STUDY #: NIDA-MDS-Modafinil-0001

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

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1 LIST OF ABBREVIATIONS

Abbreviation	Definition
ADHD	attention deficit hyperactivity disorder
AE	adverse event
AIDS	acquired immune deficiency syndrome
ALP	alkaline phosphatase
alpha-1bAR	alpha 1b-adrenergic receptors
alpha-1bAR KO	alpha 1b-adrenergic receptors knock-out
ALT/SGPT	alanine aminotransferase/serum glutamic pyruvic transaminase
ARCI	Addiction Research Center Inventory
ASI-Lite	Addiction Severity Index-Lite
AST/SGOT	aspartate aminotransferase/serum glutamic oxaloacetic transaminse
AUC	area-under-the-curve
BE	benzoylecgonine
BP	blood pressure
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
CNS	central nervous system
CRF	Case Report Form
CPK	creatine phosphokinase
CSSA	Cocaine Selective Severity Assessment
CYP2C9	cytochrome P450 2C9 isoform
CYP2C19	cytochrome P450 2C19 isoform
CYP2D6	cytochrome P450 2D6 isoform
CYP3A4	cytochrome P450 3A4 isoform
DAT	dopamine transporter
DBP	diastolic blood pressure
DSMB	Data and Safety Monitoring Board
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders Fourth Edition
DTR&D	Division of Treatment Research and Development
DVA	Department of Veterans Affairs
ECG	electrocardiogram
EDS	excessive daytime sleepiness
FDA	Food and Drug Administration
FTA-abs	fluorescent treponemal antibody absorption
GABA	gamma-aminobutyric acid

Abbreviation	Definition
GGT	gamma-glutamyl transferase
HAM-D	Hamilton – Depression Rating Scale
HIV	human immunodeficiency virus
HR	heart rate
HRBS	HIV Risk-taking Behavior Scale
IND	Investigational New Drug
IRB	Institutional Review Board
LAAM	levo-alpha-acetylmethadol
LDH	lactate dehydrogenase
MAO	monoamine oxidase
MHA-TP	microhemagglutination for *Treponema pallidum*
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MUSC	Medical University of South Carolina
NDA	New Drug Application
NET	norepinephrine transporter
NIDA	National Institute on Drug Abuse
OTC	over-the-counter
PI	Principal Investigator
PPD	purified protein derivative (test for tuberculosis)
RPR	rapid plasma reagin (test for syphilis)
RR	respiration rate
SAE	serious adverse event
SBP	systolic blood pressure
SCID	structured clinical interview for DSM-IV
SERT	serotonin transporter
SUR	substance use report
TPPA	*Treponema pallidum* particle agglutination
VAS	Visual Analog Scale

2   STUDY SCHEMA

Study Week | **Activity**

-3 — Screening/ Baseline* assessments (weeks -3 thru -1)

200 mg Modafinil (N=70)

400 mg Modafinil (N=70)

1 — Randomization

Placebo (N=70)

Treatment** & assessments (weeks 1 thru 12)

12 —
12 — **FOLLOW-UP*** assessments (week 16)
16 —
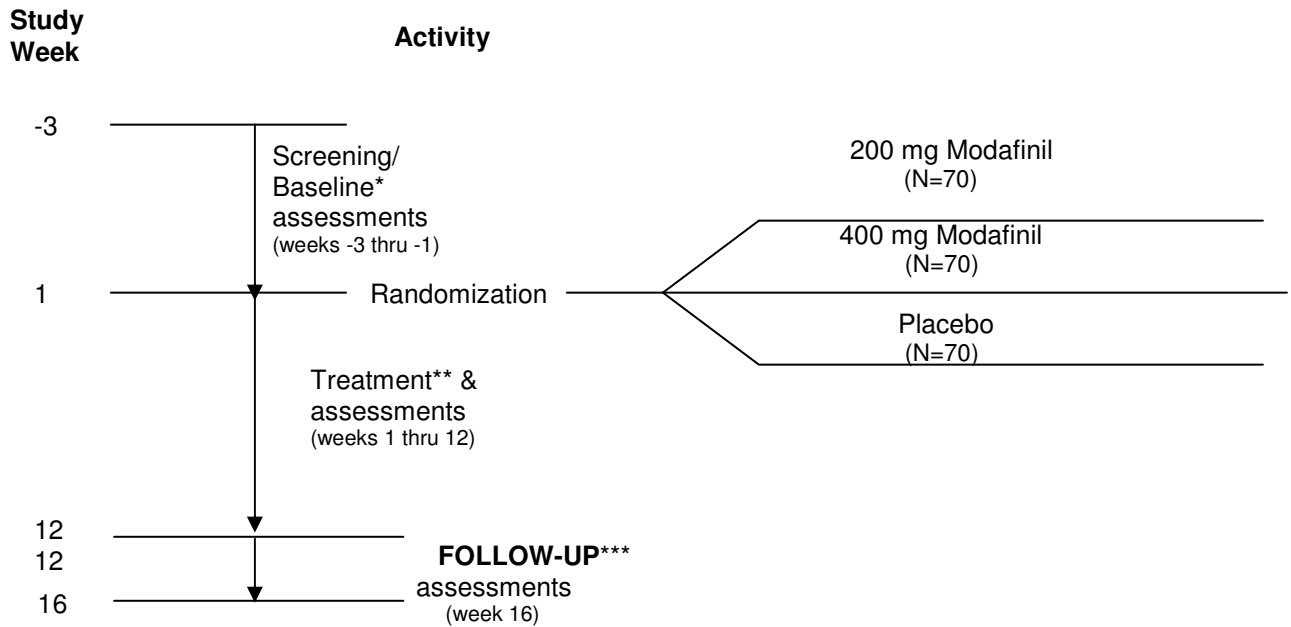
* Screening and baseline assessments are conducted concurrently; subjects must meet all eligibility criteria during the 3-week Screening/baseline period in order to be randomized into the study. One session of Motivational Enhancement Therapy will be added during the third week of screening/baseline period.

** Double-blind treatment period consists of 12 weeks of treatment with 200 mg or 400 mg modafinil or placebo administered orally as a single morning dose. All treatment groups will receive psychosocial therapy once a week.

***Follow-up period consists of a follow-up at week 16.

Adaptive randomization will be used to balance groups with respect to site, gender and frequency of cocaine use in the 30 days prior to screening ($\leq$ 18 versus >18).

3   ABSTRACT

STUDY OBJECTIVES: To evaluate the efficacy and safety of modafinil relative to placebo in reducing cocaine use in subjects with cocaine dependence as assessed by self-report confirmed with urine assays for benzoylecgonine (BE).

STUDY DESIGN: This is a double-blind, placebo-controlled, parallel group design study in which, after a 3-week screening/baseline period, subjects will be randomly assigned to one of three treatment groups to receive 200 mg modafinil, 400 mg modafinil or matched placebo daily for 12 weeks with a follow-up assessment 4 weeks after treatment completion. Adaptive randomization will be used to balance treatment groups based on site, gender, and frequency of cocaine use in the last 30 days (≤ 18 *versus* >18).

STUDY POPULATION: 210 subjects with Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria for cocaine dependence determined by the Structured Clinical Interview DSM-IV (SCID) will be randomized into one of three treatment groups (70 subjects per group; subject sample is calculated based on estimated 40% dropout rate). Subjects at least 18 years-of-age, with at least 1 BE-positive urine provided within the 3-week screening/baseline period prior to randomization, with the ability to understand and provide written informed consent, will be included.

TREATMENTS: During the 12 weeks of treatment, subjects will receive 200 mg or 400 mg modafinil daily or matched placebo. Modafinil/placebo are administered orally once a day. All subjects will receive standardized psychosocial therapy, which will consist of manual-guided cognitive behavioral therapy (CBT) once a week during the 12-week treatment period. HIV counseling will be performed at baseline, week 12 and at follow-up (week 16). One session of Motivational Enhancement Therapy will be added to the third week of screening/baseline.

SAFETY ASSESSMENTS: All candidates for study enrollment will have a physical examination, a 12-lead electrocardiogram (ECG), clinical laboratory studies (blood chemistry, hematology, urinalysis, and pregnancy test, if female), and Hamilton Depression Rating Scale (HAM-D) completed during screening or baseline. Vital signs, concomitant medication use, and a urine screen for other substances of abuse will be assessed weekly. A HAM-D and clinical laboratory studies will be performed at weeks 4, 8, and 12. Pregnancy test for females will be performed every two weeks during treatment, unless there is documentation of a hysterectomy. Adverse Events (AEs) will be assessed at each study visit and recorded weekly on a case report form (CRF). At treatment week 12 or at the time of study discontinuation, all subjects will have an ECG, vital signs, physical examination, HAM-D, clinical laboratory studies (including pregnancy test if female) and an AE assessment. A final AE assessment, and pregnancy test (on all female subjects), will be performed at follow-up (week 16).

EFFICACY ASSESSMENTS: Success in reduction of cocaine use will be determined by comparing cocaine non-use days (self-report confirmed or disproved by urine BE level at each study visit) expressed as the weekly proportion of non-use days to the total number of non-missing study days that week. Secondary assessments will include the comparison in the overall

increase in proportion of cocaine non-use days, increase in proportion of successful subjects, increase in the largest number of consecutive cocaine non-use days, decrease in weekly median of the log of urine BE levels and reduction in scores of human immunodeficiency virus (HIV) risk-taking behavior hypothesized to be associated with drug use and assessed by the HIV Risk-Taking Behavior Scale (HRBS). Severity of cocaine dependence will be assessed by comparing the change in scores of the Addiction Severity Index (ASI-Lite and ASI-Lite Follow-up), Brief Substance Craving Scale (BSCS), Cocaine Craving Questionnaire (CCQ) and Clinical Global Impression as assessed by the subject (CGI-S) and an observer (CGI-O). The ASI-Lite will be performed at baseline and ASI-Lite Follow-up at week 12. The BSCS, CGI-S, and CGI-O will be performed weekly during baseline and during the treatment period, preferably at the first visit of each study week. The CCQ will be performed once during screening/baseline and once during week 12. A Cocaine Selective Severity Assessment (CSSA) interview will be conducted weekly during baseline and during the treatment period. The HRBS will be used to characterize the population's HIV risk-taking behavior at baseline, week 12 and at follow-up (week 16). The assessments performed if patient leaves study prior to week 12 are listed in section 13.

ANALYSIS: Each primary and secondary outcome variable will be analyzed using appropriate statistical methods for the intent-to-treat population, evaluable population, and for study completers. The intent-to-treat population is defined as the subjects who are randomized to treatment and who receive the first dose of study agent. The evaluable population is defined as the subjects who are randomized and properly qualified to participate in the study in accordance with the inclusion and exclusion criteria and who contribute at least four (4) usable on-study urine samples and 21 days of self-report. Study completers are the intent-to-treat subjects minus administrative study dropouts; administrative study dropouts are defined as subjects who missed 7 consecutive study visits after randomization, were removed for medical reasons or voluntarily discontinued participation in the study. The individual effects, if any, of gender, age, race, prior cocaine use, and depression on the primary treatment effects will be determined where numbers permit. It is hypothesized that modafinil treatment, compared to placebo, will be associated with a statistically significant change in cocaine use as assessed by self-report confirmed with urine assays for benzoylecgonine (BE). Therefore, statistical tests will be two-sided at a 5% Type I error rate. Confidence intervals will be two-sided with a 95% confidence coefficient.

Summaries of the characteristics of the subject population in each treatment group at baseline will be prepared for the intent-to-treat population, evaluable subjects, and for study completers. A summary will be prepared to show dropouts/retention over time in each treatment group and for *a priori* defined subgroups. The number of missing observations will be compared between treatments and for *a priori* defined subgroups. Weekly treatment compliance will be summarized. All AEs will be reported in tabular form indicating the frequency of each type of event.

Some data are being collected for scientific use and population descriptive purposes such as CSSA.

4   INTRODUCTION

4.1   COCAINE

Cocaine is a powerfully addictive stimulant. It was first extracted from the leaf of the *Erythroxylon* coca bush in the mid-19th century. Cocaine hydrochloride has been an abused substance for more than 100 years, and coca leaves, the source of cocaine, have been ingested for thousands of years (Petersen, 1977; Evans, 1981; Katzung, 1992). In the early 1900s, it became the main stimulant drug used in most of the tonics and elixirs that were developed to treat a wide variety of illnesses. Today, cocaine is a Schedule II drug, meaning that it has high potential for abuse, but can be administered by a doctor for legitimate medical purposes, such as a local anesthetic for some eye, ear, and throat surgeries.

There are basically two chemical forms of cocaine: the hydrochloride salt and the "freebase". The hydrochloride salt, or powdered form of cocaine, dissolves in water and, when abused, can be taken intravenously or intranasally. Freebase ("crack" cocaine) refers to a compound that has been neutralized by an alkaline substance to convert the hydrochloride salt to the smokable freebase form. Cocaine is generally sold on the street as a fine, white, crystalline powder, known as "coke, "C", "snow", "flake", or "blow". Street dealers usually dilute it with such inert substances as cornstarch, talcum powder, and/or sugar, or with procaine or lidocaine (a chemically related local anesthetics) or other stimulants, such as amphetamines.

Pharmacology. Cocaine is a potent inhibitor of the dopamine transporter (DAT). Cocaine binds at the DAT and inhibits reuptake of dopamine, thus leading to a build-up of extracellular dopamine levels and potentiation of mesolimbocortical dopaminergic pathways involved in reward mechanisms (Kuhar *et al*., 1991). Neuroimaging studies indicate fewer DATs in the prefrontal cortex of cocaine users (Hitri *et al*., 1994). Pharmacologically, cocaine is a potent inhibitor of not only the DAT, but of other monoamine transporters as well, including those for serotonin (SERT) and norepinephrine (NET) (Fleckenstein *et al.,* 2000; Miller *et al.,* 2001). Single gene knockouts in mice of DAT, SERT or NET indicated that any one of these transporters might be able to mediate cocaine reward in the other's absence (Sora *et al.,* 1998; Xu *et al.,* 2000).

