STUDY #: NIDA-CTO-0008

PHASE 2, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF BUPROPION FOR THE TREATMENT OF METHAMPHETAMINE DEPENDENCE

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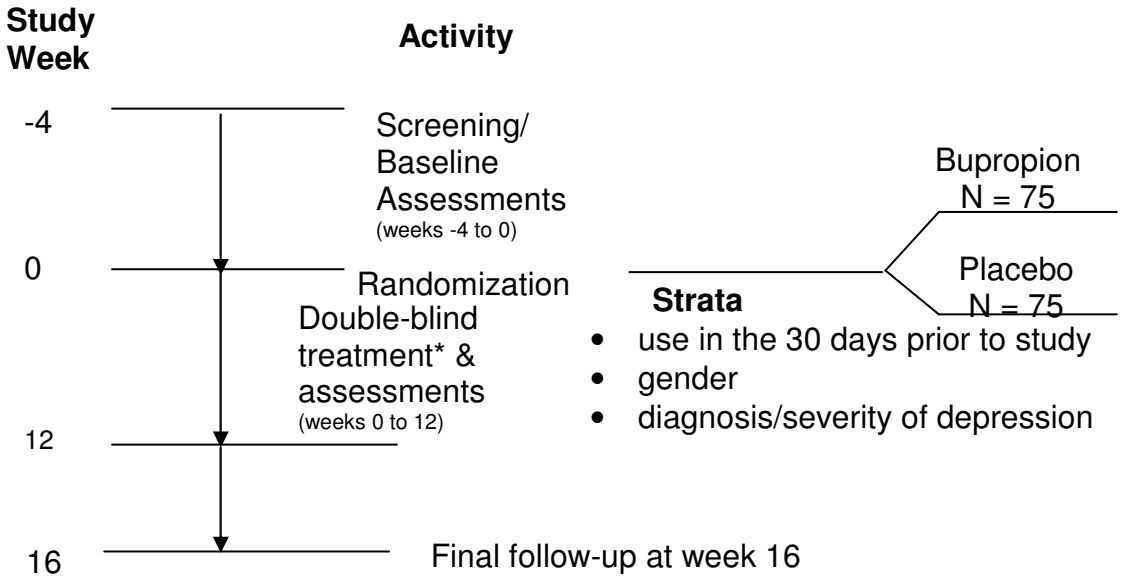
TABLE OF CONTENTS

1 LIST OF ABBREVIATIONS

Abbreviation	Definition
ADD	attention deficit disorder
ADHD	attention deficit hyperactivity disorder
AE	adverse event
ALP	alkaline phosphates
ALT/SGPT	alanine aminotransferase/serum glutamic pyruvic transaminase
ASI-Lite	Addiction Severity Index-Lite
AST/SGOT	aspartate aminotransferase/serum glutamic oxaloacetic transaminse
BE	benzoylecgonine
BSCS	Brief Substance Craving Scale
BUN	blood urea nitrogen
CAP	College of American Pathologists
CBT	Cognitive Behavioral Therapy
CGI-O	Clinical Global Impression Scale – Observer
CGI-S	Clinical Global Impression Scale – Self
CLIA	Clinical Laboratory Improvement Amendment of 1988
CRF	Case Report Form
CPK	creatinine phosphokinase
dL	deciliter
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders Fourth Edition
DTR&D	Division of Treatment Research and Development
ECG	electrocardiogram
FEV_1	forced expiratory volume in 1 second
GGT	gamma glutamyltranspeptidase
HAM-D	Hamilton – Depression Rating Scale
HIV	human immunodeficiency virus
HRBS	HIV Risk-Taking Behavior Scale
kg	kilogram
LAAM	levomethadyl acetate (L-alpha acetylmethadol)
LDH	lactate dehydrogenase
mg	milligrams
mL	milliliter
MAO	monoamine oxidase
MAWQ	Methamphetamine Withdrawal Questionnaire
NIDA	National Institute on Drug Abuse
OTC	over-the-counter
RPR	Rapid plasma reagin (test for syphilis)
SAE	serious adverse event
SCID	structured clinical interview for DSM-IV
SSRI	selective serotonin reuptake inhibitor
SUR	substance use report

2 STUDY SCHEMA



*Double blind treatment consists of daily bupropion (days 1 – 3: 150 mg, days 4 – 81: 300 mg, days 82 – 84: 150 mg) or matching placebo and thrice-weekly cognitive behavioral therapy

3 PROTOCOL SYNOPSIS

STUDY OBJECTIVES: To assess the efficacy and safety of bupropion in reducing methamphetamine use in subjects with methamphetamine dependence. It is hypothesized that bupropion treatment, compared to placebo, will be associated with fewer days of methamphetamine use as measured by quantitative urine analysis for methamphetamine.

STUDY DESIGN: This is a double-blind, placebo-controlled, parallel-group design study in which, after screening and a 2-week baseline period, 150 subjects will be randomly assigned to either placebo or bupropion for 12 weeks with a follow-up assessment 4 weeks after treatment completion. Five clinical research sites will each recruit approximately 30 participants into the trial. Adaptive randomization will be used to balance treatment groups based on gender, historical self-report of methamphetamine use (prior use in the last 30 days ≤ 18 *versus* > 18), and severity of depression (HAM-D score ≤ 12 *versus* >12).

STUDY POPULATION: 150 individuals (30 per site) 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 two treatment groups. Males and females, between 18 and 65 years-of-age, with 1 methamphetamine positive urine specimen provided during the 2-week baseline period prior to randomization who verbalize the ability to understand and provide written informed consent will be included.

TREATMENTS: Subjects randomized to bupropion treatment will receive 150 mg of sustained-release bupropion once daily for 3 days then twice daily for a total of 300 mg for a total of 12 weeks (dose taper will be performed the last 3 days of the 12 weeks to 150 mg per day). Subjects randomized to the placebo arm will receive matched placebo tablets according to the same schedule. All subjects will receive manual-guided cognitive behavioral therapy (CBT) thrice weekly during the 12 weeks of treatment.

SAFETY ASSESSMENTS: All candidates for study enrollment will have a physical examination, a 12-lead electrocardiogram (ECG), and clinical laboratory studies (blood chemistry, hematology, and urinalysis performed during screening. If the potential participant is female, a pregnancy test will also be performed during screening, at study weeks 4 and 8, and at study termination. Vital signs, concomitant medication use, and a urine screen for other substances of abuse will be assessed weekly during treatment. AEs will be assessed at each visit. 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 ECG.

EFFICACY ASSESSMENTS: The primary outcome response measures will be the weekly proportion of methamphetamine-free urines during the 12 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 3 consecutive weeks of negative urine samples as measured by 9 consecutive negative urine samples for methamphetamine, 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 score, Hamilton Depression Rating Scale (HAM-D) score, Brief Substance Craving Scale (BSCS) score, Methamphetamine Withdrawal Questionnaire (MAWQ), Clinical Global Impression scores as assessed by the subject (CGI-S) and an observer (CGI-O) and HIV risk taking behaviors using an HIV Risk-Taking Behavior Scale (HRBS). ASI-Lite is performed during screening and at study termination. The HAM-D is performed biweekly through screening, baseline, and treatment periods; it is also performed at study termination. The BSCS, CGI-S, and CGI-O are assessed weekly at screening, baseline and during treatment and also at study termination. The MAWQ is collected 3 times per week during baseline and the first two weeks of treatment and then weekly thereafter. The HRBS is assessed at screening and at study termination. There will also be neurocognitive battery done at screening and at study termination. Study agent compliance will be monitored by reconciliation of dispensed study agents. Treatment effects on other substances of abuse (amphetamines, cocaine, opiates, tetrahydrocannabinol, barbiturates, and benzodiazepines) will be determined by quantitative urinalysis at a central laboratory.

ANALYSIS: Each of the primary and secondary outcome variables will be analyzed using appropriate statistical methods for the intent-to-treat population and for the evaluable population. The intent-to-treat population includes subjects who are randomized and receive at least 1 dose of study agents. The evaluable population is those subjects who meet eligibility criteria and provide at least 6 urine specimens and 28 days of self-report of substance use (SUR). The individual effects, if any, of age, race, usual route of methamphetamine use (oral/nasal inhalation *versus* intravenous/smoked), and clinical site on the primary treatment effects will be determined where numbers permit. Interactions of these variables with gender, historical self-report of methamphetamine use (prior use in the last 30 days ≤ 18 *versus* > 18), and severity of depression (HAM-D score ≤ 12 *versus* >12) will also be assessed. Statistical tests will be two-sided at a 5% Type I error rate. Confidence intervals will be two-sided with a 95% confidence coefficient.

