treated with chemotherapy or radiotherapy (Needles *et al*., 1999; Tramer *et al*., 1997a; Tramer *et al*., 1997b; Tramer *et al*., 1998; Tramer *et al*., 1999). Both intravenous and oral doses of 4-16 mg are common in repeated and subacute (4-14 days) dosing regimens. Overall, few side effects are reported. A review of 14,800 patients treated with ondansetron found headache and diarrhea to be most common adverse events (Bryson, 1992). In chemotherapy patients receiving cisplatin, the incidence of headache was dose related and ranged from 17 to 26% following intravenous ondansetron doses ranging from 1 to 20 mg. The degree of headache or diarrhea is rarely severe and there is no reason to expect that chronic methamphetamine use will exacerbate these side effect profiles.

Rare Adverse Reactions. No systematic empirical evidence has associated ondansetron with the development of extrapyramidal symptoms. Nevertheless, there are case reports in a total of six patients describing such symptoms (Dobrow *et al*., 1991; Garcia-del-Muro *et al*., 1993; Halperin and Murphy, 1992; Krstenansky *et al*., 1994; Mathews and Tancil, 1996). Importantly, unlike antipsychotic medications which do cause extrapyramidal symptoms, ondansetron does not block post-synaptic dopamine receptors. Instead, ondansetron inhibits dopamine release via 5-HT_3 receptors on post-synaptic neurons. Since this dopamine inhibition occurs primarily at suprabasal levels of stimulation, there is little mechanistic reason to expect that ondansetron would cause extrapyramidal symptoms (Costal *et al*., 1988; Costal *et al*., 1990c; Costal *et al*., 1990d; Costal and Naylor 1992; Costal, 1993). All reported cases of extrapyramidal symptoms occurred with intravenous ondansetron administration and none were observed with oral dosing which is the route of administration for the present study. While the risk of extrapyramidal symptoms is extremely small, we will closely monitor patients for this potential side effect.

Other adverse reactions have been reported as rare occurrences with ondansetron treatment. These include two reported anaphylactic reactions (Chen *et al.,* 1993; Ross and Ferrero-Conover, 1998), two reported cases of severe thrombocytopenia (Childs *et al.,* 1994), and single reports of seizure (Sargent *et al.,* 1993), bowel occlusion (Lebrun *et al.,* 1997), pancreatitis (Alberti-Flor, 1995), and drug induced liver disease with associated jaundice (Verrill and Judson, 1994). In all of these cases a causal link to ondansetron was not established and the patients had numerous medical complications which could have caused the reported symptoms. There also are two single case reports of psychiatric complications with ondansetron. One case reported an acute and severe dysphoria that lasted 36 hours following a third oral dose of 8 mg of ondansetron (Oren, 1995). Another case reported panic symptoms associated with ondansetron (Mitchell *et al.,* 1994)

Potential Cardiac Complications of Ondansetron and Methamphetamine. Given the proposed use of ondansetron in methamphetamine users, we want to rule out cardiovascular complications with ondansetron treatment. 5-HT_3 receptors increase cardiac inotropy, chronotropy, and coronary arterial tone (Saxena and Villalon, 1991). In a human study model for blood volume loss, ondansetron was found to attenuate normal physiologic increases in plasma noradrenaline and plasma adrenocorticotrophic hormone. Nonetheless, clinical trials have shown that ondansetron lacks effects on blood pressure, heart rate, and ECG measures (Boike *et al.,* 1997; Castle *et al.,* 1992; Heyman *et al.,* 1993). The incidence of myocardial infarction and ECG abnormalities with ondansetron have not been greater than that in control populations (Bryson, 1992). The two published case reports of ondansetron associated cardiac dysrhythmias were attributable to simultaneous treatment with metoclopramide (Baguley *et al*., 1997).

Interactions of Ondansetron with Methamphetamine. The effect of ondansetron on biological and behavioral responses to D-methamphetamine has been 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-methamphetamine. A pilot study in 9 male volunteers indicated that pretreatment with ondansetron (12 mg orally over 24 hours) attenuates the methamphetamine (15 mg orally)-induced significant decrease in self-ratings for hunger (Silverstone *et al*., 1992a). In another human study, pretreatment with a low dose of ondansetron (4 mg orally) lessened the methamphetamine (15 mg orally)-induced significant decreases in self-ratings for hunger and significant increases in self-ratings for overall subjective state in 9 volunteers (Silverstone *et al*., 1992b). At the same time, ondansetron did not affect methamphetamine-induced decreases in the mean time taken to complete the psychomotor tests as well as self-ratings of mood, energy, alertness, restlessness or irritability (Silverstone *et al*., 1992b). In addition, ondansetron had no effect on the methamphetamine-induced increase in systolic blood pressure. These findings suggest that, in humans, ondansetron may partially modify the subjective effects of methamphetamine.

Clinical Trials of Ondansetron in Cocaine Abuse. 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.

Clinical Trials of Ondansetron in Alcohol Abuse. In a previous study (Johnson *et al.,* 2000), ondansetron was safely administered to outpatient alcoholics (n = 321) in oral doses up to 16 ug/kg b.i.d. for 11 weeks with no significant side effects. A pilot study has been conducted by the principal investigator in which ondansetron was administered at 64 ug/kg, b.i.d. (i.e., 4.48 mg/70 kg) to the same population. There were no unusual adverse events, which supports the safety of the highest dose of ondansetron to be used in the current study.

Ondansetron Metabolism and Potential Drug Interactions. Following oral administration, ondansetron is rapidly absorbed from the gastrointestinal tract and undergoes extensive hepatic metabolism. The cytochrome P450 (CYP) enzyme family plays a major role in oxidative metabolism of a wide range of structurally diverse environmental and dietary xenochemicals, therapeutic agents including prescription drugs and endogenous compounds like steroid hormones (Ereshefsky *et al.,* 1995; Riesenman 1995; Rosenbaum, 1995; Preskorn, 1997; Lewis, 2000). Ondansetron is metabolized to 7- and 8-hydroxyondansetron by members of CYP 1A, 3A, and 2D subfamilies, including CYP1A1, CYP1A2, CYP3A4, and 2D6 isoforms (Fischer *et al*., 1994; Dixon *et al*., 1995; Sanwald *et al.,* 1996). The fact that ondansetron is metabolized by multiple forms of CYP limits the likelihood of a clinically relevant interaction with ondansetron by a modulator of a single isoform of CYP.

Ondansetron is not the only substrate metabolized by CYP enzymes. Thus, coadministration of ondansetron and drugs that are primarily metabolized by CYP, like cimetidine, warfarin, phenobarbital, estradiol, may lead to competitive inhibition of each others metabolism and result in increased plasma concentrations of ondansetron and/or the other drug, which, in turn, could increase or prolong its therapeutic and adverse effects.

Drugs may serve not only as substrates, but as inhibitors and/or inducers (enhancers) of CYP isozymes as well. Ondansetron does not itself appear to induce or inhibit the CYP450 enzyme system of the liver. Drugs that alter (induce or inhibit) hepatic drug metabolizing enzymes of the CYP family may affect the pharmacokinetics of ondansetron. Coadministration of ondansetron and other medicines known to inhibit CYP isozymes, like quinine, quinidines, SSRIs, antidepressants, MAO inhibitors, antihistamines, beta blockers, antineoplastics, should be done with caution because that can reduce ondansetron metabolism and increase its plasma concentrations. On the other hand, coadministration of ondansetron and other medicines (including herbs) that induce CYP activity, like macrolide antibiotics, omeprazole, some steroids, St. John's Wort, should be expected to increase clearance of ondansetron, resulting in lower, and perhaps, less effective plasma levels. Thus, close monitoring of ondansetron concentration and/or its therapeutic and adverse effects is required when ondansetron is coadministered with other medication.

Environmental factors also contribute to individual variations of ondansetron metabolism. Thus, industrial workers exposed to some CYP-inducing chemicals, such as polychlorinated biphenyls used as insulating materials, plasticizers, pesticides, and defoliants, may metabolize ondansetron more rapidly than nonexposed individuals. Also, cigarette smoking can affect opioid drug use and therapy, and cigarette smoking is nearly ubiquitous among illicit drug users. Thus, smokers may metabolize ondansetron more rapidly than non-smokers because the components of cigarette smoke, such as nicotine, polycyclic aromatic hydrocarbons, carbon monoxide, and heavy metals, induce the activity of drug metabolizing CYP enzymes.

Importantly, human liver CYPs are involved in biotransformation of centrally acting drugs, including methamphetamine (Lin *et al.,* 1997; Sellers and Tyndale, 2000). CYPs can activate (e.g. codeine to morphine) or deactivate (e.g. nicotine to cotinine, methylenedioxy-methamphetamine to alpha-methylepinine) drugs of abuse. Deficiency in the *p*-hydroxylation of amphetamine was one of the observations that led to the discovery of the CYP2D6

polymorphism (Smith, 1986). A single oral administration of the radiolabelled enantiomers of amphetamine to three volunteers with subsequent analysis of urine indicated that about 5% of (+)-amphetamine was converted to *p*-hydroxyamphetamine in two subjects but to a much less extent in the third subject, who was later found to have CYP2D6 deficiency (Smith, 1986). In animal models, treatment with *d*-methamphetamine (single dose of 8 mg/kg) enhanced CYP activity at 3 hrs with a peak of activity at 12 hrs (Hamasaki and Ariyoshi, 1981). Thus, pharmacokinetic interactions with other CYP substrates are likely and may include agents proposed for the treatment of methamphetamine addiction, such as ondansetron. Interference with ondansetron metabolism can potentially lead to increased levels of the compound; however, these effects would be variable from subject to subject, may be related to prior exposure to methamphetamine, and be more pronounced in depressed and frequent users.