Cocaine Pharmacokinetics. The distribution half-life of cocaine from an intravenous (i.v.) dose is about 10 min and the elimination half-life of cocaine is about 1 hour (50-80 min) (Jeffcoat *et al.,* 1989).

Cocaine Metabolism. Cocaine is rapidly metabolized by serum cholinesterase (Stewart *et al.,* 1977) and liver carboxylesterase (Dean *et al.,* 1991) into two major deesterified metabolites that appear in serum and urine, BE and ecgonine methyl ester. In the presence of ethanol, liver carboxylesterase also catalyzes the ethyl transesterification of cocaine to form cocaethylene plus methanol (Dean *et al.,* 1991). Cocaethylene has a longer duration of action and is more toxic than either drug alone, and the mixture of cocaine and alcohol is the most common two-drug combination that results in drug-related death.

Short-term Effects of Cocaine Use. Cocaine effects appear almost immediately after a single dose, and disappear within a few minutes or hours. Taken in small amounts (up to 100 mg), cocaine usually makes the user feel euphoric, energetic, talkative, and mentally alert, especially to the sensations of sight, sound, and touch. It can also temporarily decrease the need for food and sleep. Some users find that the drug helps them to perform simple physical and intellectual tasks more quickly, while others can experience the opposite effect. The duration of cocaine's immediate euphoric effects depends upon the route of administration. The faster the absorption, the more intense the high. Also, the faster the absorption, the shorter the duration of action. The high from snorting is relatively slow in onset, and may last 15 to 30 minutes, while that from smoking may last 5 to 10 minutes. The short-term physiological effects of cocaine include constricted blood vessels, dilated pupils, and increased temperature, heart rate, and blood pressure. Large amounts (several hundred milligrams or more) intensify the user's high, but may also lead to bizarre, erratic and violent behavior. These users may experience tremors, vertigo, muscle twitches, paranoia. Some users of cocaine report feelings of restlessness, irritability, and anxiety.

Long-term Effects of Cocaine Use. Cocaine is a very addictive drug. Once having tried cocaine, an individual may have difficulty predicting or controlling the extent to which s/he will continue to use the drug. An appreciable tolerance to cocaine's high may develop with many addicts reporting that they seek but fail to achieve as much pleasure as they did from their first experience. Some users will frequently increase their doses to intensify and prolong the euphoric effects. While tolerance to the high can occur, users can also become more sensitive (sensitization) to cocaine's anesthetic and convulsant effects, without increasing the dose taken. This increased sensitivity may explain some deaths occurring after apparently low doses of cocaine. Use of cocaine in a binge, during which the drug is taken repeatedly and at increasingly high doses, leads to a state of increasing irritability, restlessness and paranoia. This may result in a full-blown paranoid psychosis, in which the individual loses touch with reality and experiences auditory hallucinations.

Medical Complications of Cocaine Abuse. Cocaine toxicity manifests itself at the level of nearly every organ system, with the most dramatic changes being observed in the cardiovascular system, liver and the brain. In the cardiovascular system, tachycardia, hypertension, ruptures of blood vessels, arrhythmias, and atherosclerotic lesions are typical complications of cocaine abuse that often precede myocardial ischemia and infarction (Karch, 1993). Cocaine seems to be hepatotoxic in humans (Marks and Chapple, 1967); this hepatotoxicity is enhanced by drugs such as barbiturates, alcohol and cocaine adulterants. Cocaine also induces pulmonary disorders, which are particularly severe in cocaine smokers. These disorders include barotrauma, inflammation and lung infections, pulmonary congestion, edema, hypertrophy of pulmonary arteries, and pulmonary necrosis (Karch, 1993). Findings from animal and clinical studies have shown that chronic use of cocaine can produce serious neuropathies. In humans, cocaine abuse can lead to seizures, optic nerve neuropathy, cerebral infarction, cerebral hemorrhage, multifocal cerebral ischemia, and cerebral atrophy (Majewska *et al.*, 1996). Psychiatric impairments associated with cocaine abuse include cognitive deficits, particularly in attention, problem solving, abstraction, arithmetic performance and short-term memory (Majewska *et al.,*1996). The most significant psychopathologies observed in cocaine addicts include anhedonia, anxiety, anergy, paranoia, depression, and bipolar mood disorder, which may predispose to suicide and

are believed to contribute to cocaine craving and relapse. Cocaine decreases food intake, and many chronic cocaine users lose their appetites and experience significant weight loss and malnutrition.

Different routes of cocaine administration can produce distinct specific sets of adverse events. Thus, regular snorting can lead to loss of sense of smell, nosebleeds, problems with swallowing, hoarseness, necrosis of the nasal septum and chronically inflamed runny nose, while ingested cocaine can cause severe bowel gangrene and intravenous cocaine users may experience allergic reactions either to the drug or to some additive(s) in street cocaine.

Potential Drug Interactions. Cocaine was reported in one *in vitro* study to inhibit the cytochrome P450 2D6 isoform (CYP2D6) of human liver CYP enzyme family (Sellers *et al.,* 1997), which plays a major role in oxidative metabolism of a wide range of structurally diverse therapeutic agents and endogenous compounds (Lin *et al.,* 1997; Sellers and Tyndale, 2000). However, since cocaine use is mostly sporadic and the majority of cocaine is metabolized very rapidly and very efficiently by plasma and liver esterases, a CYP2D6 inhibition *in vivo* will be extremely negligible. This would be expected to affect only study agents that have a very short half-life or a very rapid clearance, and are metabolized solely by CYP2D6.

Data from a human laboratory study on the effects of desipramine, which is metabolized by CYP2D6, on cocaine self-administration in chronic cocaine users (Fischman *et al.,* 1990), where cocaine was self-administered repeatedly at steady state of desipramine, showed desipramine blood levels of 134 ng/mL at baseline (before the inpatient cocaine infusion) and 121 ng/mL at the end of inpatient phase, which included repeated administration of cocaine for 10 days. These data support the conclusion that *in vivo* cocaine has no effect on CYP2D6 as reflected by lower levels of desipramine after repeated cocaine administration in chronic non-treatment seeking cocaine dependents.

4.2   COCAINE AS A MAJOR HEALTH PROBLEM

Cocaine dependence is a significant public health problem associated with serious medical, psychiatric, social, and economic consequences. Although total cocaine use has declined in the decade from 1985 until 1995, cocaine abuse has steadily increased among the young from 1992 until 1995 (National Household Survey on Drug Abuse, 1996). Monthly cocaine use among individuals under the age of twenty has risen 166% from 1994 to 1995. Cocaine-related Emergency Room admissions were up 19% during this same interval (DAWN Report, 1996). The total number of cocaine-related Emergency Room visits has increased annually since 1985, and more users are less educated and under employed (Johanson and Schuster, 1995). In 1997, an estimated 1.5 million Americans (0.7% of those age 12 and older) were chronic cocaine users; in 1999, the Office of National Drug Control Policy estimated the number of chronic cocaine users in U.S. at 3.6 million. Sociological evidence from the popular culture indicates that cocaine abuse, as well as other forms of substance abuse, are becoming more widely accepted among youth again.

4.3   SEARCH FOR EFFECTIVE TREATMENTS FOR COCAINE DEPENDENCE

Although many compounds have been evaluated for the treatment of cocaine dependence, none has been approved by the Food and Drug Administration (FDA) for this indication. Unlike methadone or naltrexone treatment for heroin addiction, disulfiram for alcohol dependence, and bupropion (Zyban) for cigarette smoking, no pharmacological agent is currently approved for the treatment of cocaine dependence. Psychosocial/behavioral therapy is currently the treatment of choice for cocaine dependence, and NIDA is pursuing the identification and testing of new pharmacological agents to add to behavioral therapy to treat cocaine dependence. Current strategies to treat cocaine dependence include: 1) blocking its effects, 2) restoration of central nervous system homeostasis, 3) reducing craving or enhancing the addict's ability to manage his/her response to craving, 4) treating underlying comorbid conditions that may predispose targeted subpopulations toward dependence, and 5) stress reduction to prevent relapse.

The earliest pharmacologic trials on cocaine dependence involved tricyclic antidepressants (Gawin, 1986; Giannini *et al.,* 1986). In one study, desipramine-treated subjects were shown to have higher rates of short-term abstinence than placebo-treated subjects (Gawin *et al.,* 1989b). In preliminary, open-label studies, Halikas and colleagues found that carbamazepine increased abstinence rates among cocaine dependent subjects (Halikas *et al.,* 1989, 1991, 1992). Other agents that have been briefly studied include mazindol (Berger *et al*., 1989), L-dopa (Rosen *et al.,* 1986), buprenorphine (Mello *et al.,* 1989), flupenthixol (Gawin *et al.,* 1989a), fluoxetine (Pollack and Rosenbaum, 1991), bupropion (Margolin *et al*., 1991, 1992), ondansetron (Jasinski *et al.,* 1991), and haloperidol (Hall *et al.,* 1993). Results of those studies were inconclusive. Replication of early efficacy findings in well-controlled, double-blind studies with appropriate outcome measures have been lacking (Weddington, 1990). More recently, trials of some of these agents that have been more rigorously controlled with longer-term follow-up have also been disappointing. Studies with fluoxetine (Grabowski *et al.,* 1995), carbamazepine (Montoya *et al*., 1994; Cornish *et al.,* 1995; Kranzler *et al.,* 1995), and desipramine (Arndt *et al*., 1992; Carroll *et al*., 1994) have all failed to find a significant benefit of drug over placebo in evaluating relapse to cocaine use. The conclusion of the Cochrane Library review of 18 studies, in which antidepressants such as desipramine, imipramine and fluoxetine were tested, was that current evidence does not support the clinical use of antidepressants in the treatment of cocaine dependence (Lima *et al.,* 2001).

In the mid-90s, the search for an effective pharmacotherapy for cocaine addiction was focused on dopaminergic agents (bromocriptine, bupropion, cabergoline) with direct or indirect agonist activity at dopamine receptors as a replacement strategy (Johanson and Schuster, 1995). Cocaine binds at the DAT and inhibits neurotransmitter reuptake, thus leading to a build-up of extracellular dopamine levels and potentiation of mesolimbocortical pathways (Kuhar *et al*., 1991). Neuroimaging (positron emission tomography) studies of human volunteers who regularly abuse cocaine indicate that doses used by cocaine abusers lead to a significant brain DAT blockade, which is associated with subjective effects of cocaine (self reported "high") (Volkow *et al.,* 1997). Dopamine receptor agonists were considered to be useful for therapy of cocaine, which itself is an indirect dopamine agonist, because, in contrast to cocaine, they do not exhibit rewarding (behaviorally reinforcing) properties. Also, by providing continuous dopaminergic tone, the dopamine receptor agonists were hypothesized to attenuate the reinforcing effects of acute dopamine overflow triggered by cocaine use. A logical conclusion was that dopamine receptor agonists will relieve the symptoms of cocaine withdrawal and

eventually prevent the relapse in cocaine patients. Early reports of dopamine agonists reducing cocaine craving in cocaine-dependent subjects appeared promising (Tennant and Sagherian, 1987; Giannini *et al.,* 1987) but the results of double-blind, placebo-controlled trials with bromocriptine (Eliler *et al.,* 1995; Handelsman, 1997) and bupropion (Margolin *et al.*, 1995) yielded no difference between placebo and dopamine agonists in reducing cocaine use as measured by urine drug screen results. The results of initial double-blind, placebo-controlled trials with amantadine indicated no difference compared to placebo in reducing cocaine use (Handelsman *et al.*, 1995). However, in a more recent controlled trial, amantadine showed modestly favorable outcomes when compared to placebo (Shoptaw *et al.,* 2002). The Cochrane Library review of 12 studies, in which amantadine and bromocriptine were compared to placebo (in 2 studies amantadine was directly compared to bromocriptine, while in 3 studies amantadine was compared to antidepressant desipramine), concluded that current evidence does not support the clinical use of dopamine agonists as single agents in the treatment of cocaine dependence (Soares *et al.,* 2001).

Despite intensive investment of resources and some promising data from a recent phase 2 placebo-controlled clinical trial with oral selegiline which has lead to a follow-on phase 3 trial of selegiline administered by a transdermal patch, no medication so far, has demonstrated clear evidence of efficacy for the treatment of cocaine dependence. The lack of success in finding an effective pharmacological treatment for cocaine abuse thus far, may in part, is due to the cocaine's apparent action on multiple neurotransmitter systems. Cocaine is a potent inhibitor of not only the DAT, but of serotonin and norepinephrine transporters (SERT and NET, respectively) (Fleckenstein *et al.,* 2000; Miller *et al.,* 2001). Single gene knockouts in mice of DAT, SERT and NET indicated that any one of these transporters might be able to mediate cocaine reward in the other's absence (Sora *et al.,* 1998; Xu *et al.,* 2000). This hypothesis was recently confirmed by a NIDA research team headed by Dr. George Uhl, which studied genetically altered (double knockout) mice that were missing one or both copies of DAT and SERT genes (Sora *et al.,* 2001). They found that cocaine reward depends on both DAT and SERT blockade and that serotonin, as well as dopamine, plays a critical role in the development of cocaine addiction. The effects of transporter gene copy numbers on the cocaine place preference test indicated a greater role for DAT than SERT in cocaine reward/reinforcement in mice, consistent with previous pharmacological studies. Thus, mice with even a single DAT gene copy and no SERT copies still experienced reward/reinforcement behavior following cocaine administration, while cocaine-induced reward/reinforcement behavior was totally blocked in mice with no DAT gene and either half-normal or absent SERT. It is obvious that previously held views that DAT blockade is the sole site for cocaine reward have been replaced by a broader picture of multi-transporter involvement (DAT, SERT and NET) in cocaine's hedonic effects (Lin and Uhl, 2002; Uhl *et al.,* 2002).