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

All adverse events will be reported in tabular form indicating the frequency of each type of event by various demographic characteristics such as gender, ethnicity, age, duration of addiction, other medical problems both related to and independent of the addiction, and combinations of these characteristics.

4 BACKGROUND AND RATIONALE

Methamphetamine. Methamphetamine (Methedrine, “speed”, “ice”) is used and misused as 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 cathecholaminergic activity. Its pharmacokinetics 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. Since the duration of action of methamphetamine is much longer than that of cocaine, intoxication may last for several days after a single smoke. Tolerance develops quickly, so that abusers may take huge doses compared with those used medically, e.g., as anorexants.

Methamphetamine is 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 and 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.

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 much of the suggestions on pharmacotherapies for methamphetamine abuse are based upon clinicians' experiences with treating cocaine abuse. Inherent in this approach is the assumption that what applies to cocaine treatment might also apply to methamphetamine. Although the efficacy of cocaine-focused treatment when applied to methamphetamine users remains largely unknown, the similarities between the two stimulants support using existing cocaine treatment research as a starting point for the development of treatment approaches for methamphetamine users.

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; Kazahaya *et al*., 1989; Peltier *et al*., 1996). Cocaine is able to cross-sensitize the locomotor responses to other psychostimulants (Elmer *et al*., 1996), and chronic methamphetamine (and amphetamine) produce cross-tolerance to the discriminative and reinforcing stimulus of cocaine (Peltier *et al*., 1996). These data, as well as similarities of biochemical modes of action of cocaine and methamphetamine - both enhance the efflux of striatal dopamine (Kazahaya *et al.*, 1989) and recruit brain nitric oxide system when behaviorally cross-sensitizing (Itzhak, 1997) - implied that effects of cocaine and methamphetamine may converge on a molecular level via induction of specific patterns of gene expression.

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 dopaminergic neurotransmitter system involved in the reward mechanism to interrupt the reinforcing action of these psychostimulants and thus reduce their use and prevent the relapse (Hyman and Nestler, 1995; Ling and Shoptaw, 1997; Mendelson and Mello, 1996). Unfortunately, there has not been developed a single agent with efficacy for the treatment of cocaine dependence, although the NIDA portfolio is impressive and lists over 30 drugs at varying stages of study for treatment of cocaine dependence, many of which have been approved for other clinical indications (Ling and Shoptaw, 1997; Mendelson and Mello, 1996).

Conceptual Support for Dopaminergic Agents as a Methamphetamine Medication. There is clear evidence that methamphetamine dependence involves the dopaminergic system (McGregor and Roberts, 1994). Many studies confirm that methamphetamine increases the concentration of dopamine in the synaptic cleft (Zetterstrom *et al*., 1988; Hernandez *et al.,* 1989; Kuczenski and Segal, 1989; Robinson *et al.*, 1990; Yamamoto and Pehek, 1990) and that withdrawal from methamphetamine is associated with decreases in extracellular dopamine (Imperato et al., 1992; Rossetti et al., 1992). Dopamine antagonists interfere with self-administration of methamphetamine, (Risner and Jones, 1976; Davis and Smith, 1974; Yokel and Wise, 1975) but these agents can augment cocaine withdrawal symptoms such as anergy, anhedonia and depression (Gawin, 1991). Indeed, aversive effects have been reported for dopamine receptor antagonists, and their usefulness in treating cocaine addiction has been limited (Shippenberg *et al*., 1987, 1991). Conceptually, restoring levels of dopamine (by increasing dopamine release, preventing uptake or slowing degradation after release) to pre-dependence levels will help methamphetamine abusers to initiate and/or maintain abstinence, to alleviate withdrawal symptoms, and prevent relapse (Johnson and Vocci, 1993).

Rationale for Studying Bupropion. We propose to evaluate the dopaminergic agent, bupropion, for treatment of methamphetamine dependence. As the list of potential candidates is extensive, this agent was selected for study based on the following criteria:

1. The investigational compound should display a dopaminergic mechanism combined with ability to alleviate the dysphoria seen in early abstinence to reduce craving, and to prevent the possibility of relapse.
2. The investigational compound should be a well-tolerated marketed drug with a good safety record.

Bupropion is an antidepressant of aminoketone class that is chemically unrelated to tricyclic, tetracyclic, selective serotonin reuptake inhibitors (SSRIs), or other known antidepressant agents. The mechanism of its antidepressant action may be related to its mild dopaminergic activity. Bupropion is considered to be a dopaminergic antidepressant based on its ability to inhibit the uptake of dopamine more selectively than it inhibits uptake of norepinephrine or serotonin. Bupropion has a favorable side effect profile: it causes fewer anticholinergic, cardiovascular, sedative or adverse sexual effects than tricyclics and does not cause weight gain (Medical Letter on Drugs and Therapeutics, 1989, Vol 31, p. 804).

Bupropion is a relatively weak inhibitor of the neuronal reuptake of dopamine and thus has a low abuse liability (Nomikos *et al*.,1989). Its potency to block dopamine reuptake in animals manifests at doses higher than those necessary for its antidepressant effect. It is possible however that the mild dopaminergic activity that bupropion does possess is sufficient to exert anti-craving effect and to treat the signs of withdrawal.

Bupropion has been proved to be effective for treatment of nicotine dependence (Hurt *et al.,* 1997; Goldstein, 1998) and is FDA-approved and marketed as Zyban, a non-nicotine aid to smoking cessation. Bupropion has been investigated for treatment of cocaine abuse. In a pilot study, Margolin *et al.* (1991) found that bupropion 300 mg/day, administered to five cocaine-dependent methadone-maintenance patients substantially reduced cocaine use in four of the five,

was well tolerated and reduced self-reported craving for cocaine. A multicenter placebo-controlled double-blind clinical trial of bupropion for cocaine dependence in methadone-maintenance patients indicates efficacy of bupropion for the subgroup of patients with depression at study entry (Margolin *et al.,* 1995).

The results of animal studies designed to test the ability of bupropion to block effects of methamphetamine support clinical use for the treatment of methamphetamine dependence (Kim *et al.,* 2000). Thus, bupropion provides complete protection against methamphetamine-induced decrease in dopamine uptake in striatum in *in vitro* model of methamphetamine-induced dopamine nerve terminal toxicity. It is logical to postulate that combination of bupropion's dopaminergic activity and antidepressant properties may guarantee its efficacy in clinical trials for treatment and relief of the signs and symptoms of methamphetamine withdrawal and for prevention of the relapse.

Bupropion Pharmacokinetics. Tablets of bupropion hydrochloride come in immediate- and sustained-release (SR) formulations. The bupropion SR, 150 mg, twice daily formulation will be used for this study. Bupropion SR has been shown to be bioequivalent to 100 mg three times daily of the immediate release formulation with regards to rate and extent of absorption and parent drug and metabolites in clinical trials for depression. Better compliance is expected with twice daily dosing as opposed to thrice daily dosing making bupropion SR an obvious choice for study.

The half-life of bupropion is approximately 21 hours after chronic dosing. Peak plasma concentrations of bupropion are achieved within 3 hours following oral administration. It appears there is no clinically significant delay in absorption due to food. Steady state plasma concentrations of bupropion are reached within 8 days. Four basic metabolites have been identified. These metabolites are pharmacologically active, but their potency and toxicity relative to bupropion have not been totally characterized. They may be of clinical importance because the plasma concentration of metabolites is higher than those of bupropion.

Psychosocial Interventions for Methamphetamine Dependence. Combinations of pharmacologic interventions with psychosocial counseling has become a standard approach in drug development trials due to the additive or synergistic efficacy of combined modalities. Methamphetamine users tend to have poor treatment retention, with only 42% completing the course of treatment and nearly 60% relapsed in the year following treatment (CALDATA, cited in NEDTAC, 1998). Psychosocial counseling improves treatment retention and thus may be a key element in pharmacologic intervention studies. This is supported by analysis of the smoking cessation literature, in which it was found that adding behavioral therapy to nicotine replacement, doubled the quit rate evident with replacement therapy alone and vice versa. Adding nicotine replacement to behavioral therapy essentially doubled smoking cessation rates (Hughes and Glazer, 1992). Similarly, the heroin, cocaine and alcohol addiction treatment literature shows good results from the combination of medication and behavioral interventions (Callahan, 1980; Grabowski *et al.*, 1992; O'Malley, 1992). The combination of behavioral interventions with methadone treatment results in reduced opiate use and increased attendance/retention rates (Hall, *et al.,* 1979; Higgins, *et al*., 1986; Iguchi, *et al*. 1988; Magura, *et al*., 1988; McCaul *et al.*, 1984; Milby *et al*., 1978; Rhoades *et al*., 1991; Stitzer *et al*., 1982;

1992; 1993). Overall, the existing evidence for combining medication and behavioral interventions indicates the efficacy of this approach in the treatment of methamphetamine dependence (Huber *et al*. 1997).