All of these factors can produce differences in metabolic capacities of CYPs among individuals, which can lead to toxicity in some subjects and sub-effective dosing in others. Thus, close monitoring of plasma ondansetron levels and its adverse effects will be performed.

4.7 PHARMACOKINETICS OF ONDANSETRON

Ondansetron is extensively metabolized in humans, with approximately 5% of a radiolabelled dose recovered from the urine as the parent compound. 7- and 8-Hydroxy-ondansetron are the primary metabolites of ondansetron (PDR, 2001). Ondansetron undergoes hepatic metabolism and has reduced oral bioavailability (<70%) due to first-pass metabolism. Ondansetron is rapidly absorbed (t_{max} < 2 hrs) with a half-life ($T_{1/2}$) of 5.2 hrs (Roila and Del Favero, 1995). Following the administration of a single 8 mg ondansetron tablet to healthy, young, male volunteers, the time to peak plasma ondansetron concentration is about 1.7 hours, the terminal elimination half-life is about 3 hours, and bioavailability is around 56% (PDR, 2001).

4.8 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 methamphetamine use in outpatients with methamphetamine dependence. The hypothesis is that ondansetron treatment compared to placebo will decrease the weekly proportion of methamphetamine positive urines. 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.

5.2 SECONDARY OBJECTIVES

Secondary objectives include:

1. Determining the safety of ondansetron in the study population.

2. Assessing the effective dose of ondansetron in other measures of success in the reduction of methamphetamine use including the proportion of successful subjects with 9 consecutive methamphetamine-free urine samples, the weekly mean proportion of non-use days assessed by self-report of use, the largest number of consecutive methamphetamine non-use days also assessed by self-report of use, and reductions in use as assessed by self-report compared to baseline (30 day history of use assessed by timeline followback).

3. Assessing the efficacy of ondansetron in reducing the severity of methamphetamine dependence [assessed by ASI-Lite (drug composite score principally, but composite scores of each section will also be analyzed, and the methamphetamine use question will be compared separately), and self and observer scored CGI, craving (assessed by BSCS), severity of depression as assessed by HAM-D, and withdrawal symptoms (assessed with a MAWQ)].

4. Assessing the efficacy of ondansetron in increasing the number of non-use days of other substances of abuse (marijuana, nicotine, and alcohol) as determined by self-report, and the number of negative urine specimens by individual drug (tetrahydrocannabinol, cocaine, amphetamines, barbiturates, opiates, and benzodiazepines), and the number of negative alcohol breathalyzer tests.

5. Assessing the effects of ondansetron on cognitive functions.

6. 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.

6 STUDY SPONSOR

This study will be conducted under an IND held by the Principal Investigator, Dr. Bankole Johnson.

7 STUDY SITES

This will be a multi center study coordinated by the University of California, Los Angeles-Integrated Substance Abuse Programs and conducted by investigators associated with 6 organizations including the University of Texas Health Science Center, San Antonio, Texas, University of Missouri-Kansas City, Kansas City, Missouri, University of Hawaii (Queens Hospital) Honolulu, Hawaii, Friends Research Institute (Matrix Institute on Addictions) Costa Mesa, California, South Bay Treatment Center, San Diego, California, and the Iowa Health Systems (Powell Chemical Dependency Center, Lutheran Hospital) Des Moines, Iowa.

8 STUDY DESIGN

8.1 EXPERIMENTAL DESIGN

This is a double-blind, placebo-controlled, randomized, 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 methamphetamine dependent outpatients. Randomization strata include investigational site, age of onset of methamphetamine use (early onset, ≤ 17 years of age, versus late onset, > 17 years of age), and frequency of methamphetamine use (current high, > 10 days versus low, ≤ 10 days of use in the last 30 days). All subjects will receive a base of standardized, manual-driven CBT (a 90 minute group session three times per week) over 8 weeks of treatment (Huber *et al*., 1997, Rawson *et al*., 1995, Shoptaw *et al.* 1994). A final follow-up assessment will be conducted 4 weeks after completion of treatment.

8.2 OUTCOME/RESPONSE MEASURES

Principal Outcome Measure: The principal outcome measure is quantitative urine methamphetamine analysis with a urine methamphetamine level ≥ 300 ng/mL being considered positive. This outcome measure was selected as the primary study endpoint to examine the effect of treatment on an objective measure of reduction in methamphetamine use. However, as methamphetamine has an excretion half-life of 12 to 14 hours, carryover could result in a positive urine specimen even when the subject has not used. Therefore, this is potentially a conservative outcome measure of treatment effect.

Data from previous methamphetamine pharmacokinetic studies as well as other outpatient studies will be used to develop rules/algorithm for determining new versus old (carryover) use utilizing urine methamphetamine levels. As the urine samples in this study are being analyzed quantitatively for methamphetamine, if an algorithm is developed to determine new use versus carryover, this algorithm will be used for additional analyses.

Secondary Outcome Measures Include:

1. Self-report of methamphetamine use (using the SUR);
2. Severity of methamphetamine dependence using the ASI-Lite (drug composite score principally, but composite scores of each section will also be analyzed, and the methamphetamine use question will be compared separately) and self and observer scored CGI;
3. Effect on craving (BSCS score);
4. Effect on depression (Ham-D score);
5. Effect on withdrawal symptoms (MAWQ score);
6. Use days of other substances of abuse (marijuana, nicotine, and alcohol) as determined by self-report (SUR), negative urine results (tetrahydrocannabinol, cocaine, amphetamines, barbiturates, opiates, and benzodiazepines), and breathalyzer results (alcohol);
7. Cognitive function tests; and
8. Safety of ondansetron in the study population (adverse events, ECG, and clinical laboratory studies.

Self report of use has been utilized and considered as a valid outcome measure for other substance abuse studies for which biological measurements of abstinence cannot logistically be utilized in outpatient studies (alcohol abuse for example). Self-report of use has a good correlation to the use profile provided by measurements of urine benzoylecgonine (a cocaine metabolite) in cocaine medication trials. Therefore, self report of methamphetamine use is considered a reliable alternative measure of the treatment effect that may have greater sensitivity than urine methamphetamine test results to discern small but significant treatment effects. Covariates in the analysis of treatment effect will include ondansetron dose level, age of onset of methamphetamine use (early onset, ≤ 17 years of age, versus late onset, > 17 years of age), frequency of methamphetamine use (current high, > 10 days versus low, ≤ 10 days of use in the last 30 days), gender, diagnosis of ADD, and alcohol use (average number of drinks per day in last 30 days determined by timeline followback). In addition, SERT genotyping and an HRBS, SSS, and BIS will be assessed for population descriptive and other scientific uses and not as a primary or secondary outcome measures.

8.3 BLINDING PLAN

The investigational agents, ondansetron and placebo, will be supplied by Murty Pharmaceuticals, Inc. in capsules that do not reveal the identity of the investigational agent. The investigational agents will be prepared in gelatin capsules containing the prescribed dose of ondansetron or placebo for each treatment group.

8.4 RANDOMIZATION PLAN

Stratified randomization will be used to balance treatment groups with respect to investigational site, onset of age of use (early onset, ≤ 17 years of age, versus late onset, > 17 years of age), and frequency of methamphetamine use/non-use (current high, > 10 days versus low, ≤ 10 days of use in the last 30 days determined during screening). Age of onset of methamphetamine use was selected as a stratum as age of onset of alcohol use was an important variable in the previous alcoholism trial (Sigmon *et al.,* 2000). In addition, groups will be balanced with respect to the current pattern of use (high use versus low use) as this is considered to be a predictor of response to therapy. Randomization of treatment assignment will be performed by the NIDA data coordinating center. Treatment assignments will be provided to the site research pharmacist or investigator for investigational agent dispensing.

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 randomized and receive the first day's study agent. The evaluable study population is defined as the subjects who are

randomized, meet the inclusion and exclusion criteria, and who contribute at least four (4) usable on-study urine samples and 21 days of self-report of methamphetamine use/non-use by SUR.

9 SUBJECT SELECTION

Approximately 180 subjects with methamphetamine dependence will be randomized into one of four treatment groups to obtain 30 evaluable subjects per group for analysis. Entry into this study is open to both men and women and to all racial and ethnic subgroups. It is expected that the demographics of subjects in this study will reflect the overall gender and ethnic characteristics of the clinic clientele. At least 30% female subjects must be enrolled at each study site.

Subjects will be recruited from a variety of sources. The primary source will be subjects seeking treatment for methamphetamine dependence at each clinic. Additional subjects will be recruited from the community by means of referrals from local treatment providers, advertising in local media, and word of mouth among subjects themselves. Recruitment advertisements will be approved by the site's 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 methamphetamine dependence as determined by SCID.

3. Be seeking treatment for methamphetamine dependence.

4. Have at least 1 methamphetamine or amphetamine positive urine specimen (> 1000 ng/mL) within the two-week baseline period prior to randomization with a minimum of 4 samples tested.

5. Be able to verbalize understanding of consent form, able to provide written informed consent, and verbalize willingness to complete study procedures.

6. Be female and have a negative pregnancy test and agree to use one of the following methods of birth control, or be postmenopausal, have had a hysterectomy or have been sterilized, or be male.

    a. oral contraceptives
    b. barrier (diaphragm or condom) with spermicide or condom only
    c. intrauterine progesterone or non-hormonal contraceptive system
    d. levonorgestrel implant
    e. medroxyprogesterone acetate contraceptive injection
    f. complete abstinence from sexual intercourse

9.2 EXCLUSION CRITERIA

Subjects must not:

1. Have current dependence, defined by DSM-IV criteria, on any psychoactive substance other than methamphetamine, nicotine, or marijuana or physiological dependence on alcohol or a sedative-hypnotic, e.g. a benzodiazepine that requires medical detoxification.