Still, for a long time cocaine was generally considered to exert its locomotor and rewarding effects exclusively through an increased dopaminergic transmission in the nucleus accumbens; therefore, much attention has been paid to the alterations in the regulation of DAT and DA receptors as a result of long-term exposure to cocaine. Far less attention has been paid, however, to the role of noradrenergic systems as mediators of the acute and chronic actions of cocaine, although cocaine accumulates in high concentrations in NE-rich brain regions of non-human primates, such as locus coeruleus, hippocampus and amygdala (Madras and Kaufman,

1994) and dose dependently increases extracellular NE in the rat hippocampus, prefrontal cortex and nucleus accumbens (Florin *et al.,* 1994; Li *et al.,* 1996). The recently reported interactions between central noradrenergic and dopaminergic systems (adrenergic excitation of DA neurons or adrenergic potentiation of central dopaminergic neurotransmission) also implicate noradrenergic transmission in the behavioral effects of stimulants, including cocaine (Darracq et al., 1998; Auclair *et al.,* 2002). This cross-talk between noradrenergic and dopaminergic neurons takes place at the level of alpha 1b-adrenergic receptors (alpha-1bAR). Brain alpha-1bAR are physiologically stimulated by NE and are critically involved in mediation of the noradrenergic influence on active behavior (locomotor activity) (Stone *et al.,* 2001); they play important role in cardiac development and/or function as well as in blood pressure response to alpha(1)-agonists via vasoconstriction and appear to be involved in CNS processes such as nociceptive responses, modulation of memory consolidation and working memory (Tanoue *et al*., 2002). Central alpha-1bAR are also important for locomotor and rewarding activities of stimulants, and locomotor hyperactivity and rewarding effects induced by *d*-amphetamine (1-3 mg/kg), cocaine (5-20 mg/kg) or morphine (5-10 mg/kg) are dramatically decreased in mice lacking alpha-1bAR (alpha-1bAR KO) compared with wild type (Drouin *et al.,* 2002). Auclair and colleagues convincingly proved the presence of a coupling between noradrenergic and dopaminergic neurons through the stimulation of alpha-1bAR (Auclair *et al.,* 2002). Thus, blunted locomotor responses to *d*-amphetamine in alpha-1bAR KO mice are correlated with an absence of *d*-amphetamine-induced increase in extracellular dopamine in the nucleus accumbens, the fact that a) points to critical role of alpha-1bAR and noradrenergic transmission in the vulnerability to addiction, and b) suggests that alpha-1bAR may be important therapeutic target in addiction (Auclair *et al.,* 2002).

This study will investigate modafinil, a putative agonist of alpha-1bAR (Stone *et al.,* 2001a, b; Stone *et al.,* 2002), as a potential medication to treat cocaine dependence.

4.4   RATIONALE FOR STUDYING MODAFINIL

Modafinil (Provigil®), 2-[(diphenylmethyl)sulfinyl]acetamide, is a novel non-amphetamine psychostimulant approved by the FDA for the treatment of narcolepsy, a sleep disorder characterized by uncontrollable sleepiness and frequent daytime sleep, and idiopathic hypersomnia. Modafinil has been found to increase wakefulness, alertness and vigilance (i.e. the ability to stay on task, thinking clearly and functioning normally) but, unlike prototypic psychostimulants, it has low propensity for euphoria, jitteriness, anxiety, excessive locomotor activity, hypertension and tachycardia at therapeutic doses (Bastuji *et al.,* 1998). Modafinil is a memory improving and mood-brightening psychostimulant, which is currently under study for the treatment of attention deficit hyperactivity disorder (ADHD), cognitive deficits in Alzheimer's disease and negative symptoms in schizophrenia. It is as effective as traditional dopamine acting stimulants for treatment of narcolepsy (Roth and Roehrs,1996; Fry, 1998; Green and Stillman, 1998) but its pharmacological profile is notably different from the amphetamines, cocaine or methylphenidate.

Modafinil acts as a putative agonist of brain alpha-1bAR (Stone *et al.,* 2001a, b; Stone *et al.,* 2002). Modafinil increases locomotor activity in animals (mice, rats, and cats) (Duteil *et al.,* 1990; Rambert *et al.,* 1990), and this hyperlocomotion is prevented by alpha1-adrenoceptor

antagonists, prazosin and phenoxybenzamine (Duteil *et al.,* 1990; Rambert *et al.,* 1990). Likewise, prazosin prevented modafinil-induced nocturnal activity in monkeys (Duteil *et al.,* 1990). The behavioral activation caused by modafinil is markedly attenuated not only by central pharmacological blockade but also by genetic ablation of alpha-1bAR (Stone *et al.,* 2002). Thus, when challenged with modafinil, mice genetically deficient in alpha-1bAR (alpha 1bAR KO) showed a significant attenuation (approximately 66%) of motor activity.

Preclinical data show that modafinil has low affinity to DAT (Mignoet *et al.,* 1994) and causes an increase in extracellular dopamine levels but does not stimulate dopamine release *in vitro* (De Sereville *et al.,*1994; Simon *et al.,*1995; PDR, 2002). In contrast to amphetamine and other stimulants, modafinil-induced increase in locomotor activity is not accompanied by induction of a stereotyped behavior typical for dopaminergic signaling and is not prevented by antagonists of D1 or D2 dopamine receptors (Duteil *et al.,* 1990; Rambert *et al.,* 1990). Unlike amphetamine, modafinil did not produce peripheral sympathetic effects in experimental animals (no salivation, no contraction of the pilomotor muscles, slight midriasis only at high doses). These observations confirm that the behavioral activation induced by modafinil does not involve direct effects on dopaminergic pathways and that mechanisms underlying the modafinil induced stimulant locomotor effect differ from that of amphetamine (Simon *et al.,*1995).

Using 2-deoxyglucose autoradiography of the rat brain, Engber and colleagues (1998) compared regional brain metabolic activity induced by amphetamine and modafinil. Both modafinil and amphetamine increase glucose utilization in all subregions of the hippocampus (subiculum, CA1-CA3 and dentate gyrus) and in the centrolateral nucleus of the thalamus; modafinil, but not amphetamine, increased glucose metabolism in the central nucleus of the amygdala. Amphetamine, but not modafinil, increased metabolic activity in the basal ganglia, frontal cortex, nucleus accumbens, ventral tegmental area and pontine reticular field. Same pattern of metabolic activity was found in the cat brain where, at equivalent wake-promoting doses, amphetamine or methylphenidate, but not modafinil activate basal ganglia, nucleus accumbens and cortical regions as measured by increases in *c-fos* expression (Lin *et al.*,1996).

Modafinil has demonstrated the ability to inhibit the release of GABA in the median preoptic area and in the posterior hypothalamus in rats (Ferraro *et al.,* 1996b). It decreases GABA release in the rat nucleus accumbens as well but its effect on dopamine release in nucleus accumbens is weak and most probably indirect (Ferraro *et al.,* 1996a,1997a). More significant is modafinil's ability to increase excitatory glutamatergic transmission (Ferraro *et al.,* 1997b); it appears to increase glutamate release in ventral medial thalamus, ventral lateral thalamus, and hippocampus of the rat which, in turn, reduces local GABAergic transmission, thereby diminishing GABA(A) receptor signaling on the mesolimbic dopamine terminals. Taken together these studies suggest that traditional stimulants such as amphetamine and methylphenidate act on dopaminergic structures in the cortex and subcortical areas, whereas modafinil may act primarily in subcortical areas to a) activate noradrenergic transmission and that way induce adrenergic excitation of mesolimbic dopamine neurons, and/or b) activate glutamatergic transmission and thus diminish GABA(A) receptor mediated inhibitory signaling on the mesolimbic dopamine terminals.

All in all, biochemical and behavioral studies point to a "non-amphetamine" mechanism of stimulant locomotor effect of modafinil in animals (Simon *et al*., 1995). Behavioral studies of modafinil compared to traditional stimulants have indicated both similarities and differences. Modafinil produces vigilance without subsequent rebound hypersomnolence when compared to amphetamine in rats (Edgar and Seidel, 1997). In this same study, modafinil increased locomotor activity far less than amphetamine and only in proportion to the increased awake time. Using a differential reinforcement of low rate of responding (DRL30-S), Bizot (1998) demonstrated that modafinil in rats increased DRL30-S response rate and decreased reinforcement rate in a similar manner to the effects of nicotine and *d*-amphetamine. Discriminative stimulus and reinforcing effects of modafinil were evaluated in comparison to *l*-ephedrine and *d*-amphetamine (Gold and Balster, 1996). In cocaine discrimination studies conducted in rats, modafinil produced dose-dependent increases in cocaine lever selection but the level of modafinil-induced response (67%) *versus* 82% and 100% for *l*-ephedrine and *d*-amphetamine, respectively, was indicative of modafinil's low selectivity in producing cocaine-like discriminative stimulus effects. Modafinil was reinforcing in rhesus monkeys maintained on intravenous cocaine self-administration but its reinforcing effect was 200-times less potent than that of *l*-ephedrine and *d*-amphetamine (Gold and Balster, 1996).

Oral modafinil does not cause elation or euphoria in non-substance abusing human volunteers (Warot *et al.,* 1993). The results of a human study that evaluated abuse potential of modafinil using methylphenidate as a reference in polysubstance abusers with a history of cocaine abuse indicate that subjects liked the effects of both modafinil (200 mg, 400 mg or 800 mg given as a single oral dose) and methylphenidate (45 mg or 90 mg given as a single oral dose) and discriminated modafinil and methylphenidate from placebo (Jasinski, 2000). However, unlike methylphenidate, modafinil did not induce a significant response on the Amphetamine Scale of Addiction Research Center Inventory. Another study investigated behavioral and physiological effects of a single oral dose of modafinil (200, 400 and 600 mg) in subjects with recent histories of cocaine abuse (i.e., positive urine for cocaine or BE during the initial screening) and compared to those of oral cocaine (100, 200 and 300 mg) and placebo (Rush *et al.,* 2002). The results of this study indicate that cocaine, but not modafinil, produced stimulant-like self-reported drug effects (e.g. increased ratings of High and Stimulated on Drug-Effect Questionnaire) and thus suggest that modafinil has minimal abuse potential. Analysis of the case reports of stimulant abusers given modafinil for clinical purposes (total of 4) is reassuring and in accord with preclinical human studies with modafinil mentioned above (Malcolm *et al.,* 2002). Thus, in the first case, treatment with modafinil in an outpatient setting to detoxify a male with a history of polysubstance abuse, including psychostimulants, led to a decrease in patient's craving for amphetamine. The patient admitted taking a higher than prescribed dose of modafinil on one ocassion but he felt that this single excessive use did not produce euphoria. The second case was a female nurse with a history of hospitalizations for amphetamine-related psychosis that was treated with modafinil to improve alertness and concentration. Although being on modafinil for several weeks, she denied using it in doses of over 200 mg/day and did not use it with stimulants or alcohol. When asked to classify modafinil in relation to euphoric effects of other stimulants, she replied that 'modafinil is not as good as dextroamphetamine, amphetamine, methylphenidate, phentermine and is not as good as pimoline either'. In the third case, a male with ADHD and a history of abuse of methylphenidate, amphetamine and cocaine, was treated with Wellbutrin with little success. Modafinil was added and the dose was increased to 200 mg/day over the first 2

weeks. This patient continued to take modafinil for several months without difficulty or abuse reported.   The fourth case is that of a male cocaine abuser who was given modafinil for the treatment of ADHD.   Modafinil was effective in improving the patient's cognitive problems and blunted the craving for and use of cocaine. Again, there was no indication of use of modafinil with other stimulants or alcohol, or of excessive use of modafinil in this patient.   All in all, both animal and human studies indicate that modafinil can serve as a reinforcer but its reinforcing properties are mild compared to classic psychostimulants (Gold and Balster, 1996; Jasinski, 2000; Malcolm *et al.,* 2002; Rush *et al.,* 2002).

Treatment with modafinil does not lead to development of dependence (US Modafinil in Narcolepsy Multicenter Study Group, 2000). During treatment discontinuation patients receiving modafinil did not experience either physical symptoms associated with psychostimulant withdrawal (feeling sick, stomach cramps, muscle spasms/twitching, cold sensation, heart pounding, muscle tension, aches and pains, yawning, runny eyes, insomnia) or mental symptoms of withdrawal, such as anxiety, agitation, irritability and craving (Lyons and French, 1991; US Modafinil in Narcolepsy Multicenter Study Group, 2000). Modafinil does not seem to produce tolerance and retains its efficacy over long-term treatment (up to 40 week) (Lyons and French, 1991; Besset *et al*., 1996; Mitler *et al.,* 2000).

Modafinil reduces the neurotoxic effects of excessive glutamate in cultured cortical neurons (Antonelli *et al.,* 1998) and demonstrates a neuroprotective effect in animal studies (Aguirre *et al.,* 1999; Jenner *et al.,* 2000). Thus, co-administration of modafinil with nigrostriatal damage inducing agent 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) restores to normal the number of neurons in mouse substantia nigra (Aguirre *et al.,* 1999).   Modafinil is also reported to reverse motor disability in MPTP-treated common marmosets and to prevent MPTP-induced nigral cell death in this species (Jenner *et al.,* 2000).

Modafinil demonstrated working memory-enhancing effect in mice (Beracochea *et al.,* 2001). In healthy human volunteers, modafinil demonstrated cognitive enhancing effects in the tests of digital span, visual pattern recognition memory, spatial planning and stop-signal reaction time (Turner *et al.,* 2002).   Modafinil improved cognitive deficits in patients with alcoholic organic brain syndrome (Saletu *et al.,* 1990).

In animal studies, modafinil administration, in contrast to dexamphetamine, is not associated with an increase in anxiety (Simon *et al.,* 1994). Moreover, modafinil may have clinically important antidepressant properties and appears to act as an augmenter of antidepressants, especially in patients with treatment-resistant depression (Menza *et al*., 2000). Thus, in patients with DSM-IV depression (4 with major and 3 with bipolar depression), it augmented a partial response (residual tiredness and fatigue) or non-response to antidepressant (HAM-D assessment) with all 7 patients achieving full or partial remission within 1 to 2 weeks of treatment with modafinil at doses of 100 to 200 mg/day. Modafinil is also reported to enhance mood in patients with myotonic dystrophy (MacDonald *et al.,* 2002). Thus, Profile of Mood States assessment of patients treated with modafinil for 2 weeks indicates a decrease in total mood disturbance scores and enhanced quality-of-life measures of energy and health change.