Psychosocial Treatment Platform. In contrast to opioid dependence treatment trials in which medication effects are large, methamphetamine dependence prevention trials require psychosocial interventions that are robust enough to make participants return to the clinic. Studies with inadequate psychosocial support may suffer from excessive early termination, which distorts conclusions regarding the efficacy of medication (Ling and Shoptaw, 1997). Thus, use of adequate cognitive behavioral therapy (CBT) strategies is very important. CBT was developed during the 1980's and is based on a set of social learning theory techniques. These techniques refer to a wide range of strategies designed to prevent relapse to addictive behaviors, including cocaine use, heavy alcohol use, overeating, and tobacco smoking. Common among the varieties of CBT strategies is the primary focus on maintenance in the habit change process, i.e., preventing occurrence of initial lapses after one has embarked on a program of habit change, and/or preventing any lapse from escalating into a total relapse (Marlatt and Gordon, 1985). Under the direction of Dr. Rawson, our group has been active in developing and assessing the Matrix Model of Relapse Prevention Counseling (Shoptaw *et al.,* 1994). The efficacy of this Model in the treatment of methamphetamine dependence has been demonstrated (Huber *et al.*, 1997), and it is currently being evaluated in seven U.S. sites as treatment for methamphetamine dependence compared to "treatment as usual". Overall, CBT is a feasible strategy that is generally well accepted by patients seeking treatment, and will be used in this study.

5 STUDY OBJECTIVES

5.1 PRIMARY OBJECTIVE

The primary objective of this study is to assess the efficacy of bupropion in reducing methamphetamine use in subjects with methamphetamine dependence (DSM-IV criteria). The null hypothesis is that bupropion treatment, compared to placebo, will result in a statistically significant difference (two-sided $p < 0.05$) in the weekly proportion of methamphetamine-free urines.

5.2 SECONDARY OBJECTIVES

Secondary objectives include:

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

2. Assessing the efficacy of bupropion in other measures of success in the reduction of methamphetamine use including the proportion of successful subjects with 3 consecutive weeks of negative urine samples as measured by 9 consecutive negative urine samples for methamphetamine, the weekly mean proportion of non-use days assessed by self report of use, the largest number of consecutive methamphetamine non-use days, and reductions in use as compared to baseline.

3. Assessing the efficacy of bupropion in the reduction in the severity of methamphetamine dependence (assessed by ASI-Lite and self and observer scored CGI) and craving (assessed by BSCS), and severity of depression (assessed by HAM-D) as compared to placebo control.

4. Assessing the efficacy of the bupropion in reducing the proportion of use-days of other substances of abuse (opiates, marijuana, cigarette smoking, alcohol, and cocaine) as determined by SUR and the number of negative urines for other substances of abuse (amphetamines, cocaine, opiates, tetrahydrocannabinol, benzodiazepines, and barbiturates) by urine drug screen, or negative alcohol breathalyzer tests.

5. Assessing the effects on HIV risk taking behaviors.

6. Assessing the effects of bupropion on neurocognitive functions.

7. Assessing the reduction in methamphetamine use as a function of the resolution of depression in bupropion *versus* placebo groups.

6 IND HOLDER

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

7 STUDY SITES

The trial will be conducted as a multi-center 5-site study coordinated by the University of California, Los Angeles- Integrated Substance Abuse Programs and conducted by investigators associated with 5 organizations including the 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 (Office of Research, Lutheran Hospital) Des Moines, Iowa.

8 STUDY DESIGN

8.1 EXPERIMENTAL DESIGN

This is a double-blind, placebo-controlled, two arm study with a parallel-group design in which, after screening and a 2-week baseline period (the screening period may be extended to 4 weeks if entry criteria are not met in the first two weeks), subjects will be randomly assigned to treatment with either placebo or bupropion for 12 weeks with a final follow-up assessment 4 weeks after completion of treatment. Adaptive randomization will be used to balance treatment groups based on gender, historical self-report of methamphetamine use (prior use in the last 30 days ≤ 18 *versus* > 18), and severity of depression (HAM-D score ≤ 12 *versus* >12). All subjects will receive a base of standardized, manual-driven CBT (a 90-minute group session) three-time-a-week used in our other stimulant trials (Huber *et al.,* 1997; Rawson *et al.*, 1995; Shoptaw *et al.,* 1994) during the 12-week treatment period.

8.2 OUTCOME/RESPONSE MEASURES

The principal outcome measure is urine methamphetamine analysis. 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. Measuring reductions in drug use assessed by self-report of use;
2. Assessing the severity of methamphetamine dependence using the ASI-Lite and self and observer scored CGI;
3. Assessing changes in craving (determined BSCS);
4. Assessing the severity of withdrawal symptoms (determined by MAWQ),
5. Assessing changes in depression (determined by HAM-D score) and the association of these changes with reductions methamphetamine use;
6. Assessing the effect on the use days of other substances of abuse (opiates, marijuana, cigarette smoking, cocaine, and alcohol) as determined by self-report and negative urine (opiates, tetrahydrocannabinol, amphetamines, cocaine, benzodiazepines, or barbiturates) or alcohol breathalyzer results;
7. Assessing the effect on HIV risk taking behaviors;
8. Assessing the effect on cognitive functions; and
9. Safety of bupropion in the study population.

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. In addition, the HRBS will be assessed for population descriptive and other scientific uses and not as a primary or secondary outcome measure.

8.3 BLINDING PLAN

The investigational agents, bupropion and placebo, will be supplied by the Murty Pharmaceuticals, Inc. in high density polyethylene bottles with child resistant caps that do not reveal the identity of the investigational agent. The bottles will be labeled with a product label and a subject label.

8.4 RANDOMIZATION PLAN

Adaptive random allocation of subjects to study groups was developed to balance groups with respect to screening prognostic variables. The procedure allocates treatment assignment based on the assignments and prognostic variable levels for all previously enrolled subjects. The treatment groups will be balanced with respect to gender, historical self-report of methamphetamine use (prior use in the last 30 days ≤ 18 *versus* > 18), and severity of depression (HAM-D score ≤ 12 *versus* >12). A new subject will be randomized with a "biased coin" procedure, which uses randomization probabilities, favoring the treatment with the deficit enrollment, to improve the balance on group assignment. The randomization process will be performed by KAI.

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 a matching placebo agent along with CBT according to the same schedule as those in the treatment arm.

8.6 DEFINITION OF STUDY POPULATIONS

The intent-to-treat study population is defined as the subjects who provide informed consent, and are enrolled, randomized, and receive at least one dose of investigational agent. The evaluable study population is defined as the subjects who are eligible to participate in the study in accordance with the inclusion and exclusion criteria, complete randomization, and provide at least 6 urine specimens and 28 days of self-report of substance use after enrollment.

9 SUBJECT IDENTIFICATION

Approximately, 30 male and female subjects with methamphetamine dependence will be randomized and enrolled at each study site (150 total). 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 participants who participate in this project will reflect the overall gender and ethnic characteristics of the clinic clientele. Participation of women and minorities in this project will be encouraged. Attempts will be made to enroll at least 30% female subjects 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 each site's Institutional Review Board (IRB).

9.1 INCLUSION CRITERIA

Participants must:

1. Be males and/or females, between 18 and 65 years-of-age.

2. Have a DSM-IV diagnosis of methamphetamine dependence as determined by SCID.

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

4. Be willing and able to comply with study procedures.

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

6. Be seeking treatment for methamphetamine dependence.

7. If female, have a negative pregnancy test and agree to use one of the following methods of birth control:

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

9.2 EXCLUSION CRITERIA

Participants must not:

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

2. Have a current or past history of seizure disorder, including alcohol- or stimulant-related seizure, febrile seizure, or significant family history of idiopathic seizure disorder.