2. Meet the diagnostic criteria for current major depression as assessed by the SCID and/or meet current or lifetime diagnostic criteria for psychosis, bipolar I disorder, schizoaffective disorder, or schizophrenia as assessed by the SCID and/or have a history or evidence of organic brain disease or dementia.

3. Have a current suicidal ideation/plan as assessed by SCID interview and/or HAM-D question #3. Current is identified as within the past 30 days.

4. Have serious medical illnesses including, but not limited to, uncontrolled hypertension, significant heart disease (including myocardial infarction within one year of enrollment), angina, hepatic or renal disorders, or any serious, potentially life-threatening or progressive medical illness other than addiction that may compromise subject safety or study conduct or any ECG/cardiovascular abnormality (e.g., QTC interval prolongation > 450 milliseconds in men or 480 milliseconds in women) which in the judgment of the investigator is clinically significant.

5. Have had a head trauma that resulted in neurological sequelae (e.g., loss of memory for greater than 5 minutes or that required hospitalization).

6. Have renal insufficiency (plasma creatinine > 1.7 mg/dL).

7. Have diabetes with unstable control of blood glucose and have any incidence of hypoglycemia in the past year before screening.

8. Be mandated by the court to obtain treatment for methamphetamine-dependence where such mandate required the results of urine toxicology tests to be reported to the court.

9. In the opinion of the investigator, be expected to fail to complete the study protocol due to probable incarceration or relocation from the clinic area.

10. Be undergoing HIV treatment with antiviral and non-antiviral therapy.

11. Have AIDS according to the current CDC criteria for AIDS - MMWR 1999;48 (no. RR-13:29-31).

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

13. Have known or suspected hypersensitivity to ondansetron.

14. Be using ondansetron or any medication that could interact adversely with ondansetron, within the following times of beginning of administration of ondansetron based on the longest time interval of A, B, and C, below or as otherwise specified:

    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, citalopram, ketanserin, ritanserin, fluoxetine, paroxetine, sertraline, methysergide, ergotamine, ergonovine;

    - psychoactive medications such as Neuroleptics;

    - drugs significantly metabolized by the P-450, i.e., cimetidine, phenobarbital, St. John's Wort;

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

15. Have participated in any experimental study within 8 weeks (the nature of excluded studies may be discussed with NIDA investigators).

16. Be pregnant or lactating.

17. Have clinically significant laboratory values (outside of normal limits), in the judgment of the investigator (Appendix I).

18. Have had electroconvulsive therapy within the past 90 days before screening.

19. Have had opiate-substitution therapy (methadone, LAAM, buprenorphine) within 2 months of enrollment.

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

21. Be actively using albuterol or other beta agonist medications, regardless of formal diagnosis of asthma. (Inhalers are sometimes used by methamphetamine users to enhance methamphetamine delivery to the lungs.) If respiratory disease is excluded and the subject will consent to discontinue agonist use, s/he may be considered for inclusion.

22. For subjects suspect for asthma but without formal diagnosis, 1) have a history of coughing and/or wheezing, 2) have a history of asthma and/or asthma treatment two or more years before, 3) have a history of other respiratory illness, e.g., complications of pulmonary disease (exclude if on beta agonists), 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 tests 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 referred for HIV testing during screening (if desired). The opportunity for testing is offered as a courtesy to the prospective subject along with HIV education.

Prospective subjects who are positive for syphilis by the RPR test will have a fluorescent treponemal antibody absorbent assay (FTP-abs) or microhemagglutinin assay-Treponema pallidum (MHA-TP) 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 successful treatment for syphilis.

The infectious disease panel for hepatitis is performed as an aid to determine if the prospective subject has been exposed to a hepatitis virus. Positive hepatitis results do not exclude a prospective subject from participation unless there is an indication of active liver disease. 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.

If any test results are positive subject will be notified of positive and confirmatory test results and will be referred to treatment.

Methamphetamine induced psychosis does not exclude a candidate from the study, however the presence of current psychotic symptoms will exclude a candidate from the study until clinically stabilized.

10 INVESTIGATIONAL AGENTS

Ondansetron hydrochloride (Zofran) is a selective antagonist of the $5\text{-}HT_3$ receptor that has been approved by FDA for the treatment of nausea and vomiting associated with emetogenic chemotherapy.

The chemical name of ondansetron is (±) 1,2,3,9-tetrahydro-9-methyl-3-[(2-methly-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one, monohydrochloride, dihydrate. It has an empirical formula of $C_{18}H_{19}N_3O{\bullet}HCl{\bullet}2H_2O$ representing a molecular weight of 365.9.

The investigational drug products, size 1 opaque gelatin capsules containing placebo, 0.25, 1.0, or 4.0 mg of ondansetron, will be prepared by Murty Pharmaceuticals, Inc. (Lexington, KY) under a contract with the National Institute on Drug Abuse.

10.1 QUALITY CONTROL TESTS ON INVESTIGATIONAL AGENTS

The release tests and stability testing will be performed on the placebo, 0.25 mg, 1 mg, and 4 mg ondansetron caplets according to the Good Manufacturing Practice and ICH/FDA Guidance to assure the quality of the products throughout the clinical study.

10.2 DISPENSING INVESTIGATIONAL AGENTS

Bottles of the investigational agents prepared by Murty Pharmaceuticals, Inc. will be distributed to investigators or designated Research Pharmacists at the clinical sites for dispensing to subjects.

Investigational agents will be dispensed to subjects 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 directly to the subject by the investigative staff depending upon local site procedures.

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 between 8:00 and 10:00 a.m. and the evening dose between 6:00 and 8:00 p.m. 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.

10.3 PACKAGING AND LABELING

Ondansetron and placebo capsules will be packaged in 1 oz. white HDPE bottles. Bottles will be labeled by Murty Pharmaceuticals, Inc. with the protocol #, the random dose code, expiration date and the following statement – Caution: New Drug – limited by federal law to investigational use. A 10-day supply of investigational agents (20 capsules) will be packaged in one bottle. Bottles will be distributed to investigational sites. When a subject is assigned to treatment, the local site research pharmacist, investigator or designee, will label the appropriate bottle based on the random dose code assigned to the patient with the following information: subject's study identification number, subject's letter identification code, the words "Study Week X", where X is the study week number (i.e., 1 through 8), and the instructions for use ("take 1 capsule twice per day as instructed").

10.4 STORAGE

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

10.5 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 bottle and all unused investigational agent. Unused study agent will be inventoried for discrepancies. 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. On each and all clinic visits (i.e. 3 times per week), self-reports of medication use since the last clinic visit will be recorded on the Medication Use Inventory.

At the end of the study or upon request, all unused, returned, and expired investigational agents, as well as, sealed or unsealed randomization cards must be returned to Murty Pharmaceuticals, Inc.

10.6 SAFETY CONSIDERATIONS

The principal adverse events in U.S. clinical trials with 8 mg of ondansetron given orally b.i.d. are in order of frequency headache, malaise/fatigue, constipation, diarrhea, abdominal pain, xerostomia, and weakness. Rare cases of anaphylaxis, bronchospasm, tachycardia, angina, extrapyramidal reactions, rash, hypokalemia, electrocardiograph alterations, vascular occlusive effects, and grand mal seizures have been reported. With the exception of extrapyramidal reactions, rash, analphylaxis, and bronchospasm, the relationship to ondansetron is unclear (PDR, 2000).

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 or investigator 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 between 8:00 and 10:00 a.m. and one between 6:00 and 8:00 p.m.

11.2 COGNITIVE BEHAVIORAL THERAPY

The CBT program during the 8-week medication treatment phase of the study will consist of thrice weekly 90-minute group sessions. However, in order to help potential participants to stop methamphetamine use, they will be introduced to the counselors and scheduled to attend two 60-minute early recovery skills groups each week after signing informed consent up until study

enrollment. Topics covered in this early recovery skills group include: Getting Rid of Paraphernalia; Triggers; Introduction to 12-Step Groups; and Brief Information on HIV (see Appendix II). Concepts presented in these sessions include the following: (1) self-monitoring and relapse analysis; (2) identification of "triggers" and cognitive strategies for coping with them; (3) teaching of problem solving skills; (4) education about methamphetamine and methamphetamine dependence; (5) education about HIV and reducing the risk of HIV transmission; and, (6) promotion of prosocial activities. The content of these group topics is prearranged and sequenced using a manualized format. This is a feasible treatment that is known to be well accepted by subjects and it represents an appropriate, ethically defensible standard treatment condition to serve as the "platform" for the medication trial. Staff members who provide CBT counseling will have attended training in the use of these materials. The CBT specialist will have a minimum of a master's degree (or equivalent) or a bachelor's degree plus counseling experience with substance users. To ensure that the integrity of these sessions is maintained, all sessions are audiotaped and reviewed centrally by the Principal Investigator or his designee. Our experience is that these sessions are valued by subjects and attendance is excellent. Thus, psychosocial involvement is seen as a standard or platform for the proposed pharmacotherapy evaluation.

12 STUDY PROCEDURES

12.1 SUBJECT RECRUITMENT

Interested candidates who are seeking treatment and are available to come to the clinic for 14-to-16 weeks will meet with the investigator or designated investigational staff and receive an explanation of the study purpose and requirements. If still interested after receiving an explanation of the study, the candidate will be given an opportunity to review, inquire about, and sign the informed consent form. If the study will be explained initially to the potential participant by investigational staff, a two-part consent form will be used with part one being consent to start screening procedures that do not include medical assessments such as blood collection and ECG. When an investigator or study physician has explained the study and answered the potential participants questions, part two of the consent form will be signed and the remaining medical procedures to be conducted during screening may be performed. Subjects are given a copy of the signed informed consent. Any participant who has difficulty understanding the information contained in the consent 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.