In summary, the rationale for studying modafinil as a potential medication to treat cocaine dependence is based on several mechanisms. First of all, modafinil may act as a weak substitutive stimulant, providing mild reinforcement and thus decreasing craving and cocaine-seeking. Modafinil is of particular interest in this regard because it has low abuse potential and does not seem to produce sensitization or tolerance. Secondly, modafinil may be useful for treatment of cocaine dependence in an indirect way by improving concentration, daytime alertness and cognitive functions of cocaine-dependent subjects and thus allowing them to benefit from CBT and other treatment compliance-enhancing forms of psychosocial therapy. The antidepressant properties of modafinil may contribute to the amelioration of dysphoria that often accompanies early abstinence and thus may promote both sustenance of abstinence and greater engagement in psychosocial therapy. Also, it is of importance that the effects of modafinil are long-lasting and persist for as long as 4 months after treatment and thus contribute to consolidation of abstinence and prevention of relapse to cocaine use (Prescribe Int, 1999).

4.5   PREVIOUS HUMAN EXPERIENCE WITH MODAFINIL

4.5.1   Clinical Trials for the Treatment of Pathological Somnolence

Modafinil was extensively studied for the treatment of pathological somnolence in patients with excessive daytime sleepiness (EDS) associated with narcolepsy. The results of two multicenter, randomized, placebo-controlled trials indicate efficacy of modafinil in the treatment of patients with narcolepsy (Fry, 1998; US Modafinil in Narcolepsy Multicenter Study Group, 1998, 2000). Thus, treatment with modafinil (200 mg and 400 mg daily for 9 weeks) effectively reduced daytime sleepiness in patients with narcolepsy with significant improvement in all subjective and objective measures of sleepiness; more improvement, as recorded on CGI scale, was seen in the modafinil than in the placebo group at all time points ($p<0.001$). Modafinil taken once daily was well tolerated, with headache the only AE to occur significantly more often in modafinil treatment group ($p<0.05$).

Modafinil has been shown to be effective and well tolerated for treating EDS associated with narcolepsy in two open-label extension studies that enrolled patients who had completed one of the two 9-week, double-blind, placebo-controlled, multicenter clinical trials of modafinil (Mitler *et al*., 2000). The results of these 40-week long trials of modafinil (400 mg daily) indicate that the most common treatment-related AEs were headache (13%), nervousness (8%) and nausea (5%), most of which were mild to moderate in nature.

Modafinil seems to have a potential in the treatment of increased daytime sleepiness in patients with Parkinson's disease (Hogl *et al.,* 2002).

4.5.2   Clinical Trials in Cocaine Dependent Populations

In an open-label pilot study, 17 cocaine-dependent subjects were treated with 100 mg modafinil b.i.d. (N=10) or 200 mg modafinil b.i.d. (N=7) in conjunction with twice weekly CBT sessions for 8 weeks (C. Dackis, 2002, personal communication). The results of this study showed a trend towards reduction in cocaine use (based on urine toxicology) with average abstinence of

47% and thus suggest a possible efficacy of modafinil in reducing cocaine use. The average treatment retention (measured by attendance of CBT sessions) was 76%.

A phase 1 randomized, double-blind, placebo-controlled, crossover design study to investigate a possible interaction between modafinil and cocaine has been recently conducted at the University of Pennsylvania Treatment Research Center (Dackis *et al.,* 2003). This study evaluated the potential of interaction between the cardiovascular effects of a single dose of cocaine (30 mg) administered by the intravenous route and oral doses of modafinil (200 mg and 400 mg) in 10 adult cocaine experienced volunteers (all male) using several drug-effect questionnaires, performance measures and physiological indices. The results of this study indicate that pretreatment with modafinil did not intensify cocaine euphoria or cocaine-induced craving (assessed by VAS, ARCI and Subjective Symptom Checklist). In fact, cocaine euphoria was significantly blunted in one of the subjective measures (ARCI Amphetamine scale) (p=0.02), and this cocaine-euphoria blunting effect of modafinil may have significant clinical value. Three subjects dropped out of the study; one completed the baseline cocaine infusion and opted out of the study due to anxiety during the infusion, while the other two dropped out because of their reluctance to remain in the hospital for the required number of days.

Another phase 1 study to investigate a possible interaction between modafinil and cocaine has been recently completed at the Medical University of South Carolina (MUSC) Treatment Research Center (R. Malcolm, 2003, Appendix VI). This study evaluated the potential of interaction between the two doses of cocaine (20 and 40 mg) administered by the intravenous route and oral doses of modafinil (200 mg and 400 mg) in 12 adult cocaine experienced volunteers (6 males and 6 females) using VAS measures and cardiovascular parameters (SBP, DBP and HR). Evaluation of the mean effects of modafinil (400 and 800 mg daily) interactions with cocaine (20 or 40 mg i.v.) using VAS assessment indicates that modafinil significantly dampened all three VAS measures ("any drug effect", cocaine "high", "worth of cocaine in dollars") as compared to baseline cocaine only condition. For cocaine "high" measure, modafinil reduced VAS by about 45% for the 20 mg cocaine condition and about 35% for the 40 mg cocaine condition, which may have a significant clinical value. Across all VAS measures and both doses of cocaine, the 800 mg dose of modafinil did not add significantly to this blunting effect as compared to the 400 mg dose of modafinil. Thus, the results of this study indicate that pretreatment with modafinil blunts cocaine euphoria and cocaine-induced craving (assessed by VAS). The analysis of safety data indicates that modafinil did not exacerbate the effects of cocaine on blood pressure and heart rate and statistical analysis indicates that an 800 mg daily dose of modafinil may even have some mild protective effect on SBP and HR by attenuating the elevation in these parameters that follows cocaine use.

Behavioral and physiological effects of modafinil have been recently studied in subjects (N=9) with recent histories of cocaine abuse (i.e., positive urine for cocaine or BE during the initial screening) and compared to those of cocaine and placebo (Rush *et al.,* 2002). The effects of single oral doses of modafinil (200, 400 and 600 mg), cocaine (100, 200 and 300 mg) and placebo were assessed with a battery of self-reported drug-effect questionnaires, performance measures and physiological indices. The results of this study suggest that modafinil has minimal abuse potential because, unlike cocaine, modafinil did not produce stimulant-like self-reported drug effects (e.g., increased ratings of High and Stimulated on Drug-Effect Questionnaire).

A double-blind placebo-controlled crossover study was conducted in male volunteers with a history of polysubstance abuse that included cocaine to compare the pharmacodynamic profiles and abuse potential of modafinil and methylphenidate (Jasinski, 2000). Each subject (N=24) was given single oral doses of methylphenidate (45 mg or 90 mg), modafinil (200 mg, 400 mg or 800 mg) and placebo. The results of this study indicate that, unlike methylphenidate, modafinil did not induce a significant response on the Amphetamine Scale of Addiction Research Center Inventory and showed greater inhibition of observed and reported sleep, less facilitation of orthostatic tachycardia and less reduction of caloric intake.

4.5.3   Clinical Trials for the Evaluation of Pharmacokinetics, Tolerability and Interactions with Dextroamphetamine and Methylphenidate

The results of a double blind, placebo-controlled, ascending dose evaluation study of the pharmacokinetics and tolerability of modafinil in healthy human volunteers (N=8; 6 modafinil, 2 placebo) indicate that 200 mg, 400 mg and 600 mg doses of modafinil administered orally once daily for 7 days are well tolerated while 800 mg dose panel was discontinued after 3 days of treatment due to the clinically significant cardiovascular changes, e.g., sustained increased blood pressure and pulse rate (Wong *et al.,* 1999). The subject's blood pressure and pulse rate returned to normal levels 2 days after discontinuation of modafinil. The safety data from this study suggest that the maximum tolerable single daily oral modafinil dose, without titration, may be 600 mg (Wong *et al.,* 1999).

Studies to examine the potential for modafinil interactions with dextroamphetamine (Hellriegel *et al*., 2002) and methylphenidate (Hellriegel *et al*., 2001) have been conducted and did not reveal substantial or clinically significant interactions. Thus, the potential of drug-drug interaction between modafinil and dextroamphetamine, each at steady state, was investigated in an open-label study in 32 healthy volunteers (Hellriegel *et al*., 2002). All subjects received modafinil orally once daily for 28 days (200 mg on days 1-7, 400 mg on days 8-28); on days 22 to 28, half of the subjects also received dextroamphetamine (20 mg) orally 7 hours after modafinil. The results of this study indicate that administration of low-dose dextroamphetamine in this dosing regimen does not alter the steady-state PK of modafinil and that this drug combination has the same tolerability profile as modafinil alone. Also, AEs in the two groups were similar and mild or moderate in nature.

An analogous study was conducted with methylphenidate. Thus, the potential of drug-drug interaction between modafinil and methylphenidate, each at steady state, was investigated in an open-label study in 32 healthy volunteers (Hellriegel *et al*., 2001). All subjects received modafinil orally once daily for 28 days (200 mg on days 1-7, 400 mg on days 8-28); on days 22 to 28, half of the subjects also received methylphenidate (20 mg) orally 8 hours after their modafinil dose. The results of this study indicate that administration of low-dose methylphenidate in this dosing regimen does not alter the steady-state PK of modafinil and that this drug combination has the same tolerability profile as modafinil alone. Also, AEs in the two groups were similar and mild or moderate in nature.

Headache and insomnia were the most commonly reported AEs in these two modafinil interactions studies (Hellriegel *et al*., 2001, 2002). Overall, modafinil-emergent AEs were similar in type and severity to those previously reported for patients with narcolepsy in large-scale, placebo-controlled clinical trials (US Modafinil in Narcolepsy Multicenter Study Group, 1998, 2000). All modafinil plus methylphenidate-emergent AEs (Hellriegel *et al*., 2001) and modafinil plus dextroamphetamine-emergent AEs (Hellriegel *et al*., 2002) in patients receiving combination treatment were mild in intensity and all of these AEs were considered unrelated or unlikely to be related to study medication. Both modafinil plus methylphenidate and modafinil plus dextroamphetamine were generally well tolerated (Hellriegel *et al*., 2001, 2002). The incidence of modafinil plus methylphenidate-emergent insomnia appeared to be slightly greater in subjects receiving combination treatment compared with subjects receiving modafinil alone (4 *versus* 1) (Hellriegel *et al*., 2001). The dose of methylphenidate used in this study (20 mg) is below the usual daily doses required for optimal therapeutic response in patients with narcolepsy. This relatively low dose of methylphenidate may be useful, when used in combination with modafinil, for augmenting short-term wakefulness, without the occurrence of problems commonly associated with higher doses of CNS stimulants.

4.6   MODAFINIL PHARMACOKINETICS

Modafinil is a racemic compound. Its chemical name is 2-[(diphenylmethyl)sulfinyl]acetamide, chemical formula is $C_{15}H_{15}NO_2S$ and the molecular weight is 273.36. Modafinil enantiomers have different pharmacokinetics (PK), e.g., the half-life of *l*-isomer is approximately three times that of the *d*-isomer in humans (PDR, 2002; Robertson and Hellriegel, 2003). The enantiomers do not interconvert. At steady state, total exposure to the *l*-isomer is approximately three times that for the *d*-isomer. The trough concentration of circulating modafinil after once daily dosing consists of 90% of the *l*-isomer and 10% of the *d*-isomer. The effective elimination half-life of modafinil after multiple doses is about 15 hours. The enantiomers exhibit linear kinetics upon multiple dosing of 200-600 mg/day once daily in healthy volunteers. Apparent steady states of total modafinil and *l*-(-)-modafinil are reached after 2-4 days of dosing (Wong *et al*., 1999; Robertson and Hellriegel, 2003). Modafinil pharmacokinetics are dose-independent between 200 and 600 mg/day doses (Robertson and Hellriegel, 2003).

Modafinil is rapidly absorbed after oral administration with peak plasma concentrations occurring at 2-4 hours (PDR, 2002). The bioavailability of modafinil tablets is approximately equal to that of an aqueous suspension. The absolute oral bioavailability was not determined because of modafinil's water insolubility (<1 mg/mL), which precludes intravenous administration. Water insolubility of modafinil and its instability at temperatures higher than 180°C reduce the potential for its abuse via intravenous injection and smoking, respectively (Jasinski and Kovacevic-Ristanovic, 2000).

4.7   MODAFINIL METABOLISM

About 90% of modafinil is metabolized by the liver with subsequent renal elimination of the metabolites. Less than 10% of the dose is excreted as unchanged parent compound. Metabolism occurs largely through hydrolytic deamidation with lesser contributions from cytochrome P450 (CYP)-mediated oxidative pathways, CYP3A4 in particular (PDR, 2002;

Robertson and Hellriegel, 2003). Due to the involvement of CYP3A4 in metabolism of modafinil, coadministration of potent inducers of CYP3A4 (e.g., carbamazepin, phenobarbital, rifampin) or inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole) could alter the levels of modafinil. The largest fraction of modafinil in urine is modafinil acid, but at least six other metabolites are present in lower concentrations.   Only two metabolites reach appreciable concentrations in plasma, i.e., modafinil acid and modafinil sulfone.   In preclinical studies, the metabolites were inactive and did not appear to mediate the arousal effects of the parent molecule. In patients who are renally or hepatically compromised, the elimination processes can be slowed, and in a similar manner (although to a lesser extent), elimination in the elderly may be reduced due to normal effects of aging.

As modafinil may be administered with other medications, the potential for metabolic drug-drug interactions has been examined both *in vitro* and *in vivo* (Robertson *et al.,* 2000; Robertson and Hellriegel, 2003).   *In vitro*, modafinil was observed to produce a reversible inhibition of CYP2C19 in human liver microsomes; no irreversible inhibition of any CYP enzyme was observed and there was no evidence of metabolism-dependent inhibition (Robertson *et al.,* 2000).   Modafinil itself does not appear to be a substrate for CYP2C19, and there are a relatively small number of marketed pharmaceutical products that are predominantly metabolized by this enzyme. Still, caution should be exercised when initiating therapy with modafinil in patients that receive *S*-mephenytoin, omeprazole, lansoprazole, proguanil, diazepam or propranolol, which serve as substrates for CYP2C19.