3. Currently be using drugs that lower seizure threshold.

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

5. Have psychiatric disorders, such as major current depression, psychosis, bipolar illness, organic brain disorder, or dementia as assessed by the SCID interview, which require ongoing medication treatment or which would make medication compliance difficult. Have had electroconvulsive therapy within the past 90 days before screening, or have a history of Bipolar I Disorder (see Notes).

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

7. Have a current or past history of anorexia nervosa or bulimia disorder.

8. Have serious medical illnesses or neurological disorders including, but not limited to, uncontrolled hypertension, significant heart disease (including myocardial infarction within one year of enrollment), angina, hepatic or renal disorders, renal insufficiency (plasma creatinine > 1.7 mg/dL), Parkinson's disease, active syphilis that has not been treated or refuse treatment for syphilis (see note), or have had therapy with any opiate-substitutes (methadone, LAAM, buprenorphine) within 2 months of enrollment, or any serious, potentially life-threatening or progressive medical illness other than addiction that may compromise subject safety or study conduct. 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.

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

10. 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.

11. 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.

12. Be undergoing HIV treatment with antiviral and/or non-antiviral therapy.

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

14. Have CD4 (+) T-lymphocytes blood counts <500 cells/mm^3.

15. Have known or suspected hypersensitivity to bupropion.

16. Be using bupropion or any medication that could interact adversely with bupropion, within the following times of beginning of administration of bupropion 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; or
C) Interval recommended by other medication's product labeling.

Medications that fall into this category include:

a. Bupropion (Wellbutrin®, Zyban®) used during the past 30 days
b. All antidepressants
c. Neuroleptics
d. Systemic corticosteroids
e. Xanthines, i.e., theophilline, theophilline sodium glycinate and aminophylline

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

18. Be pregnant or lactating.

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

20. Have active tuberculosis (positive tuberculin test and confirmatory diagnostic chest x-ray).

21. Have a diagnosis of adult (i.e., 21 years or older) asthma, or chronic obstructive pulmonary disease (COPD), including those with a history of acute asthma within the past two years, and those with current or recent (past 3 months) treatment with inhaled or oral beta-agonist or steroid therapy (because of potential serious adverse interactions with methamphetamine).

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 offered HIV testing during screening but may not have the test performed until after enrollment. This test is offered as a courtesy to the prospective subjects 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. If the prospective subject can provide evidence that they have been previously treated for syphilis or undergoes treatment for syphilis, they can be enrolled upon providing proof of successful treatment for syphilis.

The infectious disease panel for hepatitis and tuberculosis is performed as an aid to determine if the prospective subject has active hepatitis or tuberculosis. Either will exclude the prospective subject from participation according to exclusion criterion number 8 (serious medical illnesses) or number 20 (have active tuberculosis). All subjects who test positive for tuberculin PPD will be referred and scheduled to have a chest X-ray. Those that do not actually have tuberculosis will not be excluded from the study. Those that show a positive chest X-ray for tuberculosis will be excluded from the study. Prospective subjects who test positive for hepatitis will be evaluated by the site investigator for eligibility. Those subjects will be excluded if they have acute hepatitis or chronic active hepatitis, based on symptoms serology, and/or abnormal liver functions (see Appendix I). Subjects who test positive for hepatitis will be referred for treatment as well as those who show positive chest X-ray for tuberculosis.

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.

Bupropion is an antidepressant, so depressed subjects will be receiving effective treatment, granted some subjects will be randomized to placebo. This is not different from randomized double-blind trials for major depression. By monitoring subjects closely both clinically and through biweekly HAM-D scores, if we see deterioration in depression or emergence of suicidal ideation, subjects will be excluded from the study and referred for treatment.

10 INVESTIGATIONAL AGENTS

Bupropion SR tablets, 150 mg, and matching placebo will be supplied by Murty Pharmaceuticals, Inc., (Lexington, KY) under a contract with NIDA. GSK's Zyban (bupropion) SR tablets, 150 mg, will be film-coated by Murty Pharmaceuticals to mask information on tablet surface. Matching placebo will be manufactured by Murty Pharmaceuticals. Data show that the film coating has negligible effect on the dissolution of Zyban SR tablets.

10.1 DISPENSING INVESTIGATIONAL AGENTS

Murty Pharmaceuticals will distribute the investigational agents packaged in HDPE bottles with child-resistant closure to investigators or designated Research Pharmacists at the clinical sites for dispensing to subjects. Used and unused investigational agents will be collected and inventoried each week and a study agent compliance CRF will be completed.

Investigational agents will be dispensed to subjects once per week at the first clinic visit of the week. Investigational agents will be distributed directly to the subject by the investigative staff

depending upon local site procedures. The subject will be thoroughly instructed on how to administer investigational agents.

Subjects will be instructed to store the medication at room temperature without exposure to direct sunlight. Subjects will be instructed to consume the morning dose between 8:00 and 10:00 a.m. and the evening dose between 4:00 and 6:00 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. Administration of the daily dose in divided doses of maximum 150 mg twice daily, at least 8 hours apart, should minimize the risk of seizures. Unused investigational agents will be collected and inventoried each week.

10.2 LABELING

Investigational agents will be packaged in HDPE bottles with child-resistant closure with a 10-day supply. The bottles will be labeled by Murty Pharmaceuticals with the drug name ("bupropion/placebo"), the random dose code, and the following statement – Caution: New Drug – limited by federal law to investigational use. 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 12), and the number of tablets to take per day (i.e., 1 tablet on days 1-3 and days 82-84 and 2 tablets on days 4-81).

The label will also include a warning indicating that this medication should be kept out of children's reach. Special labels will be prepared for each site indicating the local Principal Investigator's name and 24-hour emergency telephone number.

10.3 STORAGE

Investigational agents will be stored at room temperature without exposure to direct sunlight in a secure location in the distributing pharmacy or at each investigator's facility.

10.4 RECORD OF ADMINISTRATION

Accurate recording of all investigational agent dispensing/administration will be made in the appropriate section of the CRF. On the first clinic visit of each week, subjects will be asked to return the bottle and all unused investigational agent. Unused study agent will be inventoried for discrepancies. Patients who have not been taking their tablets 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 Treatment Compliance Study Drug Form.

10.5 SAFETY CONSIDERATIONS

One of the potentially most serious adverse effects of bupropion is reduction in the seizure threshold (Johnston *et al.,* 1991, Settle, 1998, Storow, 1994). Bupropion is contraindicated in

patients with a seizure disorder or a predisposing factor for seizures (e.g., cranial trauma history, current seizure disorder, concomitant use of drugs that lower seizure threshold). However, the relative risk of seizures with various antidepressants, including bupropion, has not been clearly defined and the incidence of seizures at doses of 400 mg daily as extended release tablets increases to 0.4%.

The incidence of seizures with bupropion depends on dose. Minimizing the risk of seizures includes restriction of total dosage to 400 mg daily as sustained-release. Administration of the daily dose in divided doses up to 150 mg twice daily, at least 8 hours apart, should minimize the risk of seizures.

Subjects will be cautioned not to take concomitant medications, whether prescription or over the counter (OTC) medications, or herbal supplements without consulting the site principal investigator or study physician.

These include:

- All antidepressants
- Neuroleptics
- Systemic corticosteroids
- Xanthines (i.e., theophilline, theophilline sodium glycinate and aminophylline)
- Medications that interfere with methamphetamine detection in urine samples (e.g. ephedrine and pseudoephedrine)

Subjects will be asked to inform a study physician, if they decide to use any smoking cessation products such as nicotine gum, nicotine patch, nicotine nasal spray or nicotine inhaler while on study. If any agents are used, blood pressure should be monitored closely as bupropion may increase blood pressure when used with these smoking cessation agents.

10.6 USED/UNUSED SUPPLIES

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

11 TREATMENT PLAN

11.1 INVESTIGATIONAL AGENTS

Subjects assigned to receive bupropion SR will receive 150 mg every day for the first 3 days of treatment which will be increased to 300 mg daily (one tablet twice a day) for the duration of treatment until the final dose taper. The dose will be tapered to 150 mg every day for 3 days until termination or the last scheduled day of the 12-week treatment period. Subjects will be informed that they must taper the dose for three days before stopping the investigational agents completely in the event that they decide to terminate from the study prematurely. Subjects assigned to the

placebo group will receive matched placebo on the same schedule as the active treatment group. Subjects will be instructed to take study agents at least 8 hours apart when taking agents twice daily and not to take two tablets at once if a dose is missed. During the last 3 days of treatment during week 12 or before termination, subjects' investigational agents will be tapered down to 150 mg (or equivalent placebo) each day by taking only one tablet per day.