12.2 SCREENING/BASELINE ASSESSMENTS

After the subject has signed the informed consent form, the screening assessment process begins (which includes a two-week baseline assessment period). Assessments are described in section 13. Baseline assessments will occur over a two-week period. If a subject fails to provide a minimum of four completed Methamphetamine Withdrawal Questionnaires (MAWQ), at least

four urine specimens – including one positive for urine methamphetamine and the accompanying other baseline repeated measures within the required two-week period, the baseline period may be shifted or extended until the subject meets the requirements in any consecutive 14-day period but within 4-weeks before randomization. Screening assessments are considered valid if the subject enrolls on the study within 4 weeks. If the subject does not meet the requirements within the 4 weeks, then screening/baseline measures must be repeated before subject enrollment but must not be started until 30 days have elapsed after the last screening visit. An End of Trial CRF must be completed if the subject is a screen fail.

In order to help potential participants to stop methamphetamine use, they will be scheduled to attend two 60-minute early recovery skills groups each week. Topics covered in this early recovery skills group include Getting Rid of Paraphernalia; Triggers; Introduction to 12-Step Groups; and Brief Information on HIV (see Appendix II). Persons who fail to provide a minimum of four urine samples and to complete all required baseline data collection and procedures within a two-week period will not be randomized.

12.3 SUBJECT ENROLLMENT AND RANDOMIZATION

If the prospective subject meets all of the study inclusion, does not meet the exclusion criteria (a checklist will be provided in the CRFs), and has signed the informed consent form, then the subject can be enrolled onto the study. Investigators or study coordinators will submit a subject randomization form to the data coordinating center to receive the subject's random dose code number. The randomization form will contain all information pertinent to the stratification variables for treatment assignment. The data coordinating center will then return to the site, a random dose code number which assigns the participant to a dose level.

If, any subject does not actually receive any investigational agent after they have been randomized, they are considered to be a randomization failure. A randomization failure notification will be submitted to the NIDA data coordinating center so that the coordinating center can reassign that random dose code to another participant.

12.4 TREATMENT PHASE

On the first day that dosing is scheduled and before dosing occurs, all subjects will have urine collected for methamphetamine and creatinine testing, and then the subject will be given the first dose of the investigational agent in the clinic regardless of the time and will be observed for one hour to monitor for immediate adverse symptoms.

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 CBT three times per week during the 8 weeks of treatment. Clinical evaluations are described in detail in section 13.0.

12.5 TREATMENT TERMINATION INTERVIEW

After the completion of dosing (as soon as possible after the last dose of investigational agent is taken during study week 8) or at the time of premature treatment termination, subjects will be asked to come to complete a treatment termination interview. Vital signs, physical examination, a 12-lead ECG, pregnancy test and clinical laboratory studies (blood chemistry, hematology, and urinalysis) will be performed. The ASI-Lite, HRBS, CGI-O, CGI-S, MAWQ, cognitive battery, and End of Trial form will be completed in addition to the scheduled weekly assessments. Methamphetamine and creatinine and other drug urine tests, alcohol breathalyzer, and self report of substance use will be completed.

12.6 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 methamphetamine, but there will be no penalty for relapsing or for missed sessions.

Subjects will be encouraged to complete study visits, assessments, and CBT 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 CBT 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.

A subject will be considered a drop out, if the subject misses six consecutive sessions during the 8 weeks of treatment. However, s/he will be asked to complete all termination assessments at the time of drop out and will be compensated for completing these assessments.

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 expresses their decision to discontinue from further participation in the study, the research staff will cease to try to make further contact.

12.7 FOLLOW-UP (WEEK 12)

Subjects will be asked to return to the clinic approximately 30-days after completion of treatment. During the follow-up interview (week 12 or 4 weeks after the premature treatment termination date), the subject will be asked to provide a urine specimen for methamphetamine/creatinine and urine drug screen and provide a self-report for use of methamphetamine, nicotine, alcohol, and marijuana. The subject will also be asked to provide any current treatments for drug or alcohol abuse. Concomitant medications and adverse events will be assessed, and the subject will complete the follow-up questionnaire. If it is not possible to

arrange for the subject to return to the clinic, then they should be telephoned and asked to provide a current self-reported methamphetamine and other substance use, and current treatment for drug or alcohol abuse. Concomitant medications and adverse events will be assessed over the telephone as well as the follow-up questionnaire. 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.

12.8 MAINTAINING AND BREAKING STUDY BLIND

The decision to break the study blind for an individual subject lies with the site 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 is necessary for clinical management.

12.9 SAFETY PROCEDURES

Subjects judged by the site investigator and/or study physician at any point to be a danger to self or others or who are judged to be in grave danger due to continued study agent use and/or to extreme psychiatric problems will be discontinued from the study and connected with an appropriate treatment agency. All staff will receive training in identifying suicide/homicide risks and/or signs of dangerous intoxication to any substance and the steps needed to appropriately respond to these signs.

12.10 SUBJECT REIMBURSEMENT

Subjects will be reimbursed for travel expenses, for providing data, and for time contributed to this research study. Subjects will receive $10 in retail scrip or vouchers or other acceptable form of reimbursement for each visit in which a urine specimen is provided during screening and the 8 weeks of treatment as reimbursement for their time and travel expense. Travel expenses (bus and cab fares) may be paid by an acceptable form of reimbursement. Subjects will be paid $25 in retail scrip or vouchers or other acceptable form of reimbursement for the study termination interview and the week 12 follow-up assessment. Payment will be made upon completion of the specified requisite assessments for a maximum payment of $410 in retail scrip, vouchers, or other acceptable form of reimbursement. Subjects will be compensated regardless of whether they continue to receive the investigational agent.

12.11 SUBJECT CONFIDENTIALITY

To maintain subject confidentiality, all laboratory specimens, CRFs, reports, and other records will be identified by a coded number or name code only. Research and clinical records will be stored separately in a secure location and only the investigative staff will have access to the records. Subject information will not be released without the written permission, except as necessary for monitoring by the FDA, NIDA or other regulatory agencies. Upon approval of the study by the site IRB, an application will be filed with NIDA for a certificate of confidentiality.

12.12 STUDY TERMINATION

12.12.1 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

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 CBT with the approval of the investigator. Any subject who discontinues prematurely, regardless of the reason, will be requested to return for a final visit to perform the necessary procedures and obtain data for end of study/early termination.

If at any time during the course of the study, psychiatric symptoms are so severe as to require medication outside of the protocol and/or hospitalization, the participant should be terminated from the study protocol and treated clinically. 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.

12.12.2 Trial Discontinuation

The study sponsor and/or NIDA have the right to discontinue the investigation at any time.

12.13 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, citalopram, ketanserin, ritanserin, fluoxetine, paroxetine, sertraline, methysergide, ergotamine, ergonovine) and drugs significantly metabolized by the P-450, such as cimetidine and phenobarbital, herbal

supplements such as horehound and St. John's Wort, or other psychoactive medications such as neuroleptics.

13 CLINICAL EVALUATIONS

Clinical evaluations will be administered according to the schedule in Table 1. Assessments were chosen to minimize the research burden, yet collect adequate data to address study hypotheses. On average baseline assessments can be completed in 6-7 hours. Weekly and monthly assessments are completed in 20-30 minutes at each visit. Assessments conducted at termination require approximately 120 minutes to complete. The assessments during follow-up are completed in 20 - 30 minutes.

Table 1. Overview of Study Assessments

Assessment	Screening/ Baseline*	RANDOMIZATION	Treatment								Termination	Follow-up
Study Week	-4 to 0		1	2	3	4	5	6	7	8		
Screening/Subject Characteristics												
Informed consent	X											
Locator Form	X											
Demographics	X											
Timeline followback (meth/alcohol)	X											
Quantity Frequency Interview	X											
SCID	X											
ADD interview	X											
Medical history	X											
Prior medications	X											
Infectious disease panel/RPR	X											
HRBS	X										X	
HIV test (optional)	X											
Alcohol Breathalyzer	3 X/week for 2 weeks*		3X	3X	3X	3X	3X	3X	3X	3X	X	
SSS	X											
BIS	X											
Safety												
Physical exam/FEV_1[a]	X										X	
Vital signs	3 X/week		X	X	X	X	X	X	X	X	X	
Hematology	X					X					X	
Blood chemistries	X					X					X	
Medical Urinalysis	X					X					X	
Pregnancy test	X					X					X	
ECG	X					X					X	
Adverse events	3X/week		3X	3X	3X	3X	3X	3X	3X	3X	X	X
Concomitant medications	3 X/week		3X	3X	3X	3X	3X	3X	3X	3X	X	X
Efficacy												
ASI-Lite	X										X	
Ham-D	X					X					X	
BSCS	weekly for 2 weeks*		X	X	X	X	X	X	X	X	X	
CGI-S	weekly for 2 weeks*		X	X	X	X	X	X	X	X	X	
CGI-O	weekly for 2 weeks*		X	X	X	X	X	X	X	X	X	
MAWQ	3 X/week for 2 weeks*		3X	3X	X	X	X	X	X	X	X	
SUR	3 X/week for 2 weeks*		3X	3X	3X	3X	3X	3X	3X	3X	X	X
Urine methamphetamine/creatinine[b]	3 X/week for 2 weeks*		3X	3X	3X	3X	3X	3X	3X	3X	X	X
Urine tox screen at NWT[b]	2X		X	X	X	X	X	X	X	X	X	X
Urine tox screen onsite test device[c]	3 X/week for 2 weeks*		X	X	X	X	X	X	X	X	X	X
Blood sample for genotyping (optional)	X											
Cognitive function tests	X										X	
Treatment compliance – therapy			3X	3X	3X	3X	3X	3X	3X	3X	X	
Treatment compliance-capsules (timeline followback)			3X	3X	3X	3X	3X	3X	3X	3X	X	
End of Trial form	X – if screen fail										X	
Follow-up questionnaire												X

[a] FEV_1 - Performed only in subjects suspected of asthma and in the discretion of the investigator.
[b] Quantitative assay for methamphetamine and creatinine as well as the Urine tox screen at NWT will be performed only for urine samples collected from the subjects who meet the eligibility for the study.
[c] The urine tox screen at baseline will be used to assess the subject's qualitative methamphetamine urine levels for eligibility determination.
*Those measures that are a subset of the screening measures that constitute baseline assessments are indicated with an asterisk.
NOTE: Once weekly assessments are performed preferably at the first clinic visit.