Modafinil also caused a small, but concentration-dependent induction of CYP1A2, CYP2B6 and CYP3A4 activities and suppression of CYP2C9 activity in primary cultures of human hepatocytes (Robertson *et al.,* 2000). Of the three CYP450 enzymes inducible by modafinil, only CYP3A4 plays a substantial role in the metabolism of a vast range of pharmaceutical products, including cyclosporine A, triazolam and steroidal contraceptives containing ethinyl estradiol.   One case of an interaction between modafinil and cyclosporine A has been reported in a 41-year old woman who had undergone an organ transplant (PDR, 2002). After one month of administration of 200 mg/day of modafinil, her blood levels of cyclosporine A were decreased by 50%. This interaction was postulated to be due to the increased metabolism of cyclosporine A, since no other factor expected to affect the disposition of cyclosporine A has changed. Clinical studies conducted to examine the potential for modafinil interactions with ethinyl estradiol and triazolam indicate that modafinil induces CYP3A4 activity in humans *in vivo* and point to a possibility of metabolic drug-drug interactions between modafinil and substrates of CYP3A4 (Robertson *et al.,* 2002b). The possibility of interaction is higher for triazolam as the modafinil treatment group had a marked decrease in maximum observed plasma concentrations areas under the plasma-concentration-time curve for triazolam relative to placebo, with a much smaller decrease in these parameters for ethinyl estradiol; also, while the half-life of triazolam was decreased, the half-life of ethinyl estradiol did not seem to be affected.   These data indicate that induction of CYP3A4 appears to be more gastrointestinal than hepatic in nature and therefore significant metabolic drug-drug interactions are most likely to occur with compounds (such as triazolam) that undergo significant gastrointestinal CYP3A4-mediated first-pass metabolism.

Finally, the apparent suppression of CYP2C9 activity in human hepatocytes by treatment with modafinil (Robertson *et al.,* 2000) is potentially important for only one compound, warfarin (Coumadin), which has a narrow therapeutic index and whose more active enantiomer (*S*-warfarin) is primarily metabolized by CYP2C9. Clinical studies conducted to examine the potential for modafinil interactions with warfarin (Robertson *et al.,* 2002a) indicate that treatment with modafinil does not significantly alter the PK of warfarin compared to placebo; however, limitations arising from this study of single doses of warfarin preclude conclusions about the potential for more subtle interactions after chronic warfarin administration. Thus, caution should be exercised when initiating therapy with modafinil in patients who are at steady-state warfarin.

4.8   MODAFINIL DOSE JUSTIFICATION

The safety data from a double blind, placebo-controlled, ascending dose evaluation study of the pharmacokinetics and tolerability of modafinil in healthy human volunteers (200 mg, 400 mg, 600 mg or 800 mg doses administered orally once daily for 7 days) suggest that the maximum tolerable single daily oral modafinil dose, without titration, may be 600 mg (Wong *et al.,* 1999).

The 200 mg and 400 mg daily doses of modafinil to be used in this study are commonly prescribed as a single morning dose in clinical practice for the treatment of narcolepsy-related EDS (PDR, 2002). The effectiveness and tolerability of these doses were previously established in the large-scale, placebo-controlled, double-blind, clinical studies involving patients with narcolepsy (US Modafinil in Narcolepsy Multicenter Study Group, 1998, 2000). These doses of modafinil were shown to be well tolerated, without disturbing nighttime sleep and without evidence of physical dependence. Both doses appear to retain efficacy over long-term treatment, without the development of tolerance (Besset *et al*., 1996; Mitler *et al.,* 2000).

Doses of modafinil proposed in this study (200 mg and 400 mg daily) were used for 8 weeks in an open-label pilot study conducted in cocaine dependent subjects in the outpatient setting at the University of Pennsylvania Treatment Research Center (C. Dackis, 2002, personal communication).

In the previously cited human laboratory study (R. Malcolm, 2003, Appendix VI), modafinil at 400 mg and 800 mg daily did not exacerbate the effects of cocaine on BP and HR.

4.9   SAFETY OF MODAFINIL

4.9.1   Expected Adverse Events

Modafinil is a wakefulness-promoting agent for oral administration.   It has been available in France for the treatment of narcolepsy and idiopathic hypersomnia since 1994 and was approved by FDA for the same indications in 1999.   Safety profile of modafinil is well established. Modafinil has been evaluated for safety in over 2200 subjects, 900 were patients with narcolepsy and the remainder were normal controls. The most commonly reported adverse events (AEs) (>5% of the time) associated with the use of modafinil are mild, usually resolve after a few weeks of treatment and include:

- Headache
- Nervousness
- Nausea
- Anxiety
- Insomnia

In general, modafinil has been used in single or divided doses of 200-400 mg/day. At these doses, modafinil consistently has demonstrated less sympathomimetic side effects, less tolerance, and less negative effects on nighttime sleep than traditional stimulant medications. Modafinil is well-tolerated, and in many clinical studies, only headache occurs significantly more often in the active treatment group versus placebo.

In a Canadian clinical trial, a 35 year old, obese narcoleptic male with a prior history of syncopal episodes experienced a 9-second episode of asystole after 27 days of modafinil administration (150 mg twice a day) (PDR, 2002). Three individuals with mitral valve prolapse and/or left ventricular hypertrophy developed chest pain, palpitations, shortness of breath, and transient ischemic T-wave alterations on electrocardiograms. One healthy male volunteer (non-patient) reported sleep deprivation and developed ideas of reference, paranoid delusions, and auditory hallucinations in association with multiple daily 600 mg doses of modafinil; psychosis was completely eliminated 36 hours after modafinil discontinuation. The safety data from a study of modafinil in patients with mild to moderate obstructive sleep apnea syndrome indicate that modafinil did not raise blood pressure or pulse although most patients were obese with mild hypertension (Heitmann et al., 1999). Adverse events were mild with the exception of one case of supraventricular tachycardia, which resolved with medication cessation.

Clinical chemistry, hematology and urinalysis parameters were monitored in US phase 1, 2 and 3 studies of modafinil (PDR, 2002). In these studies, mean plasma levels of gamma-glutamyl transferase (GGT) were found to be higher following administration of modafinil, but not placebo; however, few subjects (1%) had GGT elevations outside of the normal range. Shift to higher but not clinically significantly abnormal GGT values appeared to increase with time in the population treated with modafinil in the 9-week US phase 3 clinical trials. No differences were apparent in alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total protein, albumin or bilirubin.

Clinical cases of modafinil overdose have been described with ingested modafinil doses as high as 4.5 gm (PDR, 2002). Doses of 4.0 gm and 4.5 gm were taken intentionally (suicide attempts) by two patients participating in foreign depression studies. In both cases, the AEs observed were limited, expected and not life-threatening, and the patients recovered fully by the next day. The AEs included excitation or agitation, insomnia, and slight or moderate elevations in hemodynamic parameters. In neither of these cases nor in other instances of doses of more than 1 gm/day, including experience with up to 21 consecutive days of dosing at 1.2 gm/day, were any unexpected effects or organ toxicities observed.   Other observed high dose effects in clinical studies have included anxiety, irritability, aggressiveness, confusion, nervousness, tremor, palpitations, sleep disturbances, nausea, diarrhea and decreased prothrombin time (PDR, 2002). The treatment of overdose is symptomatic as there is no specific antidote and should include cardiovascular monitoring.

Subjects should be cautioned about operating an automobile or other hazardous machinery until they are reasonably certain that modafinil therapy will not adversely affect their ability to engage in such activities.

4.9.2   Safety in Pregnant and Lactating Women

Modafinil is assigned pregnancy "Category C" labeling by FDA. Studies in animals have shown that modafinil at a dose of 200 mg/kg/day (10 times higher the maximum recommended daily human dose of 200 mg on a mg/m^2 basis), increases the chance of incomplete or slow development of bones in the fetus with increase in resorption, skeletal variations and hydronephrosis.

The effects of modafinil on labor and delivery in humans have not been systematically investigated. Seven normal births occurred in patients who received modafinil during pregnancy. One patient gave birth 3 weeks earlier than the expected range of delivery dates to a healthy male infant; another woman with a history of spontaneous abortions suffered a spontaneous abortion while being treated with modafinil (PDR, 2002). It is not known whether modafinil or its metabolites are excreted in human milk but caution should be exercised when modafinil is administered to a nursing woman (PDR, 2002).

4.9.3   Safety of Modafinil in Cocaine Using Populations

4.9.3.1   Data from Outpatient Studies

In a recently completed open-label pilot study, 17 cocaine-dependent subjects were treated with 100 mg modafinil b.i.d. (N=10) or 200 mg modafinil b.i.d. (N=7) in conjunction with twice weekly CBT sessions for 8 weeks (C. Dackis, 2002, personal communication). There were no SAEs or unexpected AEs reported.   The most frequent AEs were "difficulty with sleeping" and feelings of "racey" that self resolved in 3-4 days with the exception of two cases when the dosage of modafinil had to be titrated down from 400 mg to 200 mg daily.

4.9.3.2   Data from Inpatient Studies

A phase 1 randomized, double-blind, placebo-controlled, crossover design study to investigate a possible interaction between modafinil and cocaine has been recently conducted at the University of Pennsylvania Treatment Research Center (Dackis *et al.,* 2003). This study evaluated the potential of interaction between the cardiovascular effects of a single dose of cocaine (30 mg i.v.) and oral modafinil (200 mg and 400 mg) in 10 adult cocaine experienced male volunteers. All subjects received an initial baseline cocaine infusion (30 mg i.v.) followed by 3 cocaine infusion sessions (30 mg i.v. each) performed after 4 days of treatment with low dose of modafinil (200 mg/day), high dose of modafinil (400 mg/day) or placebo. Low dose modafinil always preceded high dose modafinil for safety reasons, and four-day long administration was selected to achieve the steady state of modafinil. Cocaine infusions were performed 3 hours after oral modafinil or placebo administration to assess the interaction at the peak modafinil levels. Vital signs, e.g., systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), and ECG were continuously monitored and recorded on the day of each cocaine infusion session.

The results of this study indicate that co-administering modafinil and a single dose (30 mg) of cocaine i.v. is not associated with medical risks in terms of blood pressure, pulse, respiratory rate, temperature or ECG measures. Three subjects dropped out of the study; one completed the baseline infusion and opted out of the study due to anxiety during the infusion, while the other two dropped out because of their reluctance to remain in the hospital for the required number of days. Pretreatment with modafinil did not intensify cocaine euphoria or cocaine-induced craving (assessed by VAS, ARCI and Subjective Symptom Checklist). In fact, cocaine euphoria was significantly blunted in one of the subjective measures (ARCI Amphetamine scale) (p=0.02), and this cocaine-euphoria blunting effect of modafinil may have significant clinical value.

Another safety study has been recently conducted at the Medical University of South Carolina Treatment Research Center to evaluate the potential for interaction between the cardiovascular effects of cocaine administered by the intravenous route and oral modafinil in 12 adult, cocaine-experienced volunteers (R. Malcolm, 2003, Appendix VI). In that study, subjects were treated with 200 mg modafinil b.i.d. for 7 days (days 8-14), then with 400 mg modafinil b.i.d. for another 7 days (days 15-21). A baseline cocaine challenge was done on days 6 and 7, by giving in random order either a saline or cocaine infusion; the 20mg cocaine dose was always given on the first day for safety reasons. After 5 days' administration of 200 mg modafinil b.i.d. (steady-state condition), all subjects were challenged with cocaine (20 or 40 mg i.v.) and placebo (saline) infusions on two consecutive days (days 13 and 14). Again, after 5 days' administration of 400 mg modafinil b.i.d., all subjects were challenged with cocaine (20 or 40 mg i.v.) and placebo on two consecutive days (days 20 and 21). Vital signs, i.e., SBP, DBP, and HR were frequently monitored and recorded during, and for 6 hours after, each infusion session. Table 1a presents the mean and standard deviation of the maximum absolute value of SBP, DBP, and HR reached after each cocaine or placebo infusion (with 0, 400, or 800mg of modafinil). By subtracting that day's shared baseline values of vital signs (not shown), the table also presents the *maximum increase* over baseline for each vital sign, after infusions of either cocaine or placebo (saline). Of great interest to us is the cocaine-induced change (elevation) in these hemodynamic measures, expressed by the difference between a vital sign's *maximum increase* after cocaine infusion and its *maximum increase* after saline. Table 1a shows that this difference must be equivalent to the difference between the maximum absolute value of a vital sign after that day's cocaine infusion and its maximum absolute value after placebo.

Table 1a. Average of 12 Subjects' Vital Sign Values (Mean ± Standard Deviation) for each Infusion. (R. Malcolm, 2003, Appendix VI, Table 2a)

Study Day	Modafinil Dose	Infusion Dose	Maximum SBP	Maximum SBP Increase*	Maximum DBP	Maximum DBP Increase*	Maximum HR	Maximum HR Increase*
6	0mg	cocaine 20mg	149.92 ± 15.25	25.88 ± 15.96	85.75 ± 8.14	13.07 ± 6.31	97.42 ± 22.59	30.42 ± 17.77
		saline	136.25 ± 7.90	12.22 ± 15.05	81.83 ± 4.90	9.15 ± 11.79	85.58 ± 9.34	18.58 ± 13.93
7	0mg	cocaine 40mg	157.17 ± 18.64	35.39 ± 17.16	94.58 ± 6.16	23.91 ± 7.65	102.42 ± 20.14	35.00 ± 16.21
		saline	138.17 ± 14.29	16.39 ± 18.61	83.00 ± 8.64	12.33 ± 11.83	80.25 ± 9.76	12.83 ± 16.47
13	400mg	cocaine 20mg	144.17 ± 11.91	18.95 ± 8.22	86.58 ± 12.84	11.71 ± 8.25	92.58 ± 13.58	21.13 ± 13.09
		saline	140.50 ± 14.73	15.28 ± 14.84	82.17 ± 10.98	7.30 ± 8.38	85.67 ± 16.05	14.21 ± 21.52
14	400mg	cocaine 40mg	157.67 ± 12.64	34.20 ± 14.28	93.08 ± 12.54	19.00 ± 11.15	107.17 ± 16.17	37.54 ± 16.28
		saline	141.92 ± 8.43	18.45 ± 13.37	82.67 ± 9.36	8.58 ± 8.22	80.67 ± 9.32	11.04 ± 13.12
20	800mg	cocaine 20mg	148.67 ± 15.15	18.56 ± 14.11	87.58 ± 12.10	12.07 ± 10.07	92.25 ± 13.57	18.29 ± 14.72
		saline	143.25 ± 7.52	13.14 ± 14.34	81.92 ± 7.46	6.40 ± 9.84	82.00 ± 9.89	8.04 ± 16.69
21	800mg	cocaine 40mg	149.08 ± 6.83	19.25 ± 10.01	90.25 ± 9.86	12.30 ± 14.30	95.33 ± 13.94	19.50 ± 9.29
		saline	133.00 ± 8.72	3.17 ± 17.36	81.33 ± 11.18	3.38 ± 13.79	86.00 ± 14.30	10.17 ± 20.17

* Increase over baseline pre-infusion values (not shown)

Table 1b shows the calculated mean and standard deviation for each day's difference between the maximum absolute SBP, DBP, and HR after cocaine infusion and the maximum absolute SBP, DBP, and HR after saline infusion, as well as their statistical significance (*p*-values are from Appendix VI, Table 3).