11.2 COGNITIVE BEHAVIORAL THERAPY

The CBT program will consist of thrice weekly, 90-minute group sessions through the 12-week trial. 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 16-to-20 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 and baseline 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 12. Baseline assessments will occur over a two-week period. If a subject fails to provide a minimum of four completed 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 after consent is signed. 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 screening failure.

12.3 SUBJECT ENROLLMENT AND RANDOMIZATION

If the prospective subject meets all of the study inclusion criteria, 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 KAI 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 KAI 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 KAI.

12.4 TREATMENT PHASE

At the first clinic visit, subjects will be given instructions on how to administer the investigative agent, Bupropion or placebo, and will be given a one-week supply. This is a double-blind study in which neither the subject nor the site staff will know if the subject is receiving the investigational drug or the placebo. 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.

Subjects will be scheduled for treatment and assessment visits three times per week usually on a Monday, Wednesday, and Friday for 12 weeks. Two consecutive days may be scheduled around

holidays or other schedule conflicts. All subjects will be offered an opportunity for HIV testing and counseling and HIV/AIDS education (Appendix II). All subjects will be provided with CBT three times per week during the 12 weeks of treatment. Clinical evaluations are described in detail in section 12.

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 12) or at the time of premature treatment discharge, subjects will be asked to come to complete the 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 SUR will be completed.

12.6 DROP-OUT PREVENTION

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 investigational agents. If a subject decides to drop out of the study prior to week 12, 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 CBT sessions, s/he will continue to have all scheduled assessments according to the protocol and will complete the study at week 12. 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 12 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 16)

Subjects will be asked to return to the clinic 30-days after completion of treatment. During the follow-up interview (week 16 or 4 weeks after the premature treatment discharge 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, cocaine, opiates, alcohol, cigarette smoking, 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 form. 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 drug use, current treatment for drug or alcohol abuse. Concomitant medications and adverse events will be assessed over the telephone as well as the follow-up form. 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 principal investigator and project principal investigator or with the NIDA medical monitor, but should be resorted to only in cases of life-threatening emergency when knowledge of the treatment arm investigational drug will influence clinical management.

12.9 SAFETY PROCEDURES

Participants judged by the site principal 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 clinic visit in which a urine specimen is provided during screening and the 12 weeks of treatment as reimbursement for their time and travel expense. Travel expenses (bus and cab fares) may be paid with 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 16 follow-up assessment. Payment will be made upon completion of the specified requisite assessments for a maximum payment of $530 in retail scrip or vouchers. They 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 and 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 of the following reasons: (1) significant side effects from investigational agents, (2) serious or unexpected AEs, (3) failure to comply with the study protocol, (4) protocol violation, (5) positive pregnancy test, (6) serious intercurrent illness or a benzodiazepine or barbiturate medication use (see below), and (7) the subject becomes a danger to self or others. Persistent alcohol abuse will be assessed by the PI or study physician and after the third warning and consultation with NIDA, the subject may be terminated from the study.

Benzodiazepine and Barbiturate Abuse. If a subject starts using a benzodiazepine or barbiturate medication while in the study, they will likewise be given a warning by the site principal investigator or study physician to stop using these drugs, and any benzodiazepine or barbiturate urine positive beyond 3 weeks after the date the warning was given will result in discontinuation of bupropion. A three-week interval is warranted due to the long elimination time of some benzodiazepines. If a subject is prescribed a benzodiazepine or barbiturate for legitimate medical purposes, subjects will be warned that any abrupt discontinuation of either medication are known to lower seizure threshold.

Failure to comply with protocol. A subject will no longer be eligible for study participation, if s/he is absent from the clinic for more than two consecutive weeks and does not provide any data. Study participation will end if subjects miss six consecutive relapse prevention groups or consecutive urine samples. In any event, subjects will be contacted 4 weeks after treatment discharge to schedule a follow-up data interview.

Voluntary withdrawal. A subject may withdraw from the study anytime s/he wishes. In the event a subject is discontinued from receiving the investigational agents, s/he will be allowed to continue the CBT treatment with the approval of the site principal 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 the treatment discharge interview as well as 4 weeks after discharge for the follow-up interview.

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

All study participants will be encouraged to carry a wallet card that identifies them as a participant in a clinical research study. The card will provide the name and phone number of the site principal investigator (physician) at the site who can be contacted in the event of an emergency. If possible, the card should 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

NIDA and/or the study sponsor 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 site principal investigator. Medications that should not be taken at any time during the study are presented in section 10.5.

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 approximately 20-30 minutes. Assessments conducted at termination require no more than 120 minutes to complete. The assessments during follow-up are completed in 20-30 minutes.

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 fails to be eligibility requirements are discontinues screening before eligibility is established.

1. Informed consent
2. Locator form
3. Demographics
4. Complete medical history and medical history addendum for females.
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 follow-back for methamphetamine and alcohol use in the prior 30 days
9. ADD interview
10. Prior medications for the 30 days prior to informed consent
11. ASI-Lite

Table 1. Overview of Study Assessments

Assessment	Screening/ Baseline*	Treatment							Termin-ation	Follow -up
Study Week	-4 to 0	1	2 &3	4	5. 6, & 7	8	9, 10, & 11	12		
Screening/Subject Characteristics										
Informed consent	X									
Locator Form	X									
Demographics	X									
Timeline follow-back (meth/alcohol)	X									
SCID	X									
ADD interview	X									
Medical history/addendum for females	X									
Prior medications	X									
Infectious disease panel/RPR	X									
HIV test (optional)	X									
Alcohol breathalyzer	3 X/week	3X	3X	3X	3X	3X	3X	3X	X	
Safety										
Physical exam/FEV_1[a]	X								X	
Vital signs	X	X	X	X	X	X	X	X	X	
Hematology	X								X	
Blood chemistries	X								X	
Medical urinalysis	X								X	
Pregnancy test	X			X		X			X	
ECG	X								X	
Adverse events	3X/week	3X	3X	3X	3X	3X	3X	3X	X	X
Concomitant medications	3 X/week	3X	3X	3X	3X	3X	3X	3X	X	X
Efficacy										
ASI-Lite	X								X	
HAM-D	biweekly		X[d]	X	X	X	X	X	X	
BSCS	weekly*	X	X	X	X	X	X	X	X	
CGI-S	weekly*	X	X	X	X	X	X	X	X	
CGI-O	weekly*	X	X	X	X	X	X	X	X	
MAWQ	3 X/week*	3X	3X	X	X	X	X	X	X	
HRBS	X								X	
SUR	3 X/week*	3X	3X	3X	3X	3X	3X	3X	X	X
Urine methamphetamine/creatinine[b]	3 X/week*	3X	3X	3X	3X	3X	3X	3X	X	X
Urine tox screen at NWT[b]	once weekly*	X	X	X	X	X	X	X	X	X
Urine tox screen onsite test device[c]	3 X/week*	X	X	X	X	X	X	X	X	X
Cognitive function tests	X								X	
Treatment compliance – CBT		3X	3X	3X	3X	3X	3X	3X	X	
Treatment compliance-tablets (timeline follow-back)		X	X	X	X	X	X	X	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] 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 criteria 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.
[d] HAM-D will be performed biweekly at screening, baseline, at week 2, 4, 6, 8, 10 and at termination.
*Those measures that are a subset of the screening measures that constitute baseline assessments are indicated with an asterisk. Baseline measures are collected for 2 weeks. BSCS, CGI-S and CGI-O will be done once weekly during screening, baseline, treatment and at termination. NOTE: Once weekly assessments are performed preferably at the first clinic visit.

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 will 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: Methamphetamine assay will be performed only for the urine samples collected for the subjects who meet the eligibility criteria 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). This is only for subjects who are randomized on the study.

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

4. HAM-D will be administered biweekly.

13.3 ASSESSMENTS DURING TREATMENT

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

At each visit:
1. 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 (starting at week 3 – for the first two weeks it is collected 3 times per week)
7. Vital signs

At weeks 4 and 8, preferably at the first visit of the week:
1. Pregnancy test

At week 2, 4, 6, 8, 10 and 12, preferably at the first visit of the week:
1. HAM-D

NOTE: Blood chemistries and hematologies will be performed during the course of treatment if considered necessary by a study principal investigator.