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. An End of Trial CRF must be completed if a subject screen fails.

1. Informed consent
2. Locator form
3. Demographics
4. Complete medical history
5. 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 site investigator and/or study physician
6. Vital signs
7. Psychiatric evaluation and SCID evaluation for DSM-IV diagnosis of methamphetamine dependence and Axis-I disorders
8. Timeline followback for methamphetamine and alcohol use in the prior 30 days
9. Quantity Frequency Interview for lifetime methamphetamine use
10. ADD interview
11. Prior medications for the 30 days prior to informed consent
12. ASI-Lite
13. HAM-D evaluation
14. SSS
15. BIS
16. Hematology
17. Blood chemistries
18. Blood sample for SERT genotyping (optional)
19. Medical Urinalysis
20. Pregnancy Assessment
21. Cognitive function tests
22. AEs at each visit
23. Concomitant medication use at each visit
24. Infectious disease panel
25. Syphilis test
26. HRBS
27. ECG
28. HIV test (optional)
29. End of Trial form (if screen fail)

13.2 BASELINE ASSESSMENTS

Baseline assessments to be completed over a 14-day consecutive period within the screening period include the following:

1. The following must be obtained three times a week for two weeks:
   a. Alcohol breathalyzer test.
      - A minimum of 4 breathalyzers must be collected in a consecutive 2-week period
   b. Urine toxicology screen using an onsite testing device.
      - Subjects must provide at least 4 urine specimens in a consecutive 2-week period, at least one of which must be positive for urine methamphetamine (> 1000 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.
   c. Urine methamphetamine plus creatinine measurements.
      - Note: Quantitative methamphetamine assay will be performed only for the urine samples collected for the subjects who meet the eligibility for the study.
   d. MAWQ
      - A minimum of 4 MAWQs must be collected in a consecutive 2-week period

2. The following must be obtained weekly for two weeks:
   a. BSCS
   b. CGI-S
   c. CGI-O
   d. Urine toxicology screen (urine specimen sent to NWT for analysis).

3. Daily report of methamphetamine, marijuana, nicotine, and alcohol use will be recorded at each visit on a SUR eCRF.

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. SUR
2. Urine methamphetamine and creatinine
3. Alcohol breathalyzer
4. AEs
5. MAWQ (the first two weeks only)
6. Concomitant medications
7. Treatment compliance (study agents and CBT)

Once per week preferably at the first visit of each week:
1. Urine toxicology screen using an onsite testing device
2. Urine toxicology screen (urine specimen sent to NWT for analysis)
3. BSCS
4. CGI-S
5. CGI-O
6. MAWQ (assessed weekly after the first two weeks of treatment)

7. Vital signs

At week 4, preferably at the first visit of the week:
1. Hematology
2. Blood chemistries
3. Medical Urinalysis
4. HAM-D
5. ECG
6. Pregnancy Assessment

13.4 ASSESSMENTS AT TERMINATION

As soon after the last dose of investigational agent is administered (at the end of treatment 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 (no FEV_1)
3. Vital signs
4. SUR
5. Urine methamphetamine and creatinine
6. Alcohol breathalyzer
7. AEs
8. Urine toxicology screen (urine specimen sent to NWT for analysis)
9. Urine toxicology screen using an onsite testing device
10. BSCS
11. CGI-S
12. CGI-O
13. MAWQ
14. Hematology
15. Blood chemistries
16. Medical Urinalysis
17. Pregnancy Assessment
18. ASI-Lite
19. HRBS
20. HAM-D
21. ECG
22. Cognitive function tests
23. Concomitant medications
24. End of Trial form

13.5 ASSESSMENTS AT FINAL FOLLOW-UP (WEEK 12)

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

1. Urine methamphetamine and creatinine
2. Urine toxicology screen (urine specimen sent to NWT for analysis)

3. Urine toxicology screen using an onsite testing device
4. SUR
5. AEs
6. Concomitant medications
7. Follow-up questionnaire

13.6 ASSESSMENT METHODS

13.6.1 Follow-up Locator Form

A locator form developed by Dr. Douglas Anglin's group at the UCLA Drug Abuse Research Center (1996) and altered for use with substance using populations will be used to assist in finding subjects at follow-up. This form asks subjects to give consent for follow-up and to provide names, addresses, and phone numbers of several friends and family members. This information is essential and will be collected during screening, after consent, and will be updated throughout the study as necessary.

13.6.2 Demographics

A subject demographics form will be used to collect demographic information on each subject during screening.

13.6.3 Medical History

To monitor the health of all study subjects, health profiles will be collected prior to participation in the study. A review of systems will be conducted by the site investigator/study physician during screening to assure medical fitness.

13.6.4 Medical History Addendum for Females

For female subjects only, an addendum to the medical history profile will be conducted by the site investigator/study physician. This addendum will ensure that all female subjects are currently using an approved form of birth control. Any participant who is unwilling to agree to study procedures will be excluded from the study.

13.6.5 Vital Signs

Vital signs to be assessed include oral temperature, sitting blood pressure, pulse rate, respiratory rate, and standing blood pressure and pulse rate (standing 1 minute), and standing blood pressure and pulse rate (standing 3 minutes). Vital signs will be assessed at each visit during baseline assessments, weekly during treatment and at termination.

13.6.6 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 site investigator and/or study physician (an FEV_1 < 70 % will exclude a potential subject from study participation).

13.6.7 Hematology

Blood will be collected in anticoagulant containing evacuated venous blood collection tubes (e.g., Vacutainer™) for hematologic assessments. Complete blood counts (CBC) with differentials and platelet count will be performed. Quantitative analyses for hemoglobin, hematocrit, red blood cells, platelets, total white blood cells, and percentage of neutrophils, eosinophils, basophils lymphocytes, and monocytes will be performed. Analyses will be performed at a central 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. Blood for hematologic assessments will be collected once during screening, at study week 4, and at study termination.

13.6.8 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 dehydrogenase (LDH), creatine phosphokinase (CPK), alkaline phosphatase (ALP), blood urea nitrogen (BUN), uric acid, and iron. Blood chemistries will be performed at a central clinical laboratory. 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. Blood for chemistry assessments will be collected once during screening, at study week 4, and at study termination.

13.6.9 Infectious Disease Panel/Syphilis Test

During screening, 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. If positive, an FTA-abs and MHA-TP confirmatory test will be performed. These tests will be conducted at a central clinical laboratory.

13.6.10 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. Subjects will be referred to a local laboratory for testing.

13.6.11 Pregnancy Test and Assessment

A urine pregnancy test designed to measure human β-chorionic gonodotropin will be used. All female subjects will be tested regardless of their child-bearing capacity. A pregnancy test will be performed during screening, at study week 4, and at study termination. A pregnancy eCRF must be completed for all subjects (including males).

13.6.12 Inclusion/Exclusion Form

The Inclusion/Exclusion form must be completed prior to randomization. This information will be used to determine whether the patient may be enrolled in the study. This form will document final eligibility, date of first study day and, if applicable, the reason patient was not enrolled in the study.

13.6.13 Breathalyzer Test

The breathalyzer or breath alcohol test will be administered at each clinic visit to assess recent alcohol use.

13.6.14 Timeline Followback

Detailed histories of methamphetamine and alcohol use over the past 30 days prior to screening will be obtained using the timeline followback method. The timeline followback method was described and validated by Sobell *et al.,* (1986) for reporting alcohol use. It has also been found to be a reliable method for assessing the history of psychoactive substance use in drug-abusing populations (Fals-Stewart *et al.,* 2000). In addition, this method will be applied to counting capsule usage reported by the subject for treatment compliance determinations.

13.6.15 Quantity Frequency Interview

A quantity frequency interview will be used to establish the subject's history of methamphetamine use. This instrument collects data on the amount and frequency of use over the lifetime of the subject. This interview will be conducted during screening.

13.6.16 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 methamphetamine dependence (22. Helplessness, 23. Hopelessness, and 24. Worthlessness). The Ham-D interview will be conducted once during screening, at study week 4, and at study termination.

13.6.17 SCID

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

13.6.18 ADD Interview

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

13.6.19 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. The ASI-Lite interview will be conducted once during screening and at study termination.

13.6.20 Urine Collection and Analyses

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

1. Methamphetamine/amphetamine, creatinine, tetrahydrocannabinol, cocaine, barbiturates, opiates, and benzodiazepines analysis performed at a central laboratory.
2. Urine Toxicology Screen performed with a qualitative onsite test device for methamphetamine, cocaine, tetrahydrocannabinol, amphetamines, barbiturates, opiates, benzodiazepines, phencyclidine, and tricyclics.
3. Medical Urinalysis performed at a central clinical laboratory.
4. Urine pregnancy test performed using an onsite test device.

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 tested immediately or will be frozen as appropriate. Specimens will be collected and tested as follows:

Methamphetamine, Creatinine, Tetrahydrocannabinol, Cocaine, Amphetamines, Barbiturates, Opiates, and Benzodiazepines Analysis.
During the screening and baseline period of the study, urine will be collected 3 times per week (generally Monday, Wednesday, and Friday, barring holidays and schedule conflicts). Upon randomization, the urine samples collected from subjects during the screening/baseline period will then be sent to NWT. NWT will screen the 1st sample of the week for cocaine, tetrahydrocannabinol, methamphetamine/amphetamines, barbiturates, opiates, benzodiazepines and creatinine. NWT will screen the 2nd and 3rd samples of the week for amphetamines/methamphetamine and creatinine only, and NWT will do quantitative analysis for

methamphetamine and amphetamines for all the samples screened positive by NWT for methamphetamine/amphetamines.