Table 1b. Average of 12 Subjects' Changes in Hemodynamic Variables after Cocaine Infusion, with and without Modafinil. (R. Malcolm, 2003, Appendix VI, Table 2b)

Study Day	Modafinil Dose	Cocaine Dose	Maximum SBP (cocaine) – Maximum SBP (saline)	Maximum DBP (cocaine) – Maximum DBP (saline)	Maximum HR (cocaine) – Maximum HR (saline)
6	0mg	20mg	13.67 ± 16.41*	3.92 ± 9.36	11.83 ± 26.87‡
7	0mg	40mg	19.00 ± 18.08*	11.58 ± 10.97*	22.17 ± 23.87*
13	400mg	20mg	3.67 ± 9.71	4.42 ± 10.49	6.92 ± 17.53
14	400mg	40mg	15.75 ± 12.53*	10.42 ± 15.27*	26.50 ± 17.84*
20	800mg	20mg	5.42 ± 14.80	5.67 ± 10.59†	10.25 ± 16.82†
21	800mg	40mg	16.08 ± 11.52*	8.92 ± 10.88‡	9.33 ± 23.20†

† $p \leq .05$ ‡ $p < .005$ * $p < .0005$

In other words, Table 1b presents the magnitude of blood pressure and heart rate increases after 2 doses of cocaine infusions, with and without modafinil (0, 400 or 800 mg), and whether these increases are statistically significantly different from increases in vital signs after a saline infusion. Data presented indicate that, as expected, there are significant, generally dose-dependent, increases in hemodynamic measures after cocaine 20 mg and 40 mg infusions, both with and without modafinil. One exception was that increases in SBP, DBP and HR during a 20 mg cocaine infusion were not significant when 400 mg of modafinil was in steady state.

To answer whether modafinil caused an interaction, or additive effect with cocaine, Malcolm, et al computed multiple pair-wise comparisons for various modafinil and cocaine conditions, see Table 2 below (Malcolm, 2003, App VI, Table 4). In general, modafinil did not significantly modify the cocaine-induced blood pressure or heart rate increases at either the 400 mg or 800 mg daily dose.

Table 2. Level of Significance of the Difference Between Hemodynamic Variables For Various Modafinil and Cocaine Conditions Based on Pair-wise Comparisons (R. Malcolm, 2003, Appendix VI, Table 4)

Outcome / Comparisons	Maximum SBP of cocaine infusion − maximum SBP of saline infusion	Maximum DBP of cocaine infusion − maximum DBP of saline infusion	Maximum HR of cocaine infusion − maximum HR of saline infusion
Modafinil 0 mg vs. 400 mg at Cocaine 20 mg	**0.02**	0.90	0.42
Modafinil 0 mg vs. 800 mg at Cocaine 20 mg	0.06	0.66	0.80
Modafinil 400 mg vs. 800 mg at Cocaine 20 mg	0.69	0.75	0.59
Modafinil 0 mg vs. 400 mg at Cocaine 40 mg	0.46	0.77	0.48
Modafinil 0 mg vs. 800 mg at Cocaine 40 mg	0.50	0.50	**0.04**
Modafinil 400 mg vs. 800 mg at Cocaine 40 mg	0.94	0.70	**0.007**
Cocaine 20 mg vs. 40 mg at Modafinil 0 mg	0.22	0.06	0.10
Cocaine 20 mg vs. 40 mg at Modafinil 400 mg	**0.007**	0.13	**0.002**
Cocaine 20 mg vs. 40 mg at Modafinil 800 mg	**0.02**	0.41	0.88

There are several statistically significant exceptions noted in Table 2. One example is the dampening of heart rate increase at cocaine 40 mg when comparing a) modafinil 0 mg vs. 800 mg (p=0.04), and b) modafinil 400 mg vs. 800 mg (p=0.007); it appears that modafinil 800 mg significantly attenuated the expected heart rate increase compared to modafinil 0 or 400 mg. Similarly, the expected increase in systolic blood pressure at cocaine 20 mg, was significantly dampened by modafinil 400 mg compared to modafinil 0 mg (p=0.02). Also, three other statistically significant comparisons show that the increase in SBP and HR at modafinil 400mg, and in SBP at modafinil 800 mg, was greater for cocaine 40 mg than for cocaine 20 mg. However, this may be an expected dose-dependent response to cocaine, which showed the same tendency but did not reach significance, in the baseline condition of modafinil 0 mg.

In conclusion, the analysis of safety data (Tables 1a,b and Table 4) indicates that modafinil did not exacerbate the effects of cocaine on blood pressure and heart rate in the present sample of subjects with a history of cocaine dependence. Modafinil in steady state (400 and 800 mg daily), added to cocaine (20 or 40 mg i.v.), did not appear to further increase SBP or DBP or HR over the effect of cocaine alone. Rather, the statistical analyses (p-values of pair-wise comparisons presented in Table 4) indicate that at 800 mg daily dose modafinil may even have some mild effect of attenuating the expected increase (protective effect) in SBP and HR in cocaine users.

The four most common AEs for subjects completing this study included headache (ten subjects), insomnia (nine subjects), dyspepsia (four subjects), and nasal congestion (four subjects). Side

effects were mild, and either untreated or symptomatically treated, and no subject was terminated from the study due to modafinil side effects.

Evaluation of the mean effects of modafinil (400 and 800 mg daily) interactions with cocaine (20 or 40 mg i.v.) using VAS assessment indicates that modafinil significantly dampened all three VAS measures ("any drug effects", cocaine "high", "worth of cocaine in dollars") as compared to baseline cocaine only condition (R. Malcolm, 2003, Appendix VI,). For cocaine "high" measure, modafinil reduced VAS by about 45% for the 20 mg cocaine condition and about 35% for the 40 mg cocaine condition. Across all VAS measures and both doses of cocaine, the 800 mg dose of modafinil did not add significantly to this blunting effect as compared to the 400 mg dose of modafinil.

One study investigated acute behavioral and physiological effects of a single dose of modafinil (200, 400 and 600 mg) and compared it to those of oral cocaine (100, 200 and 300 mg) and placebo in 9 subjects with recent histories of cocaine abuse (i.e., positive urine for cocaine or BE during the initial screening) (Rush *et al.,* 2002). Four (4) subjects completed the modafinil dose-response function and then the cocaine dose-response function while for the other 5 participants this order was reversed; within a drug condition the order of dose administration was quazi-random. Heart rate and blood pressure were recorded for 30 minutes before and at 30-minute intervals after modafinil, cocaine or placebo administration for a total of 5 hours. The effects of cocaine generally were distinguishable from placebo by 0.5-1 hour after oral administration, peaked 1 hour after administration and did not differ from placebo by the end of experimental session. The effects of modafinil were distinguishable from placebo 1 hour after oral administration, peaked 4-5 hours after administration and continued to differ from placebo at the end of experimental session. The results of this study indicate that both cocaine and modafinil dose-dependently increased heart rate and blood pressure but although the highest dose of modafinil (600 mg) increased these measures significantly above the placebo levels it still did not produce clinically significant cardiovascular effects. Thus, significant elevation of heart rate following administration of 600 mg modafinil relative to placebo was largely attributable to a decrease in heart rate across the experimental session following the administration of placebo, and, importantly, the heart rate generally remained below 80 beats per minute following the administration of the highest dose of modafinil. Unlike cocaine, modafinil has a minimal abuse potential and was practically devoid of psychoactive effects across the range of doses tested except for a single instance of 600 mg modafinil-induced increased rating of Any Effect significantly above placebo levels on the Drug-Effect Questionnaire.

A double-blind placebo-controlled crossover study was conducted in male volunteers with a history of polysubstance abuse that included cocaine to compare the pharmacodynamic profiles and abuse potential of modafinil and methylphenidate (Jasinski, 2000). Each subject (N=24) was given single oral doses of methylphenidate (45 mg or 90 mg), modafinil (200 mg, 400 mg or 800 mg) and placebo. Both modafinil and methylphenidate produced dose-related increases in 6-hour area-under-the-curve (AUC) scores for supine and standing mean blood pressure and pulse rate. In addition, both agents produced significant orthostatic increases in pulse rate and blood pressure compared to placebo but the effect of modafinil in enhancing orthostatic tachycardia was significantly less than that of methylphenidate. The durations of observed and reported sleep following administration of modafinil 200 mg and 400 mg were similar to those

observed following methylphenidate 45 mg and 90 mg, while that of modafinil 800 mg was significantly reduced relative to modafinil 200 mg, 400 mg and methylphenidate. When comparing modafinil and methylphenidate, modafinil 200 mg and 400 mg had a significantly lesser effect than methylphenidate on reducing caloric intake, while the effect on caloric intake for modafinil 800 mg was similar to that of methylphenidate 90 mg. The results of this study indicate that at the doses tested modafinil did not appear to have reinforcing effects and did not induce a significant response on the Amphetamine Scale for Addiction Research.

4.10   EFFECT OF MODAFINIL ON PHARMACOKINETICS OF COCAINE

The effect of modafinil on the PK of cocaine was investigated in the study conducted at the Medical University of South Carolina Treatment Research Center that evaluated the potential for interaction between the cardiovascular effects of cocaine administered by the intravenous route and oral modafinil in twelve (12) adult cocaine experienced volunteers (R. Malcolm, 2003, Appendix VI). In that study, subjects were treated with 200 mg modafinil b.i.d. for 7 days (days 8-14) and after that with 400 mg modafinil b.i.d. for another 7 days (days 15-21). After 5 days-long administration of 200 mg modafinil b.i.d. (steady-state condition), all subjects were challenged with cocaine (20 mg and 40 mg i.v.) on two consecutive days (days 13 and 14). After 5 days-long administration of 400 mg modafinil b.i.d. (steady-state condition), all subjects were again challenged with cocaine (20 mg and 40 mg i.v.) on two consecutive days (days 20 and 21). In comparison to baseline infusions, modafinil caused statistically significant decreases in the primary variables defining cocaine exposure, such as maximum cocaine concentration in plasma (C_{max}; $p < 0.01$; $p < 0.001$) and the area under the cocaine concentration *versus* time curve (AUC) from time zero to 180 minutes ($p < 0.01$; $p < 0.001$) (C. Lindsay DeVane, 2003, Appendix VI). Figure 1 shows mean plasma cocaine concentration *versus* time following i.v. infusions of 20 mg cocaine (C20) or 40 mg cocaine (C40) at baseline and following 400 mg/day modafinil (M400) and 800 mg/day modafinil (M800) to steady state. The mechanism of the observed modafinil induced decrease in plasma concentration of cocaine may relate to modafinil's ability to induce cytochrome P450 3A. These results support safety of modafinil for treatment of cocaine dependence as modafinil does not seem to increase subjects' exposure to cocaine. The apparent decrease in cocaine exposure may contribute to a lack of reinforcement from cocaine abuse and enhance any inherent pharmacodynamic effects in pomoting abstinence.

Fig. 1   Mean Plasma Cocaine Concentration *versus* Time Following i.v. Infusions of 20 mg Cocaine (C20) or 40 mg Cocaine (C40) at Baseline and Following 400 mg/day Modafinil (M400) or 800 mg/day Modafinil (M800) to Steady State
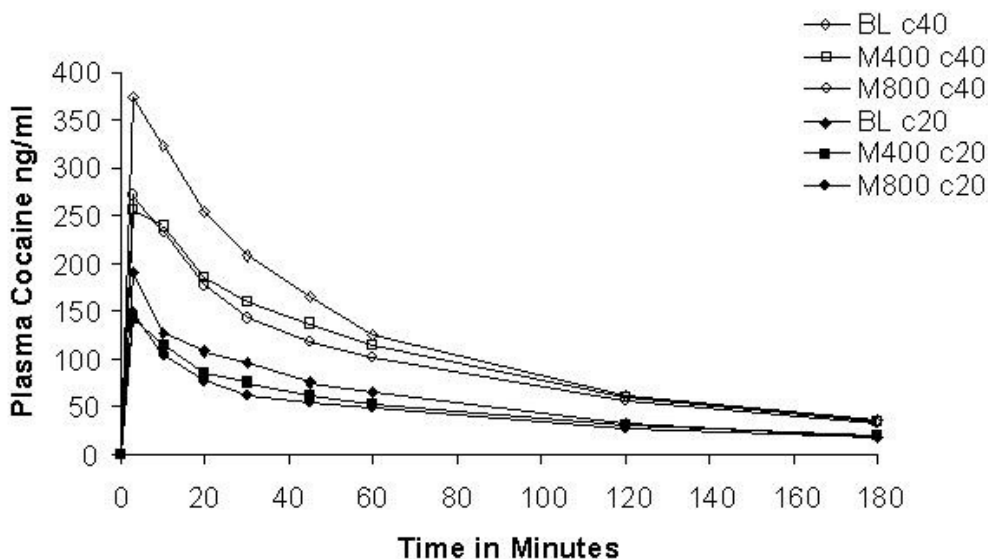
5   STUDY OBJECTIVES

5.1   PRIMARY OBJECTIVE

The primary objective of this study is to evaluate the efficacy of modafinil relative to placebo in increasing the weekly mean proportion of cocaine non-use days over the treatment period as determined by self-report of cocaine use confirmed with urine assays for BE.