13.4 ASSESSMENTS AT TERMINATION

As soon after the last dose of investigational agent is administered (at the end of treatment week 12) or if the subject discontinues prematurely, regardless of the reason (request that the subject return for final assessments), the following assessments will be performed:

1. If the subject discontinued prematurely, determine the reason for termination.
2. Physical exam (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 Test
18. ASI-Lite
19. HRBS

20. HAM-D
21. ECG
22. Cognitive function tests
23. Concomitant medications
24. Treatment compliance (study agents and CBT)
25. End of Trial form

13.5 ASSESSMENTS AT FINAL FOLLOW-UP (WEEK 16)

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 participants at follow-up. This form asks participants 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 updated throughout the study as necessary.

13.6.2 Structured Clinical Interview (SCID)

A SCID to assess the subject's methamphetamine-dependence according to DSM-IV criteria, severity of depression, and Axis-I disorders will be conducted.

13.6.3 ADD Interview

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

13.6.4 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 principal investigator/study physician to assure medical fitness.

13.6.5 Medical History Addendum for Females

For female participants only, an addendum to the medical history profile will be conducted by the principal investigator/study physician. This addendum will ensure that all female participants 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.

13.6.6 Prior Medications

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

13.6.7 Vital Signs

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

13.6.8 Physical Exam

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

13.6.9 Hematology

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

13.6.10 Blood Chemistries

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

dehyrodrogenase (LDH), creatinine phosphokinase (CPK), alkaline phosphatase (ALP), blood urea nitrogen (BUN), uric acid, and iron. Blood chemistries will be performed at a central clinical laboratory. Laboratories performing these assessments should be either directly regulated by CAP or CLIA or indirectly according to CLIA guidelines. The laboratory will need to provide a copy of current certification.

13.6.11 Infectious Disease Panel/Syphilis Test

Blood will be collected in serum separation vacutainer tubes 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 or MHA-TP confirmatory test will be performed. These tests will be conducted at a central clinical laboratory.

13.6.12 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.

13.6.13 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 childbearing capacity. A pregnancy form must be completed for all subjects (including males).

13.6.14 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, tricyclics, and phencyclidine). Samples positive for amphetamine (the onsite testing device has a cutoff of greater than or equal to 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.

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.

13.6.15 Breathalyzer Test

The breathalyzer or breath alcohol test will be administered to assess recent alcohol use.

13.6.16 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.

13.6.17 Inclusion/Exclusion

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.

13.6.18 Adverse Events (AEs)

AEs will be assessed and recorded at each visit by an investigative staff nurse or 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 staff nurse, research assistant or the physician will assess AEs by asking the participant "How have you been feeling since I saw you last". The type of AE, severity of the AE, and the relationship to the study treatments will be recorded on an AE CRF according to the procedures described in section 13.6.

13.6.19 Methamphetamine Withdrawal Questionnaire (MAWQ)

The current version of the MAWQ created for NIDA sponsored clinical trials for the treatment of methamphetamine dependence will be used.

13.6.20 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 form. The reported medications will be reviewed by the site investigator/study physician for possible drug interactions. Medications that should not be taken at any time during the study are the following: all antidepressants, neuroleptics, systemic corticosteroids, and xanthines, i.e., theophilline, theophilline sodium glycinate and aminophylline.

13.6.21 Hamilton Depression Rating Scale (HAM-D)

The HAM-D is an interviewer-administered assessment of the subject's level of depression (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 will be administered by study research staff (i.e., project coordinator, research assistant) who will receive training on completing this measure.

13.6.22 Addiction Severity Index (ASI)-Lite CF Version

The ASI-Lite, 2000 version (McLellan *et al.,* 1992), will be administered by a research staff member having at least a bachelor's degree in the social sciences or equivalent training and experience as determined by the site's investigator. The ASI-Lite is the interviewer's estimate of the severity of the subject's status in seven areas (medical, employment, drug use, alcohol use, legal, family/social, and psychological). Composite scores will be calculated according to the procedures described by McGahan *et al*. (1982) and Carroll *et al*. (1994). The Lite version is a shorter version of the ASI that still retains all questions used to calculate the ASI composite scores.

13.6.23 Substance Use Report (SUR)

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

13.6.24 Brief Substance Craving Scale (BSCS)

The BSCS is a self-administered assessment that asks the participant 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. If the participant 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 participant and/or marking the participant's response on the CRF. However, study personnel are not to offer interpretations of the questions.

13.6.25 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 symptoms 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.

13.6.26 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.

13.6.27 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. Study personnel are not to offer interpretations of the questions.

13.6.28 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 discharge. Each participant will be tested twice on all of the tests with the exception of the Repeated Memory Test (RMT). RMTs are tests that show an effect of repeated administration (Basso, 1999). Two forms of the RMT will be administered.

The participants 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 D2 test of Attention takes an additional 8 minutes. The total time to administer the battery is about 25-30 minutes.

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.

13.6.29 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.

13.6.30 Treatment Compliance

Treatment compliance will be monitored by recording the amount of investigational agents taken by each subject at each treatment and recorded on a form weekly. The timeline followback method will be used to assist the subject in reporting of the amount of tablets 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 Treatment Compliance Study Drug Form. Compliance with CBT will be monitored by recording the length of time the subject spent in attendance at each therapy session and recorded on a form for each visit.

13.6.31 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.

13.6.33 Timeline Follow-back

Detailed histories of methamphetamine and alcohol use over the past 30 days prior to screening will be obtained using the timeline follow-back 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 tablet usage reported by the subject for treatment compliance determinations.

14 REGULATORY AND REPORTING REQUIREMENTS

14.1 FDA FORM 1572

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

14.2 IRB APPROVAL

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

14.3 INFORMED CONSENT

A two-part informed consent form will be used. 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. The consent will be for the 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.

14.4 DRUG ACCOUNTABILITY

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

14.5 OUTSIDE MONITORING

Data and Safety Monitoring Board: Safety data will be reviewed by a data and safety monitoring board that will meet after the first 50 subjects have been enrolled and again at the end of the study. Additional meetings may be held on an *ad hoc* basis. The board will be unblinded to subjects' actual treatment assignments for the safety data. Reports from the DSMB will be sent

to the project principal investigator and site principal investigators for transmission to their respective IRBs, in accordance with NIH policy.

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

Clinical Monitors: All investigators will allow representatives of the sponsor to periodically audit, at mutually convenient times during and after the study, all CRFs and corresponding source documents for each subject. These monitoring visits provide the sponsor with the opportunity to evaluate the progress of the study and to inform the sponsor of potential problems at the study sites. The monitors will assure that submitted data are accurate and in agreement with source documentation; verify that investigational medications are properly stored and accounted for, verify that subjects' consent for study participation has been properly obtained and documented, confirm that research subjects entered into the study meet inclusion and exclusion criteria, and assure that all essential documentation required by good clinical practices guidelines are appropriately filed.

Monitors will conduct a site initiation visit prior to the start of the study. At this visit, they will assure that proper study-related documentation exists, assist in training investigators and other site personnel in study procedures and compliance with good clinical practice guidelines and FDA regulations, 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 investigational agents. All sites should anticipate visits by NIDA, the IND sponsor, 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.

14.6 ADVERSE EVENTS REPORTING

In accordance with FDA reporting requirements, all AEs occurring during the course of the clinical trial will be collected, documented, and reported by the principal 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 at each study visit and an AE CRF completed weekly.

An AE is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial, whether or not the event is considered medication-related 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 Form. The AE Form is also used to record follow-up information for unresolved events reported on previous visits.

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

14.7 SERIOUS ADVERSE EVENTS

Each adverse event or reaction will be classified by the study investigator as serious or non-serious. Based on the seriousness of the adverse event or reaction appropriate reporting procedures will be followed. The International Conference on Harmonization (ICH) Guideline for Industry: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH-E2A March 1995, as implemented by the U.S. Food and Drug Administration defines serious adverse event (SAE) or reaction as any untoward medical occurrence that at any dose:

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

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

Any SAEs due to any cause, that occur during the course of this investigation, whether or not related to the investigational agent, must be reported within 24-hours by telephone to: the Study Medical Monitor, the NIDA Project Officer/Project Manager, the UCLA Coordinating Center, 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

NIDA Project Manager: Edwina " Pat" Smith, RN,BC, M.S. 301/443-1061

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 Concomitant Medication Form, and the Medical History Form from the subject's CRFs. All serious medical events are also to be reported to the responsible IRB according to local regulatory requirements. All participating investigators will be notified of any serious and unexpected AE requiring submission to the FDA in an IND safety report from the investigator-sponsor.