Note: The sites will store samples from screening until the subject is randomized, and once randomized then samples can be sent to NWT for analysis.

Following randomization, during the treatment phase of the study and at each of the follow-up visits, urine will be collected 3 times per week (generally Monday, Wednesday, and Friday, barring holidays and schedule conflicts) and NWT will screen the first sample collected each week for cocaine, methamphetamine/amphetamines, tetrahydrocannabinol, barbiturates, opiates, and benzodiazepines. NWT will screen all samples for amphetamines/methamphetamine and quantitative creatinine, and NWT will quantitate amphetamines and methamphetamine for all samples which screen positive by NWT for methamphetamine/amphetamines.

All specimens collected during this time frame and screened positive by NWT for methamphetamine/amphetamines will be subjected to methamphetamine quantitative analysis performed at NWT for the determination of "new use." The back-up sample retained at the site will be stored frozen until the NIDA data-coordinating center has notified the site that it can be disposed.

Urine Toxicology Screen Using an Onsite Testing Device. During the screening and baseline period, urine will be collected 3 times per week (generally Monday, Wednesday, and Friday, barring holidays and schedule conflicts). After the backup aliquot and central laboratory testing aliquot has been taken, these samples will be analyzed using an on-site testing device (tetrahydrocannabinol, methamphetamine, cocaine, amphetamines, barbiturates, opiates, benzodiazepines, phencyclidine, and tricyclics). Samples positive for amphetamine (the onsite testing device has a cutoff of $\geq$ 1000 ng/mL) will be considered as positive for methamphetamine for inclusion criteria purposes.

During treatment and after the backup aliquot and central laboratory testing aliquot has been taken, the first urine sample collected each week will be analyzed using an on-site testing device (tetrahydrocannabinol, methamphetamine, cocaine, amphetamines, barbiturates, opiates, benzodiazepines, phencyclidine, and tricyclics).

A frozen aliquot of every sample will be stored at the site. At treatment termination and follow-up, samples will be sent to a central lab for analysis, be subjected to onsite testing, and an aliquot will be frozen on site as back up. Results of on-site testing will be provided to the clinical staff as well as the investigative staff for the safety of the subjects.

Medical Urinalysis. Urine will be collected and analyzed for specific gravity, pH, blood, protein, glucose, ketones, leukocytes, and nitrites. The analysis will be conducted at a central clinical laboratory.

Urine Pregnancy Test. An onsite qualitative urine pregnancy test that evaluates human β-chorionic gonodotropin will be used.

13.6.21 Substance Use Report (SUR)

The SUR includes the subject's report of use of methamphetamine, marijuana, nicotine, and alcohol use for each day of the week. The subject is asked to report any use during 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.

13.6.22 BSCS

The BSCS is a self-administered assessment that asks the subject to rate his or her craving for methamphetamine. 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. The BSCS questionnaire will be collected once per week during the baseline assessment period, once per week during treatment, and at study termination.

13.6.23 Clinical Global Impression-Observer (CGI-O)

The CGI-O requires the observer to rate the global severity of the subject's methamphetamine dependence symptoms and to rate the improvement of the subject's methamphetamine dependence since the beginning of the study. The severity of the subject's methamphetamine dependence is rated according to eight specific problem areas often associated with methamphetamine dependence. The GCI-O interview will be conducted once per week during the baseline assessment period, once per week during treatment, and at study termination.

13.6.24 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 methamphetamine dependence symptoms and to rate the improvement of his or her methamphetamine dependence symptoms since the beginning of the study. The GCI-S questionnaire will be collected once per week during the baseline assessment period, once per week during treatment, and at study termination.

13.6.25 Methamphetamine Withdrawal Questionnaire (MAWQ)

A modified MAWQ will be created for this study based on the current version in use for NIDA sponsored behavioral intervention study for the treatment of methamphetamine dependence. The MAWQ will be performed at each visit during the baseline assessment, at each visit during the first two weeks of treatment, then weekly thereafter, and at study termination.

13.6.26 Prior Medications

All medications taken by the subject for the 30 days prior to informed consent will be documented on a Prior Medication eCRF. The reported medications will be reviewed and approved by the site investigator/study physician.

13.6.27 Concomitant Medications

All medications taken by the subject after consent during screening, while on study, and at the final follow-up assessment will be recorded on a Concomitant Medications eCRF. The reported medications will be reviewed by the site investigator/study physician for possible drug interactions.

13.6.28 Adverse Events (AEs)

AEs will be assessed starting as soon as the informed consent process is completed and at each study visit by an investigative staff nurse, physician, or qualified research assistant. If an AE that requires medical attention is reported to a nurse or research assistant, it will 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?" All AEs will be assessed for severity and relationship to the study treatments and will be recorded on an AE eCRF according to the procedures described in section 14.7.

13.6.29 HIV Risk-Taking Behavior Scale (HRBS)

The HRBS is assessed by interview 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. The HRBS questionnaire will be collected during baseline and at study termination.

13.6.30 ECG

Twelve-lead electrocardiograms will be performed according to standard procedures. The results will be reviewed by the investigator or study physician for interpretation. The investigator may consult a board-certified cardiologist, if necessary. ECGs will be performed during screening, week 4, and at study termination.

13.6.31 Blood Collection for Serotonin Transporter Polymorphic Variation Testing

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. This test is considered optional and will be consented for separately in the informed consent form. Blood samples will be coded by subject number only for the genetics lab to conduct the analyses.

Thirty ml of blood will be collected into sodium heparin containing evacuated tubes and shipped to the University of Texas Health Science for analysis (except for the samples collected locally for analysis). Once at the University of Texas Health Science Center, the white blood cells (WBC) will be centrifuged and separated from the plasma. WBC will be re-suspended and lysed in a phenol/chloroform/aqueous mixture. The DNA separates into the aqueous phase and will be purified through two phenol/chloroform/aqueous extractions and overnight exposure to proteinase K. The DNA will be precipitated by suspension in ethanol and then re-suspension in

TE-buffer wherein it can be stored indefinitely. DNA samples will be stored at - 20°C until the time of analyses. DNA samples will be coded for storage without patient identifying information. DNA samples will also be stored for future unidentified analyses.

13.6.32 Cognitive Battery

This battery of tests is designed to evaluate memory, attention, perceptual speed, and aspects of executive function. Tests have been selected for ease of administration, length, and sensitivity to the deficits found with stimulant abusers (Simon *et al.,* 1999). These assessments will be collected once during the screening/baseline period and at treatment termination. Each participant will be tested twice on all of the tests with the exception of the Repeated Memory Test (RMT). Two different forms of the RMT will be administered so that the tests show no effect of repeated administration (Basso, 1999).

The subjects are shown the RMT memory cards, then given the Trails A & B, then the digit symbol. At this point 10 minutes have passed and they are given the recall, the recognition test and the Stroop. The Continuous Performance Test takes an additional 5 minutes. The D2 test of Attention takes an additional 8 minutes. The RVIPT test takes an additional 8 minutes as well. The total time to administer the battery is about 35-40 minutes. It is not suggested to perform the D2 test of Attention and the RVIPT consecutively.

Trail Making A, B. The Trail Making tests tap attention, sequencing, psychomotor speed, and mental flexibility. Trail Making A requires the participant to connect 25 numbers, randomly arranged on a page, in proper order by drawing lines between them. Test B consists of 25 alternating letters and numbers. The participant connects the items (e.g. 1,A,2,B,3,C) by drawing lines. The dependent measure is time (Reitan, 1958; Giovagnoli, 1996).

WAIS-R Digit Symbol sub-test**.** Digit Symbol sub-test, (Wechsler, 1981) is a measure of psychomotor speed and manipulation of information. The participant is given 90 seconds to fill in the symbols that correspond to a page of numbers using a key with nine numbers and nine corresponding meaningless geometric symbols.

Stroop. Stroop measures selective attention and the ability to ignore irrelevant information by measuring the ease with which a person can conform to changing demands suppress a habitual response in favor of an unusual one (Golden, 1978; Stroop, 1935; MacLeod, 1991).

Repeated Memory Test (RMT). RMT is a test of recall and recognition for pictures and words. Stimuli are controlled for frequency, familiarity, word length and picture complexity and the test provides a measure of source memory and intrusions (Simon, 1999). Two forms of the RMT will be administered. The two forms are equivalent for frequency, word length, picture complexity, and familiarity and have been used in repeated testing with over 500 stimulant abusers and controls without testing effects.

d2 Test of Attention. The d2 test is a concise measure of selective attention and mental concentration. It measures processing speed, rule compliance, and quality of performance in response to the discrimination of similar visual stimuli.

Rapid Visual Information Processing Task (RVIPT). RVIPT is a test of attention that has been used widely in human studies to assess the effects of psychostimulant and sedative drugs (Johnson *et al*., 1996, 1998, 1999). RVIPT requires subjects to monitor digits which are presented sequentially on a computer screen at a rate of 100/min for 7.5 min. Subjects are instructed to detect and respond to targets of three consecutive odd or even digits as quickly as possible. Independent measures are made of both the speed and accuracy of decision making. These measures are recorded for each 250 trial block: hits – correct responses within 600 ms; delayed hits – responses which occurred between 600 ms and 1200 ms; false alarms – incorrect responses, and reaction time for both hits and delayed responses.

13.6.33 Treatment Compliance

Treatment compliance will be monitored by recording the amount of investigational agents taken by each subject at each treatment. The timeline followback method will be used to assist the subject in reporting of the amount of capsules taken between clinic visits. The timeline followback will be administered by the research staff three times a week and reviewed weekly by a physician. On each and all clinic visits (i.e. 3 times per week), self-reports of medication use since the last clinic visit will be recorded on the Medication Use Inventory. Compliance with CBT will be monitored by recording the length of time the subject spent in attendance at each therapy session.