5.2   SECONDARY OBJECTIVES

Secondary objectives include determining modafinil's:

1. Safety in the study population.
2. Efficacy in increasing the proportion of subjects who achieve abstinence for 3 weeks and for the duration of the treatment phase of the trial.

3. Efficacy in reducing the proportion of cocaine use-days as determined by self-report alone.
4. Efficacy in increasing the proportion of subjects who achieve measured reductions in cocaine use (25% and 50% reductions in the number of use-days compared to baseline use).
5. Efficacy in reducing the weekly median of the log of the urine BE levels.
6. Efficacy in the reduction in the severity of cocaine dependence (assessed by changes in ASI-Lite and ASI-Lite Follow-up and Self and Observer scored CGI) and craving (assessed by BSCS scores).
7. Efficacy in reducing the proportion of use-days of other substances of abuse (alcohol, marijuana, amphetamines, opiates, benzodiazepines and barbiturates) as determined by self-report and the percentage of urines positive for other drugs of abuse (amphetamines, opiates, benzodiazepines and barbiturates).
8. Efficacy in reduction of HIV risk-taking behaviors (assessed by HRBS).

6   STUDY SPONSOR

NIDA is the study sponsor.

7   STUDY SITES

This study will be conducted at six sites. Each site will enroll 35 subjects. All participating institutions will be geographically located within the United States. Based on the enrollment rate of other Phase II NIDA studies it is anticipated that sites will enroll approximately 5 subjects per month. With a total of six sites, it is estimated that enrollment will take 8 to 12 months to complete.

8   STUDY DESIGN

This is a double-blind, placebo-controlled, three arm study with a parallel group design. After a three-week screening/baseline period, subjects will be randomly assigned to one of three treatment groups to receive 200 mg modafinil, 400 mg modafinil or matched placebo daily for 12 weeks with a follow-up assessment 4 weeks after treatment completion. Adaptive randomization will be used to balance treatment groups based on site, gender, and days of cocaine use in the 30 days prior to screening ($\leq$ 18 *versus* >18). All subjects will receive standardized manual-guided CBT once a week during the 12-week treatment period.

9   SUBJECT SELECTION

210 male and female subjects with cocaine dependence will be enrolled in the study (70 subjects per treatment group). Entry into this study is open to both men and women and to all racial and ethnic subgroups. An attempt will be made to randomize at least 30% female subjects. Subjects will be recruited from a variety of sources. The primary source will be subjects seeking treatment for cocaine dependence via referrals from local treatment providers, advertising in local media, and word of mouth among subjects themselves. Additional subjects will be recruited from the community by advertising in the local media. Recruitment advertisements will be approved by the site's Institutional Review Board (IRB).

9.1   INCLUSION CRITERIA

Potential subjects <u>must</u>:

1.   Be at least 18 years-of-age.

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

3.   Be seeking treatment for cocaine dependence.

4.   Have at least 1 positive urine BE specimen (> 300 ng/mL) within the three-week screening/baseline period prior to randomization, with a minimum of 6 of the 9 scheduled samples tested, with no more than two specimens collected on consecutive days, and no more than three specimens collected in one week. (Urines should generally be collected 3 times a week on M, W, F)

5.   Be able to understand, and having understood, provide written informed consent.

6.   If female, be surgically sterile, 2 years postmenopausal, or if of childbearing potential, be using an accepted method of birth control and agree to continue use of this method for at least 30 days after the last dose of study drug. For this study, accepted methods of birth control are barrier method **with** spermicide; steroidal contraceptive [oral, implanted, injected, or patch] used **in conjunction with a barrier method**, or intrauterine device [IUD]). Participants who do not engage in heterosexual sex must agree to use one of these methods if they decide to do so during the study and for 30 days after last dose of study drug.

9.2   EXCLUSION CRITERIA

Potential subjects <u>must not</u>:

1.   Have current dependence, defined by DSM-IV criteria, on any psychoactive substance other than cocaine, alcohol, nicotine, or marijuana or physiological dependence on alcohol requiring medical detoxification.

2.   Be mandated by the court to obtain treatment for cocaine-dependence.

3.   Have been enrolled in an opiate-substitution program (methadone, LAAM, buprenorphine) within 2 months of screening.

4.   Be anyone who in the opinion of the investigator would not be expected to complete the study protocol due to probable incarceration or relocation from the clinic area.

5.   Have a psychiatric disorder, as assessed by the SCID, or a neurological disorder, brain disease, dementia or any disorder that, in the opinion of the study physician requires

ongoing treatment that would make study participation unsafe or which would make treatment compliance difficult.

6. Have had electroconvulsive therapy within the past 3 months preceding screening.

7. Have current suicidal ideation or plan (within the past 30 days) as assessed by the SCID.

8. Be pregnant or lactating.

9. Have serious medical illnesses including, but not limited to:

    • uncontrolled hypertension,
    • significant heart disease (including myocardial infarction within one year of enrollment), or any clinically significant cardiovascular abnormality (ECG),
    • hepatic, renal or gastrointestinal disorders that could result in a clinically significant alteration of metabolism or excretion of the study agent,
    • potentially life-threatening or progressive medical illness other than addiction that may compromise subject safety or study conduct.

10. Have clinically significant abnormal laboratory values, including those referenced in Appendix I.

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

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

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

14. Have a diagnosis of adult onset asthma (i.e., 21 years or older), 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 cocaine).

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

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

17.   Have received medication that could interact adversely with modafinil, with the time of administration of study agent and other medications based on the longest time interval of A, B, or C, below:

   A) Five half lives of other medication or active metabolite(s), whichever is longer
   B) Two weeks
   C) Interval recommended by other medication's product labeling

   Medications that fall into this category include:

   • Psychostimulants: amphetamine, dextroamphetamine, methylphenidate, dexmethylphenidate, pemoline, and sibutramine, due to possible additive effects of modafinil with these agents.
   • Potent inducers of CYP3A4: carbamazepine, phenobarbital, rifampin, and primidone as these can reduce plasma concentrations of modafinil
   • Potent inhibitors of CYP3A4: ketoconazole and itraconazole as these can increase plasma concentrations of modafinil
   • Substrates of CYP3A4: cyclosporine, triazolam, and ethinyl estradiol as modafinil has been shown to lower the plasma concentrations of these agents
   • Substrates of CYP2C19: diazepam, phenytoin, mephenytoin, propranolol, bupropion, citalopram, escitalopram, clomipramine, desipramine, imipramine, amitriptyline, and progesterone as modafinil is a potent CYP 2C19 inhibitor and has the potential to increase plasma concentrations of these agents
   • MAO Inhibitors: phenelzine, tranylcypromine, isocarboxazid, and selegiline as concomitant administration of these agents with modafinil has not been evaluated

18.   Have participated in any experimental study within 2 months preceding screening.

19.   Have known or suspected hypersensitivity to modafinil.

20.   Be taking modafinil for any reason currently or during the past year.

21.   Have alcohol dependence requiring medical detoxification in the opinion of the study physician.

Notes on inclusion/exclusion criteria: Although AIDS is an exclusion criterion, a positive antibody titer to HIV is not.   All potential subjects will be offered HIV testing. This test is offered as a courtesy to the prospective subject along with HIV education.

Potential subjects who are positive for syphilis by the RPR test will have a fluorescent treponemal antibody absorption assay (FTP-abs), a microhemagglutination for *Treponema pallidum* (MHA-TP), or a *Treponema pallidum* particle agglutination (TPPA) confirmatory test performed. If this test is positive, potential subjects must be treated for syphilis to be enrolled in the study or provide evidence of completion of treatment for syphilis.

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

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

10   INVESTIGATIONAL AGENTS

10.1   MODAFINIL

Modafinil (Provigil®) is a white to off-white crystalline powder that is practically insoluble in water (<1 mg/mL) and cyclohexane. It is sparingly to slightly soluble in methanol and acetone. Its chemical name is 2-[(diphenylmethyl)sulfinyl]acetamide, chemical formula is $C_{15}H_{15}NO_2S$ and the molecular weight is 273.36.

Modafinil tablets contain 100 or 200 mg of modafinil and the following inactive ingredients: lactose, corn starch, magnesium silicate, crosscarmelose sodium, magnesium stearate, povidone and talc. Modafinil is manufactured by Cephalon, Inc. (West Chester, PA) and will be supplied for this trial by Cephalon, Inc. (West Chester, PA) as 100 mg tablets for oral administration.

Modafinil should be stored away from heat, sunlight, and moist areas such as the bathroom where the wetness may cause it to break down.

10.2   PLACEBO

Placebo will be supplied by Cephalon, Inc. (West Chester, PA) as an exact match of modafinil.

10.3   DISPENSING INVESTIGATIONAL AGENTS

A ten-day blinded supply of modafinil and/or matched placebo will be dispensed by the research pharmacist weekly for daily self-administration by subjects. The investigational agents will be distributed by the research pharmacist directly to the subject or to the investigator or designee for dispensing to the subject. Subject will be instructed to take investigational agents one time per day in AM, by taking one dose packet (4 tablets) from the study medication bottle.

Note: Subjects should be instructed to take a missed dose as soon as they remember. However, if it is after 5pm, they should skip the missed dose and continue their regular dosing schedule the following morning. Subjects should not take a double dose to make up for a missed one.

Subjects should be cautioned about operating an automobile or other hazardous machinery until they are reasonably certain that modafinil therapy will not adversely affect their ability to engage in such activities.

10.4 RANDOMIZATION PLAN

Adaptive random allocation of subjects to study groups will be used 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 site, gender, and frequency of cocaine use in the last 30 days prior to screening ($\leq$ 18 *versus* >18). A 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. Randomized treatment assignment will be performed by the VA Cooperative Studies Program, Perry Point, MD. Sites will call the Perry Point automated telephone randomization system, enter the requested site and subject information, and will be given a randomization number which corresponds to numbered kits at each site's research pharmacy.

10.5 BLINDING PLAN

The investigational agents, modafinil and placebo, will be packaged in childproof bottles. Each treatment week, a participant will receive a bottle containing 10 doses, one dose for each day of the week plus an additional three day supply. Each dose consists of four tablets in a unit dose package (two 100 mg tablets and two placebo tablets for the 200 mg group; four 100 mg tablets for the 400 mg group; four placebo tablets for the placebo group). Subjects will be instructed to take one dose each day in the AM.

10.6 LABELING

The investigational agents, modafinil and placebo, will be packaged in units-of-use packages and supplied by the research pharmacist in childproof bottles. The bottles will be labeled with a product label and a subject label. The product label will include the protocol number, treatment number, study week number, number of doses in the bottles and the following statements - "Caution: New Drug--Limited by Federal Law to Investigational Use" and "Caution: Federal law PROHIBITS the transfer of this drug to any person other than the patient for whom it was prescribed". The subject label, supplied by the study site will include subject name, study physician's name, number of doses dispensed, directions for use, and will be labled "Modafinil or Placebo, thus identifying the drug but preserving the blind. It will also contain the name and address of the dispensing institution.

10.7 STORAGE

Investigational agents will be stored at room temperature, protected from light, in a secure location at dispensing pharmacy.

10.8   RECORD OF ADMINISTRATION

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

10.9   USED/UNUSED SUPPLIES

At the end of the study, all unused investigational agents must be inventoried. If any investigational agent is lost or damaged, its disposition should be documented. Unused investigational agents will be retained at the clinic sites pending instructions for disposition by the Sponsor at the end of the study.

10.10   SAFETY CONSIDERATIONS

The most commonly reported adverse events (AEs) (>5% of patients) associated with the use of modafinil are mild, usually resolve after a few weeks of treatment and in order of frequency include:

- Headache
- Nervousness
- Nausea
- Anxiety
- Insomnia

In general, modafinil is well-tolerated and in many clinical studies only headache occurs significantly more often in the active treatment group *versus* placebo.

To avoid drug-drug interactions, modafinil **should not** be administered concurrently with:

- Psychostimulants: amphetamine, dextroamphetamine, methylphenidate, dexmethylphenidate, pemoline, and sibutramine, due to possible additive effects of modafinil with these agents.
- Potent inducers of CYP3A4: carbamazepine, phenobarbital, rifampin, and primidone as these can reduce plasma concentrations of modafinil
- Potent inhibitors of CYP3A4: ketoconazole and itraconazole as these can increase plasma concentrations of modafinil
- Substrates of CYP3A4: cyclosporine, triazolam, and ethinyl estradiol as modafinil has been shown to lower the plasma concentrations of these agents
- Substrates of CYP2C19: diazepam, phenytoin, mephenytoin, propranolol, bupropion, citalopram, escitalopram, clomipramine, desipramine, imipramine, amitriptyline, and progesterone as modafinil is a potent CYP 2C19 inhibitor and has the potential to increase plasma concentrations of these agents
- MAO Inhibitors: phenelzine, tranylcypromine, isocarboxazid, and selegiline as concomitant administration of these agents with modafinil has not been evaluated

Medications that are substrates of CYP 1A2, 2B6, 2C9, 2C19, and 3A4 **should be used cautiously** during treatment with modafinil.

Appendix VII contains a list of substrates for these enzymes. Additional information for these interactions is available at www.drug-interactions.com. This website contains a comprehensive cytochrome P450 drug-interaction table that categorizes medications as substrates, inducers, or inhibitors of various hepatic enzymes. The information in Appendix VII is a modified version of what is available on this website.

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

11   TREATMENT PLAN

11.1   INVESTIGATIONAL AGENTS

Depending upon treatment group assignment, subjects will receive 200 mg modafinil, 400 mg modafinil or matched placebo daily for 12 weeks with a follow-up assessment 4 weeks after treatment completion.