Any fatal or life-threatening SAE that is investigational agent related and unexpected must be reported initially to the FDA within 7 calendar days via telephone, facsimile or e-mail with a written follow-up within an additional 8 calendar days. Any additional clinical information that is obtained must be reported, as it becomes available to the FDA.

The investigator-sponsor will inform NIDA of all SAEs that occur during the study. The investigator-sponsor is required by FDA regulations to report these to the FDA in a timely fashion. All AEs that are both serious and unexpected must be reported to the FDA, in writing, within 15 calendar days of notification of NIDA of the SAE.

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 of investigational agents or progresses to death.

15 ANALYTICAL PLAN

15.1 PRIMARY OBJECTIVE

The primary objective of this study is to assess the efficacy of bupropion in reducing methamphetamine use in subjects with methamphetamine dependence (DSM-IV criteria).

15.2 SECONDARY OBJECTIVES

Secondary objectives include:

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

2. Assessing the efficacy of bupropion in other measures of success in the reduction of methamphetamine use including the proportion of successful subjects with 3 consecutive weeks of negative urine samples as measured by 9 consecutive negative urine samples for methamphetamine, the weekly mean proportion of non-use days assessed by self report of use, the largest number of consecutive methamphetamine non-use days, and reductions in use as compared to baseline.

3. Assessing the efficacy of bupropion in the reduction in the severity of methamphetamine dependence (assessed by ASI-Lite and self and observer scored CGI), craving (assessed by BSCS), severity of withdrawal symptoms (assessed by MAWQ), and severity of depression (assessed by HAM-D) as compared to placebo control.

4. Assessing the efficacy of the bupropion in reducing the proportion of use-days of other substances of abuse (opiates, marijuana, cigarette smoking, alcohol, and cocaine) as determined by SUR and the number of negative urines for other substances of abuse (amphetamines, cocaine, opiates, tetrahydocannabinol, benzodiazepines, and barbiturates) by urine drug screen or negative alcohol breathalyzer tests.

5. Assessing the effects on HIV risk taking behaviors.

6. Assessing the effects of bupropion on neurocognitive functions.

7. Assessing the reduction in methamphetamine use as a function of the resolution of depression in bupropion versus placebo groups.

15.3 STATISTICAL HYPOTHESES

The null hypothesis is that bupropion treatment, compared to placebo, will result in a statistically significant difference (two-sided $p < 0.05$) in the weekly proportion of methamphetamine-free urines. Hypotheses for the secondary outcome measures include that bupropion treatment, compared to placebo, will reduce the pattern and quantity of methamphetamine use by various measures of success, reduce the severity of methamphetamine dependence (assessed by ASI-Lite and self and observer scored CGI), methamphetamine craving (assessed by BSCS), severity of

withdrawal symptoms (assessed by MAWQ), and depression (assessed by HAM-D), and decrease the amount of use-days of other substances of abuse (opiates, marijuana, nicotine, alcohol, and cocaine) as determined by self report of use or urine drug determination (amphetamines, cocaine, opiates, tetrahydrocannabinol, benzodiazepines, and barbiturates).

There is no generally accepted definition of clinically significant improvement in the treatment of methamphetamine dependency. The primary and secondary objectives are intended to explore various aspects of response to therapy and to help define a clinically meaningful response. The secondary objectives also add a measure of clinical relevance to the reduction of use by exploring the effect of therapy on psychosocial aspects of methamphetamine dependency.

15.4 OUTCOME MEASURES

15.4.1 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 less than 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.

15.4.2 Secondary Outcomes Measures

Effect on methamphetamine and other drug use during the 12-week treatment period

A. Log weekly median quantitative methamphetamine level.

B. The proportion of successful subjects with different patterns in the reduction in drug use examined as follows:

1. Proportion of subjects with 3 consecutive weeks of abstinence as measured by 9 consecutive methamphetamine negative urine samples.

2. Proportion of subjects who reduce the overall proportion of methamphetamine quantitative urine concentration to 50% or less of his/her baseline rate.

3. Proportion of subjects who reduce the overall proportion of methamphetamine quantitative urine concentration to 25% or less of his/her baseline rate.

C. Weekly mean proportion of methamphetamine non-use days based on subjects self report of use (SUR) during the 12-week treatment period.

D. The maximum number of consecutive methamphetamine non-use days by subjects self report of use (SUR).

E. The proportion of methamphetamine negative urines during the 12-week period.

F. Weekly mean proportion of non-use days of other drug use, by other drug according to SUR.

G. Proportion of negative urines or alcohol breathalyzer results for other drug use, by drug.

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

H. CGI-O scores.

I. CGI-S scores.

J. ASI-Lite scores.

K. BSCS scores.

L. MAWQ scores

Severity of Depression

M. HAM-D scores.

Changes in Cognitive Functions

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

HIV Risk Taking Behaviors

O. Change in HRBS scores since baseline.

Treatment Retention

P. Number of days in treatment.

Safety of Bupropion

Q. AEs, laboratory data, physical exams, and vital signs.

15.5 INTENT-TO-TREAT AND EVALUABLE SUBJECT POPULATIONS

The intent-to-treat population is defined as subjects who were randomized and received at least 1 dose of study agent. The evaluable population is defined as the subjects who are eligible to

participate in the study in accordance with the inclusion and exclusion criteria and who contribute at least six (6) usable on-study urine samples and 28 days of self-report of substance use.

15.6 ANALYSIS PLAN

15.6.1 Efficacy Assessments

Each of the primary and secondary efficacy outcome measures 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.

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.

As a secondary analysis, the individual effects, if any, of age, race, site, and usual route of methamphetamine use (oral/nasal inhalation versus intravenous/smoked) on the primary treatment effects will be determined where numbers permit. The first order interactions of these variables with gender, historical self-report of methamphetamine use (prior use in the last 30 days ≤ 18 *versus* > 18), and severity of depression (HAM-D score ≤ 12 *versus* >12) will also be included in the model. Presentation will include the full model with all terms and a reduced model containing only significant terms.

Secondary Efficacy Outcomes

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

1. Log weekly median quantitative methamphetamine, weekly mean proportion of methamphetamine non-use days by self-report, weekly mean proportion of non-use day of other drug use, measures A, C, and F, will be assessed by GEE.

2. Proportion of successful subjects and negative urines for other drugs or alcohol breathalyzer tests, measures B and G, will be assessed by Chi-square tests.

3. The maximum number of consecutive methamphetamine non-use days, proportion of methamphetamine negative urines, change in cognitive function, and change in HRBS scores at termination compared to baseline measures D, E, N, and O will be assessed by t-test.

4. Repeated measures of CGI-S, CGI-O, BSCS, ASI-Lite, MAWQ, and HAM-D scores, measures H, I, J, K, L, and M will be assessed by GEE.

5. Survival analysis will be performed on retention data (measure P). The Wilcoxon (Gehan) test will be used to test the hypothesis that the survival distribution of the bupropion group will be the same as those of the placebo group.

6. Adverse events, laboratory data, physical exams, and vital signs will be reported in tabular form. AEs will be listed indicating the frequency of each type of event by various demographic characteristics such as gender, ethnicity, age, duration of addiction, other medical problems both related to and independent of the addiction, and combinations of these characteristics. The frequencies of adverse events by type will be compared between study arms using Chi-square analyses.

15.6.2 Descriptive Statistics

Summaries of the characteristics of the subject population in both treatment arms at baseline will be prepared for both the intent-to-treat and evaluable subjects. A summary will be prepared to show dropouts/retention over time in each treatment group and for major subgroups. The number of missing observations will be compared between treatments and for major subgroups. Weekly treatment retention will be presented. Study agent compliance will be presented by investigational agent reconciliation, and subject report of use.

15.7 SAMPLE SIZE CALCULATION

The study sample size was planned to be 50 subjects in each treatment arm. As the primary outcome measure had only begun to be used for methamphetamine dependence studies, it is not possible to statistically calculate sample sizes. The number of 50 subjects in each arm was selected based on other NIDA studies of substance abuse as a number that is sufficient to provide some indication of treatment effect during preliminary investigations. To substantiate the study

sample size selected, the data of the first fifty randomized subjects was to be used to obtain estimates of the treatment effect and its variance and to estimate the total number of subjects required for the study to have 80% power at the 5% significance level. Upon this analysis, NIDA would decide to take one of three possible actions: 1) Stop the trial, 2) Complete the study of 100 patients as per the original protocol, or 3) Increase the sample size to that estimated as needed to have a definitive result.