13.6.34 End of Trial Form

If the potential subject screen fails, complete the End of Trial form documenting the screen fail. In addition, during the treatment termination interview, all data relevant to subject's termination: reason for termination; date of final visit; and study day of final visit will be collected.

13.6.35 Follow-up Questionnaire

The Follow-up Questionnaire will document the information collected at the 30-day follow-up interview including if contact was made with the subject or documenting the subject's death. In addition, the form asks questions regarding the subject's drug use, and current treatment for drug and alcohol abuse.

14 REGULATORY AND REPORTING REQUIREMENTS

14.1 GOOD CLINICAL PRACTICES

This study will be conducted in accordance with the most current version of the International Conference on Harmonization Guide for Good Clinical Practices (GCP). An Operations Manual will be provided to all investigational sites as a study quality assurance tool.

14.2 FDA FORM 1572

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

14.3 IND AMENDMENTS

If the study protocol is revised during the conduct of the study and the changes significantly affect the safety of the subjects, the scope of the investigation, or the scientific quality of the study, the revised protocol will be submitted to the FDA as an IND amendment.

14.4 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.

The site investigator will ensure that a duly constituted IRB at the study site that conforms with FDA regulations (21 CFR part 56) will review the protocol and the volunteer informed consent form. Each investigator will follow IRB and FDA guidance regarding reporting of AEs. Each investigator will promptly report to the IRB all changes in research activity and all unanticipated problems involving risks to human subjects or others and will not make any changes in the protocol without IRB approval, except where necessary to eliminate immediate hazards to human subjects. Following procedures outlined by the IRB, each investigator will describe the study, its risks and benefits, to each subject and ensure that each subject understands the study prior to obtaining the subject's signature. A copy of the consent form will be given to the subject.

14.5 INFORMED CONSENT

All potential candidates for the study will be given a current copy of the Informed Consent Form to read. The investigator, sub-investigators, or study physician or designated staff at each site will explain all aspects of the study in lay language and answer all of the candidate's questions regarding the study. If the candidate desires to participate in the study, s/he will be asked to sign the Informed Consent. No study procedure will be performed prior to signing Informed Consent. Subjects who refuse to participate or who withdraw from the study will be treated without prejudice. A two part informed consent form will be used with an optional consent for blood collection for genotyping. The consent will be for study with part one being consent to start screening procedures that do not include medical assessments such as blood collection and ECG. When an investigator has explained the study and answered the potential participant's questions, part two of the consent form will be signed and the remaining medical procedures to be conducted during screening may be performed.

14.6 DRUG ACCOUNTABILITY

The research pharmacist or site investigator 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.

At the end of the study or upon request, all unused, returned, and expired investigational agents, as well as, sealed or unsealed randomization cards must be returned to Murty Pharmaceuticals, Inc.

If a subject loses medication, replace with existing medications and order a replacement bottle. Do not use medications left over from previous week/s.

14.7 OUTSIDE MONITORING

Data and Safety Monitoring Board (DSMB): Safety and efficacy data will be reviewed by a DSMB that will meet after the first 60 subjects and at least 10 from each group have completed/terminated from the study. Additional meetings after that will be held on an *ad hoc* basis. The board will be blinded to subjects' actual treatment assignments.

Medical Monitor: An independent medical monitor has been 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 from the coordinating center 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, the coordinating center, and the FDA.

Study Coordination: The Coordinating Center (UCLA) will oversee activities of the other investigational sites where the protocol is being conducted. The Coordinating Center staff, in collaboration with NIDA and the data coordinating center, contracted by NIDA, organize and

manage all meetings to facilitate the study, provide training, and offer technical assistance. The Coordinating Center also serves as liaison between, NIDA, the other participating sites, and the data coordinating center responsible for monitoring the study.

14.8 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 as soon as the informed consent process is completed and at each study visit.

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 eCRF. The AE eCRF is also used to record follow-up information for unresolved events reported on previous visits.

Each week, a study investigator must review the AE eCRF 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.

14.9 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 investigator-sponsor as follows.

NIDA Medical Monitor: Roberta Kahn, M.D. 301/443-2281

NIDA Project Officer: Jurij Mojsiak, M.S., 301/443-9804

Investigator-Sponsor: Bankole A. Johnson, M.D., Ph.D., 210/562-5404 and 210/562-5405

Coordinating Center Principal Investigator: Richard A. Rawson, Ph.D., 310/312-0500

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 Prior and Concomitant Medication Form, and the Medical History Form from the subject's CRFs. All serious medical events are also to be reported to all of the responsible IRBs 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 investigator-sponsor.

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

There can be serious consequences including ultimately, criminal and/or civil penalties for sponsors who fail to comply with FDA regulations governing the reporting of SAEs to FDA. The study investigators in this study have the responsibility of promptly reporting all SAEs to NIDA and the investigator-sponsor in order that the investigator-sponsor 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 methamphetamine 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. The secondary measures add a measure of clinical relevance to the reduction of use by exploring the effect of therapy on psychosocial aspects of methamphetamine dependency. It is the intention of NIDA to use the data from clinical trials studying pharmacotherapies to treat methamphetamine dependence to develop an algorithm for combining self-report of use with urine methamphetamine assays to utilize both outcome measures to establish each day on study as a use-day or non-use day.

15.1.1 Primary Outcome Measure

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

Data from previous methamphetamine pharmacokinetic studies and other outpatient studies will be used to develop rules/algorithm for determining new versus old (carry over) use utilizing urine methamphetamine levels. The data generated in this study will be used with the algorithm, if developed, to determine new use versus carryover analyses.

15.1.2 Secondary Outcomes Measures

Effect on methamphetamine and other drug use during the 8 week treatment period

B. Proportion of subjects with 3 consecutive weeks of abstinence as measured by 9 consecutive methamphetamine-free (<300 ng/ml) urine samples.

C. Weekly mean proportion of methamphetamine non-use days based on subject's self report of use (SUR) during the 8-week treatment period.

D. The proportion of subjects who decrease the overall proportion of methamphetamine use to 50% or less of their use in the month prior to the study based on timeline followback for the before study period and self report using the SUR during the on study period.

E. The maximum number of consecutive methamphetamine non-use days by subject's self report of use (by SUR).

F. The number of methamphetamine-free urines during the 8-week period.

G. Weekly mean proportion of non-use days of other drug use, by other drug according to SUR including marijuana, nicotine, and alcohol.

H. Number of negative urines for tetrahydrocannabinol, cocaine, amphetamines, barbiturates, opiates, and benzodiazepines, and negative alcohol breathalyzer tests.

H. Log weekly median quantitative urine methamphetamine levels.

I. Proportion of subjects who reduce overall median of methamphetamine quantitative urine concentration to 50% of his/her baseline values.

J. Proportion of subjects who reduce the overall median of methamphetamine quantitative urine concentration to 25% of his/her baseline value.

Reduction in the severity of methamphetamine dependence, craving, and withdrawal

K. CGI-O scores (dependence).

L. CGI-S scores (dependence).

M. ASI-Lite composite score of the drug section and methamphetamine use question individually (dependence) and composite scores of the other sections (other global measures of improvement).

N. BSCS scores (craving)

O. MAWQ scores (withdrawal)

Severity of Depression

P. HAM-D scores.

Changes in Cognitive Functions

Q. Change in cognitive function at study end compared to baseline.

Treatment Retention

R. Number of days in treatment.

Safety of Ondansetron

S. AEs, laboratory data, physical exams, ECG results, and vital signs.

15.2 STATISTICAL HYPOTHESES

15.2.1 Primary Efficacy Outcome

It is hypothesized that ondansetron as compared to placebo will decrease the weekly proportion of methamphetamine positive urine specimens over the treatment period.

15.2.2 Secondary Efficacy Outcomes

It is hypothesized that ondansetron as compared to placebo will increase the proportion of successful subjects, the weekly mean proportion of methamphetamine non-use days according to self-report alone, the number of methamphetamine negative urine samples, and the weekly mean proportion of other drug non-use days or alcohol according to self-report and proportion of negative urines for other drugs use or negative breathalyzer tests. It is further hypothesized that ondansetron will reduce the severity of methamphetamine dependence, craving, and withdrawal and depression as assessed by ASI-Lite, BSCS, CGI-S, CGI-O, MAWQ, and HAM-D.

15.2.3 Other Hypotheses

We hypothesize that measurement of platelet serotonin transporter genotype in tandem with psychosocial assessment of baseline characteristics related to serotoninergic functioning of subjects (i.e. impulsivity) will identify subgroups that may differentially respond to ondansetron. Separate subset analysis of these populations may be of interest depending upon the results of the primary analysis.

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. Also, it is possible that other genetic polymorphisms in co-related neurotransmitter systems (e.g. opioid) also may interact with the serotonin system. Since this pharmacogenomic approach to treatment is developing rapidly, and all possibilities are not currently evident, we propose to collect and archive DNA for future analysis investigating the relationship between ondansetron and genetic polymorphisms at multiple neurotransmitter targets.

15.3 INTENT-TO-TREAT AND EVALUABLE SUBJECT POPULATIONS

The intent-to-treat population is defined as the subjects who are randomized and receive the first day's study agents. The evaluable population is defined as the subjects who are randomized, meet

all of the inclusion and exclusion criteria, and who contribute at least four (4) usable on-study urine samples and 21 days of self report of methamphetamine use/non-use by SUR.

15.4 ANALYSIS PLAN

15.4.1 Efficacy Assessments

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

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

Primary Efficacy Outcomes

The weekly mean proportion of methamphetamine-free urines on study will be compared between treatment groups using Generalized Estimating Equations (GEE) for ordinal categorical response (Lipsitz *et al.,* 1994). GEE provide a model-based regression method applicable for the analysis of the correlated data that will result from this repeated measures longitudinal study. The GEE procedure was first proposed by Liang and Zeger (1986) and Zeger and Liang (1986) and models the population average. GEE 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.

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:

Outcome Measure	Test
A, C, G, I, J	Chi-square tests
D, E, G, L, Q	Analysis of Variance
B, F, H, K, L, M, N, O, P	GEE
R	Wilcoxon (Gehan)
S. 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.	

15.4.2 Secondary Analyses

As a secondary analysis, ondansetron dose level, prior use of methamphetamine in the last 30 days (≤ 10 and > 10 days), age of onset of methamphetamine use (≤ 17 years of age versus > 17 years old), gender, diagnosis of ADD, alcohol use (average number of drinks per day in last 30 days determined by timeline followback) 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.

15.4.3 Dose Response Analysis

Dose response curves will be generated using the slope of the GEE for the primary outcome measure. 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.

15.4.4 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.

15.5 SAMPLE SIZE

There is no data to determine what type of effect ondansetron will have on the study population because this is a pilot study. Based on other clinical trials of drug abuse treatments, 30 evaluable subjects in study arms will give an indication of treatment effect. It was estimated that 30% of subjects will not meet the evaluable subject criteria, thus to obtain 30 evaluable subjects in each treatment arm, 45 subjects will need to be randomized to each arm for a total of 180 subjects randomized and enrolled on the study.

15.6 CONTROL OF BIAS

The treatment groups will be stratified based on investigational site, age of onset of methamphetamine use (≤ 17 years old versus ≥ 17 years old), and frequency of methamphetamine use (current high > 10 days of use in the past 30 days versus low ≤ 10 days of use in the past 30 days). The randomization process will be performed by computer at the NIDA data coordinating center.

15.7 POST HOC ANALYSES

Data will be collected in this study for scientific use and not as primary or secondary outcome measures. This includes SERT genotype, HRBS, BIS, and SSS assessments. Additional *post hoc* analysis may be performed to evaluate other confounding factors on outcomes such as age or patterns of methamphetamine use at baseline and after treatment.

16 DATA MANAGEMENT AND CASE REPORT FORMS (CRF)

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

16.1 DATA COLLECTION

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

16.2 DATA EDITING AND CONTROL

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

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

16.3 DATA ENTRY, PROCESSING AND ANALYSES

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

16.4 STUDY DOCUMENTATION AND RECORDS RETENTION

Study documentation includes all eCRFs, 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 a new drug application (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, eCRFs, reports and other records will be identified by a coded study subject number or name code only. Research and clinical records will be stored separately in a secure location. 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.

The procedure for applying for a certificate of confidentiality is provided in Appendix IV.

17 PUBLICATIONS OF THE STUDY RESULTS

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

18 SIGNATURES

NIDA Representatives

Typed Name	Signature	Date
Edwina Smith, RN, BC, M.S. Project Manager	_____	_____
Jurij Mojsiak, M.S. Project Officer	_____	_____
Ahmed Elkashef, M.D. CMB Branch Chief	_____	_____

Investigators

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
Bankole Johnson, M.D., Ph.D. Principal Investigator	_____	_____
John Roache, Ph.D. Subinvestigator	_____	_____
Nassima Ait-Daoud, M.D. Subinvestigator	_____	_____
Richard A. Rawson, Ph.D. Coordinating Center Principal Investigator	_____	_____
Thomas Newton, M.D. Subinvestigator	_____	_____
Walter Ling, M.D. Subinvestigator	_____	_____

Investigators

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
Jan Campbell, M.D. Site Principal Investigator	_____	_____
Charles Gorodetzky, M.D., Ph.D. Subinvestigator	_____	_____
William Haning, M.D. Site Principal Investigator	_____	_____
Barry Carlton, M.D. Subinvestigator	_____	_____
Joseph Mawhinney, M.D., F.A.P.A. Site Principal Investigator	_____	_____
Roger Donovick, M.D. Site Principal Investigator	_____	_____
Dennis Weis, M.D. Site Principal Investigator	_____	_____

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APPENDIX I: Criteria for Identifying Laboratory Values as Clinically Significant 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

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

A. GENERAL INSTRUCTIONS

1. Adverse events should be assessed at each study visit starting after completion of the informed consent process.

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

3. 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 termination 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 principal investigator, who is the IND sponsor, is required to report SAEs to the FDA:

- in 7 days if the SAE is unexpected (or, if expected, unusually serious or rarely seen), life-threatening or lethal, and at least possibly related to the study agent, with a follow-up written report in 8 days;

- in 15 days if the SAE is unexpected (or, if expected, unusually serious or rarely seen), but not immediately life-threatening; and

- in an annual report in all other cases.

APPENDIX IV: Procedure for Applying for a Certificate of Confidentiality

The only people who will know the identity of the subjects are members of the research team and, if appropriate the physicians and nurses. No information about the subjects, or provided by the subjects during the research, will be disclosed to others without the subjects' written permission, except:

- if necessary to protect subjects' rights or welfare, or
- if required by law.

When the results of the research are published or discussed in conferences, no information will be included that would reveal subjects' identity. Authorized representatives of the FDA and NIDA study monitors may need to review records of individual subjects. As a result, they may know subjects' names, but they are bound by rules of confidentiality not to reveal their identity to others. The results of this study including laboratory results and clinical information collected during this study will be submitted to the FDA and may be used for research purposes. The results of this study may be published but will not personally identify any subjects. All records will be kept in locked storage locations that will be accessible only to authorized study personnel.

Applying for a Certificate of Confidentiality

A Certificate of Confidentiality helps researchers protect the privacy of subjects in health research projects against compulsory legal demands (e.g., court orders and subpoenas) that seek the names or other identifying characteristics of research subjects. The certificate was developed to protect against the involuntary release of personally identified research information of a sensitive nature sought through any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. This authority was granted under the Comprehensive Drug Abuse Prevention and Control Act of 1970, Public Law No. 91-513, Section 3(a).

Investigators will obtain a certificate to avoid being required to involuntarily disclose personally identifiable research information about individual study subjects. Under this statute:

"The Secretary [of the Department of Health and Human Services] may authorize persons engaged in biomedical, behavioral, clinical, or other research (including research on mental health, and on the use and effect of alcohol and other psychoactive drugs) to protect the privacy of individuals who are the subject of such research by withholding from all persons not connected with the conduct of such research the names or other identifying characteristics of such individuals. Persons so authorized to protect the privacy of such individuals may not be compelled in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings to identify such individuals" (Public Health Service Act 301 (d), 42 U. S. C. 241 (d), as amended by Public Law No. 100-607, Section 163 (November 4, 1988)).”

Accordingly, this special privacy protection can be granted only to research (i.e., a systematic

investigation, designed to develop or contribute to generalizable knowledge). It is granted only when the research is of a sensitive nature where the protection is judged necessary to achieve the research objectives.

The Investigator will submit the application, as outlined in the Confidentiality Certificate Application Instructions (http://www.nida.nih.gov/Funding/ConfidentialityInstruct.html), along with IRB review documentation and a copy of the informed consent/assent forms to be used in the study. The Principal Investigator must sign the application and submit everything to:

Ms. Jacqueline R. Porter
NIDA Certificate of Confidentiality Coordinator
or
Ms. Sandra Solomon,
Certificate of Confidentiality Assistant

Office of Extramural Affairs
6001 Executive Boulevard, Room 3158, MSC 9547
Bethesda, Maryland 20852-9547
Rockville, MD 20852 (courier or express mail)
TEL: 301-443-2755
FAX: 301-443-0538
E-MAIL: jporter@nida.nih.gov or ssolomo1@nida.nih.gov

Since a certificate is generally issued to a sponsoring research institution, the application and its assurances, must be signed by a faculty member or a senior official. The principal investigator, or their staff, will not represent the issuance of a Certificate to potential participants as an endorsement of the research project by DHHS or use it in a coercive manner for recruitment of subjects. The investigator must use the authority of the Certificate to resist compulsory disclosure of individually identifiable research data.

The study subjects should be informed that a Certificate is in effect, and be given a fair and clear explanation of the protection it affords, including the limitations and exceptions. This information will be included in the informed consent. Please see below some suggested wording:

"We have received a Certificate of Confidentiality from the National Institute on Drug Abuse, which will help us protect your privacy. The Certificate protects against the involuntary release of information about your participation in this study. The researchers involved in this project cannot be forced to disclose your identity or your participation in this study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, you or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if you or your guardian requests disclosure of your participation, the researchers will provide research data. The Certificate does not protect against that voluntary disclosure.

Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or a Food and Drug Administration request under the Food, Drug and Cosmetics Act."

or

"A Certificate of Confidentiality has been obtained from the Federal Government for this study to help insure your privacy. This Certificate means that the researchers cannot be forced to tell people who are not connected with the study, including courts, about your participation, without your written consent. If we see [learn] something that would immediately endanger you, your child, or others, we may discuss it with you, if possible, or seek help."

Study subjects will be notified that a Certificate has expired if they are recruited to the study after the expiration date of the Certificate and an extension of the Certificate's coverage has not been granted.

If the research scope of a project covered by a Certificate should change substantially, the PI will request an amendment to the Certificate; however, the NIDA Certificate Coordinator may require a new Certificate depending on the extent of the change in scope. An extension of coverage must be requested if the research extends beyond the expiration date of the original Certificate, as research information collected after the expiration of a Certificate is not protected from compelled release.

A Certificate of Confidentiality is a legal defense against a subpoena or court order, and is to be used by the researcher to resist disclosure. The researcher should seek legal counsel from his or her institution if legal action is brought to release personally identifying information protected by a certificate. The Office of General Counsel for DHHS is willing to discuss the regulations with the researcher's attorney.