Upon preparation of the blinded analysis of the first fifty randomized subjects for DSMB review in April 2004, it was determined that the dropout rate was 46%-50%, which was higher than expected. Thus, NIDA proposed to extend the study to 150 patients instead of 100 patients to be able to increase the amount of patient information available with approximately 12 weeks of data; this will make NIDA's evaluation more certain as to whether or not to further study the Bupropion/methamphetamine combination therapy, and, if further studied, assist in the choice of a future study design and power requirements.

15.8 CONTROL OF BIAS

The randomization process will be performed by KAI. The treatment assignment will be blinded to the subject and the research staff.

15.9 POST HOC ANALYSES

Data will be collected in this study for scientific use and not as primary or secondary outcome measures. These data are being collected to build a database that will help characterize the study population. Additional post hoc analysis may be performed to evaluate other confounding factors on outcomes such as depression or patterns of methamphetamine use at baseline and after treatment. In addition, a post hoc analysis is anticipated by *a priori* developing an algorithm for determining use and non-use days by combining self-reports of use with urine methamphetamine levels. Clinical laboratory studies are currently in progress to evaluate the pharmacokinetics of methamphetamine urine clearance. Based on the results of these studies, it is anticipated that rules for assessing new use similar to those developed by Preston (1997) for cocaine will be developed for methamphetamine. These rules will then be applied to the dataset generated by this study for analysis.

16 DATA MANAGEMENT AND CASE REPORT FORMS (CRF)

General Training. Good clinical practice (GCP) and study specific training will be held for all research staff. This training will include an overview of GCPs, site's training manuals, Standard Operating Procedures (SOP) for Clinical Research, and the study operations manual. Staff members will also receive copies of the study protocol, CRFs, operations manual, and SOPs and these materials will be reviewed with the full staff. All study personnel currently must pass a proficiency examination on the information presented in these materials prior to data collection activities. Ongoing SOP meetings are expected to focus attention toward maintaining accurate data collection and documentation procedures.

Developing an Operations Manual. An operations manual will be prepared for this study that incorporates procedures from this protocol with those procedures necessary for the day-to-day

conduct of the trial. The operations manual will be used to train study staff, to provide reference for study procedures, and to guide quality assurance activities.

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 KAI. eCRFs are to be completed on an ongoing basis during the study. The medical chart and the source documents are the source of verification of data. eCRFs should be completed according to the instructions in the study operations manual. The principal investigator is responsible for maintaining accurate, complete and up-to-date records for each subject. The principal investigator is also responsible for maintaining any source documentation related to the study, including any films, tracings, computer discs or tapes.

16.2 DATA EDITING AND CONTROL

Data received at the KAI will be reviewed. If incomplete or inaccurate data are found a data clarification request will be forwarded to the sites for a response. Sites will resolve data inconsistencies and errors prior to returning data to the KAI. All corrections and changes to the data will be reviewed prior to being entered into the main study database. NIDA/DTR&D and the participating sites will receive reports at least monthly regarding the quality and quantity of data submitted to KAI.

Participating investigators agree to routine data audits by the sponsor's designated staff, audits by the staff of the KAI and by NIDA's programmmatic staff. Monitors will routinely visit each site to assure that data submitted on the appropriate forms are in agreement with source documents. They will also verify that of 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 GCP 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 established procedures specified in the study operations manual.

16.3 DATA ENTRY, PROCESSING AND ANALYSES

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

16.4 STUDY DOCUMENTATION AND RECORDS RETENTION

Study documentation includes all CRFs, data correction forms, workbooks, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence and regulatory

documents (e.g., signed protocol and amendments, Ethics or Institutional Review Committee correspondence and approved consent form and signed subject 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 an exact duplication of the original document.

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

16.5 CONFIDENTIALITY

16.5.1 Confidentiality of Data

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

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

16.5.2 Confidentiality of Patient Records

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

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

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 each participating site's 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 bupropion 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.

A publication committee will be formed and comprised of representatives from NIDA, the UCLA Coordinating Center, and principal investigators to review and approve all documents to be submitted for publication.

18 SIGNATURES

NIDA REPRESENTATIVES

Typed Name	Signature	Date
Ahmed Elkashef, MD NIDA Investigator	_____	_____
Roberta Kahn, MD NIDA Medical Monitor	_____	_____
Jurij Mojsiak, M.S. NIDA Project Officer	_____	_____
Edwina Smith, R.N.,B.C., M.S. NIDA Project Manager	_____	_____

INVESTIGATOR (S)

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

Typed Name	Signature	Date
Richard Rawson, Ph.D. Coordinating Center Principal Investigator	_____	_____
Thomas Newton, M.D. Subinvestigator	_____	_____
Walter Ling, M.D. Subinvestigator	_____	_____
Michael J. McCann, M.A. Site Principal Investigator	_____	_____
Jan Campbell, M.D. Site Principal Investigator	_____	_____
William Haning, M.D. Site Principal Investigator	_____	_____

SIGNATURES CONTINUED

Joseph Mawhinney, M.D. _____ _____
Site Principal Investigator

Dennis Weis, M.D. _____ _____
Site Principal Investigator

Thomas Pham, M.D. _____ _____
Site Subinvestigator

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

Blood Chemistry and Hematology

Analyte	Values	
Glucose (mg/dL)	<40	>140
AST (SGOT)		> 2.5X ULN*
ALT (SGPT)		> 2.5X ULN
Alkaline Phosphatase		> 2.5X ULN
Lactate Dehydrogenase		> 2.5X ULN
Gamma Glutamyltranspeptidase		> 2.5X ULN
Creatinine (mg/dL)		>1.7
Bilirubin (total) (mg/dL)		>1.5
Hemoglobin (g/dL)		
Male	<11.0	
Female	< 9.5	
Red Blood Cells (mill/mm^3)	<3.5	
White Blood Cells (per mm^3)	<2,800	> 16,000
Neutrophils (%)	<35	>80
Eosinophils (%)		> 10
Basophils (%)		>5
Lymphocytes (%)	<10	>50
CD4 (+)T-lymphocytes (per mm^3)	<500	
Monocytes (%)		>15
Platelet Count (per mm^3)	<75,000	>700,000

*ULN = upper limit of normal

Urinalysis

Protein	any detectable amount
Glucose	any detectable amount
Ketone	any detectable amount
Nitrite	any detectable amount
Leukocytes	any detectable amount
Blood	any detectable amount (in the absence of vaginal bleeding)

APPENDIX II: HIV/AIDS Education

Discuss with the Subject:

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

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

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

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

Offer outside referrals

APPENDIX III: Instructions for Evaluating and Reporting Adverse Events

A. GENERAL INSTRUCTIONS

1. The Adverse Events (AE) CRF must be completed weekly.

2. If no AE occurs, check the box marked NONE and sign and date form.

3. Enter only AEs that occur after the subject begins taking the investigational agent.

4. Enter only **one** AE per CRF.

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

6. 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.
Life threatening:	At immediate risk of death.
Lethal:	Death

C. DEFINITIONS – RELATEDNESS OF EVENTS

Investigators must review the information and offer an educated opinion about the relatedness of the event to the study agent. Do not leave blank.

Use codes provided:

Definitely – The adverse event:

a) Follows a reasonable temporal sequence from drug administration.
b) Abates upon discontinuation of the drug (de-challenge).
c) Is confirmed by reappearance of the reaction of repeat exposure (re-challenge).

Probably – The adverse event:

a) Follows a reasonable temporal sequence from drug administration.
b) Abates upon discontinuation of the drug (de-challenge).
c) Cannot be reasonably explained by the known characteristics of the subject's clinical state.

Possibly – The adverse event:

a) Follows a reasonable temporal sequence from drug administration.
b) Could have been produced by the subject's clinical state or by other modes of therapy administered to the subject.

Unlikely – The temporal association between the adverse event and the drug is such that the drug is not likely to have had any reasonable association with the observed event. Temporal association is defined as an association between a drug and the observed reaction or event such that the drug was present prior to the reaction or event as defined by history or drug blood level.

Unrelated – The adverse event definitely did not produce the subject's clinical state or by other modes of therapy administered to the subject.

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).

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.