On the first day of treatment, the subject will be sent home with sufficient amount of investigational agent for study week 1, plus enough additional investigational agent for an extra 3 days of dosing. The subjects will be instructed on how to take investigation agents during the upcoming days and asked to bring back empty bottles or any unused medication during the first clinic visit of study week 2.   Ideally, subjects will receive investigation agents during the first clinic visits of study weeks 1 to 12.

11.2   PSYCHOSOCIAL THERAPY

All subjects will receive standardized manual guided CBT provided by a certified therapist once per week during the 12-week treatment period. This CBT manual is the 2000 version of the Boston Cognitive Behavioral Therapy Manual developed at the Boston Behavioral Treatment Training Center at Boston University. In addition to the weekly therapy sessions, this program provides for additional emergency crisis management sessions up to a maximum of four. Patients are not discouraged from seeking other forms of psychosocial therapy outside the study. There will be no negative consequences based on urine toxicology results or patient revelations regarding use of illicit substances. In addition, one session of Motivational Enhancement Therapy (MET) will be provided during the third week of the screening/baseline period to assist subjects in completing screening and reaching the treatment period.

A standardized psychosocial behavioral program provides the therapy platform upon which pharmacological interventions may be evaluated. The goal of this behavioral treatment is to educate the subject about his/her dependence and factors associated with drug use, to assist study subjects in achieving abstinence from cocaine without obscuring the impact of the pharmacological treatment and to increase protocol compliance. Given the high rate of dropouts in this population, psychosocial therapy may also help to keep subjects in treatment. The primary purpose of using a manual-guided CBT is to achieve consistency of theoretical orientation, therapeutic style, and behavioral intervention across subjects and sites. Each therapy

session may be audiotaped to monitor drift and assure adherence to the manual-guided therapy. Approximately one tape per month per therapist may be reviewed and feedback provided to the therapist.

12   STUDY PROCEDURES

12.1   SUBJECT RECRUITMENT

Interested candidates who have been determined to meet the diagnostic criteria for cocaine dependence, are seeking treatment, and are available to come to the clinic for 14-to-16 weeks will meet with the investigator and receive an explanation of the study purpose and requirements. During the telephone interview, questions should not be asked in such a way as to reveal the eligibility criteria for study entry. 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. Participants are then given a copy of the signed informed consent. Following written informed consent, participants are given a subject identification number and proceed to the screening/baseline assessments phase of the study. Any participant who has difficulty understanding the information contained in the consent will receive further explanation 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 AND BASELINE

Screening and baseline assessments will be conducted as shown in Table 3. These assessments are conducted concurrently over a three week period. Subjects must meet eligibility requirements during the screening/baseline period in order to be randomized into the treatment phase.

During the third week of the screening/baseline period, one session of Motivational Enhancement Therapy will be conducted to assist subjects in completing screening/baseline and reaching the treatment phase.

12.3   SUBJECT ENROLLMENT

A prospective subject who meets all of the study inclusion and does not meet any of the exclusion criteria may be randomized into the study. Before randomization, the candidate will be asked to re-sign the informed consent to affirm agreement to participate in the study. The subject will then be given a copy of the signed consent form.

12.4   TREATMENT PERIOD

Subjects will be scheduled for assessments three times per week, usually on a Monday, Wednesday, and Friday for the duration of the treatment period (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 standardized manual-guided CBT once a week during the 12 weeks of treatment. Clinical evaluations are described in detail in section 13.0.

12.5   FOLLOW-UP

Four weeks after the end of the double-blind treatment period, subjects will be asked to come to the clinic for a follow-up visit (week 16). The subject will be asked to provide a urine specimen for BE/creatinine and urine toxicology screen, provide a self-report of substance use, and report any AEs or SAEs. The subject will be asked to report any current treatments for drug or alcohol abuse and to give an overall impression of the study agent. All female subjects will have a pregnancy test. If it is not possible to arrange for the subject to return to the clinic, the subject will be telephoned and asked to provide a current self-reported cocaine and other drug use, current treatment for drug or alcohol abuse, AEs/SAEs, and an impression of the study agent.

Whenever a subject leaves the study without notification and fails to return to clinic, a concerted effort will be made to contact the individual to assure no ill effects of study participation were experienced. 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.

12.6   MAINTAINING AND BREAKING STUDY BLIND

The decision to break the study blind for an individual subject should be made by the site investigator or with the NIDA medical monitor, but should be resorted to only in cases of life-threatening emergency when knowledge of the treatment group investigational agent will influence clinical management. Whenever the blind is broken the site investigator must notify Roberta Kahn, MD, Nida medical monitor and Edwina Smith, NIDA study director.

12.7   SUBJECT REIMBURSEMENT

Subjects will be reimbursed for travel expenses, for providing data, and for time contributed to this research study. Amount and schedule of reimbursement must be approved by the IRB. Subjects will be reimbursed (*amount and type of reimbursement - in cash or equivalent in retail scrip or vouchers to be added*) for each visit during the treatment period in which a urine specimen is supplied (*payment schedule to be added*). Subjects will receive (*amount and type of reimbursement - in cash or equivalent in retail scrip or vouchers to be added*) for each of the visits in which blood is drawn. Subjects will be paid (*amount and type of reimbursement - in cash or equivalent in retail scrip or vouchers to be added*) for the week 16 follow-up assessment. The maximum payment is (*to be added*). Subjects will be compensated regardless of whether they continue to receive the investigational agent, as long as they continue to complete all scheduled study assessments. This remuneration is for time and expenses incurred (e.g., gasoline, public transportation), not for compliance to the protocol.
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12.8   STUDY TERMINATION

12.8.1 Subject Termination

An investigator may terminate a subject if s/he deems it clinically appropriate or for any of the following reasons:

1) significant side effects from the investigational agents
2) serious or unexpected AEs which would make further study participation not in the patient's best interest
3) inability to comply with the study protocol
4) serious or chronic protocol violations
5) 7 consecutive missed visits
6) serious intercurrent illness
7) administrative reasons such as presenting a danger to staff or other participants

A subject may withdraw from the study anytime s/he wishes.

A subject may miss up to six consecutive visits and still continue to receive study agent. If seven consecutive visits are missed, the subject may not continue to receive study medications.

A subject who is discontinued from receiving the investigational agent for any reason will be allowed to continue psychosocial therapy with approval of the investigator, and will be encouraged to continue to complete all scheduled study assessments.

Any subject who discontinues prematurely, regardless of the reason, will be requested to return for a final visit to perform the necessary procedures listed in section 13.3 and to obtain data for end of study/early termination. Whenever a study participant stops coming to the clinic without notification, staff will make a concerted effort to contact the participant (or the designated contact person if participant cannot be contacted) to assure that they have had no untoward effects from study participation.

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

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

12.8.2 Trial Discontinuation

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

12.9   CONCOMITANT MEDICATIONS

Any medications (including prescription, over-the-counter, herbal supplements and health store products) to be taken during the study must be approved by the investigator. Modafinil should not be administered concurrently with:

- <u>Psychostimulants</u>: amphetamine, dextroamphetamine, methylphenidate, dexmethylphenidate, pemoline, and sibutramine, due to possible additive effects of modafinil with these agents.
- <u>Potent inducers of CYP3A4</u>: carbamazepine, phenobarbital, rifampin, and primidone as these can reduce plasma concentrations of modafinil
- <u>Potent inhibitors of CYP3A4</u>: ketoconazole and itraconazole as these can increase plasma concentrations of modafinil
- <u>Substrates of CYP3A4</u>: cyclosporine, triazolam, and ethinyl estradiol as modafinil has been shown to lower the plasma concentrations of these agents
- <u>Substrates of CYP2C19</u>: diazepam, phenytoin, mephenytoin, propranolol, bupropion, citalopram, escitalopram, clomipramine, desipramine, imipramine, amitriptyline, and progesterone as modafinil is a potent CYP 2C19 inhibitor and has the potential to increase plasma concentrations of these agents
- <u>MAO Inhibitors</u>: phenelzine, tranylcypromine, isocarboxazid, and selegiline as concomitant administration of these agents with modafinil has not been evaluated.

Medications that are substrates of CYP 1A2, 2B6, 2C9, 2C19, and 3A4 should be used <u>cautiously</u> during treatment with modafinil.

> Appendix VII contains a list of substrates for these enzymes. Additional information for these interactions is available at www.drug-interactions.com. This website contains a comprehensive cytochrome P450 drug-interaction table that categorizes medications as substrates, inducers, or inhibitors of various hepatic enzymes. The information in Appendix VII is a modified version of what is available on this website.

13   STUDY ASSESSMENTS

Study assessments should be completed according to the schedule provided in Table 3.

Table 3. Overview of Study Assessments

Assessment	Screening/Baseline		Randomization	Treatment						Follow-up
Study Week	-3 thru -1*			1-3	4	5-7	8	9 -11	12	16
Informed Consent signed										
Demographics	X									
SCID/Psychiatric evaluation	X		R							
Medical history	X		A							
Prior medications	X		N							
Infectious disease panel/syphilis test/PPD	X		D							
HIV test (optional)	X		O							
Safety			M							
Physical exam	X		I						X^c	
Vital signs**		Each visit	Z	X^a	X^b	X^b	X^b	X^b	X^c	
Hematology	X		A			X^b		X^b	X^c	
Blood chemistries	X		T			X^b		X^b	X^c	
HAM-D		X	I			X^b		X^b	X^c	
Urinalysis	X		O			X^b		X^b	X^c	
Pregnancy test	X		N	Every other week during treatment period						X
ECG	X				X				X^c	
Adverse events^d	X^d			$3X^d$	$3X^d$	$3X^d$	$3X^d$	$3X^d$	$3X^d$	X
Concomitant medications		Weekly X^b		X^b	X^b	X^b	X^b	X^b	X^c	X
Efficacy										
ASI-Lite***		X								
ASI-Lite Follow-up									X^c	
HRBS***		X							X^c	X
HIV counseling		X							X^c	X
BSCS		Weekly X^b		X^b	X^b	X^b	X^b	X^b	X^c	
CSSA		Weekly X^b		X^b	X^b	X^b	X^b	X^b	X^c	
CCQ		One time							X^c	
CGI-S		Weekly X^b		X^b	X^b	X^b	X^b	X^b	X^c	
CGI-O		Weekly X^b		X^b	X^b	X^b	X^b	X^b	X^c	
SUI		Every visit		3X	3X	3X	3X	3X	3X	X
Urine cocaine rapid test		Every visit								
Urine BE and creatinine**		Every visit		3X	3X	3X	3X	3X	3X	X
Urine tox screen**		Weekly X^b		X^b	X^b	X^b	X^b	X^b	X^c	X
Modafinil compliance				3X	3X	3X	3X	3X	3X	
CBT compliance ****		Week –3		X	X	X	X	X	X	
Missed visit log		PRN		Completed as a log only when subject misses visits						
Follow-up interview										X

* Screening and baseline assessments are conducted concurrently. ** Vital Signs and Urine Tox/Urine BE are both screening and baseline measures, and will serve as a possible basis for exclusion from study. *** ASI-Lite and HRBS also serve as both screening and baseline measures, but will not be used as a basis for exclusion from study. **** CBT to be conducted once a week during 12 weeks of treatment period.

X^a - Vital signs are taken at each visit the first three weeks of treatment, then weekly thereafter

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

X^c - **At the final scheduled study visit or if the subject discontinues prematurely**

X^d - AEs to be assessed by study staff at every visit; **a study physician must meet face to face with the subject weekly to assess all medical and psychiatric AEs since the previous MD visit, including those recorded by other study staff;** AEs are recorded on CRF weekly.

Notes on the Schedule of Assessments

Screening and Baseline 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 treatment with study agent. Screening and baseline occur simultaneously, and subjects must meet all eligibility requirements during the three-week screening/baseline period in order to be randomization into the treatment phase (Table 3).

During screening/baseline each urine specimen (usually collected on Monday, Wednesday and Friday) will be tested on the site via dipstick test for cocaine, then sent to the central laboratory for analysis of BE and weekly, other drugs of abuse (amphetamines, opiates, benzodiazepines and barbiturates).

Baseline assessments include the following:

1.   Three-times weekly urine BE plus creatinine measurements. Subjects must provide at least 6 of the nine scheduled urine specimens, at least one of which must be positive for urine BE (> 300 ng/mL). No more than 2 specimens may be obtained on consecutive days, no more than 3 specimens may be obtained in any one week and there may be no more than 4 days between specimens, including between end of screening/baseline period and sample collected on Week 1, Day 1. Specimens are generally collected on M/W/F.

2.   The following must be obtained weekly:
        a.   BSCS
        b.   CGI-S
        c.   CGI-O
        d.   CSSA
        e.   Urine oxicology screen
        f.   Concomitant medications

3.   Self-report of substance use will be conducted at each visit using the timeline/follow-back approach. Daily report of cocaine, alcohol, amphetamine, marijuana, opiate, benzodiazepine and barbiturate use will be recorded on an SUI CRF, covering each day since the last visit. This SUI will yield a report of the subject's substance use for each day of the study.

4.   HAM-D, ASI-Lite, CCQ and HRBS must be obtained once.

5.   AEs will be assessed by study staff at every visit; **a study physician must meet face to face with the subject once a week to assess all medical and psychiatric AEs since the previous MD visit, including those recorded by other study staff;** AEs are to be recorded on the CRF weekly.

Assessments During Treatment. Throughout the treatment period, subjects will be scheduled to return to the clinic three times per week for assessments. Those assessments occurring once per week should be performed at the first clinic visit of the week whenever possible. In addition a

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

Assessments at the End of Treatment or when a Participant Leaves Study Prior to the end of the Treatment Period. Urine BE and creatinine, SUI, concomitant medications, adverse events and treatment compliance are to be assessed three times during the last week of the treatment period. All other assessments scheduled for study week 12 (Table 3) should be completed, ideally at the final scheduled study visit. When a subject discontinues prematurely, regardless of the reason, all Table 3 week 12 assessments are to be completed. This may require requesting the subject to return specifically for final assessments.

Assessments at Follow-up (Week 16). The follow-up visit should be scheduled to occur approximately 4 weeks after the final in-clinic examination during the treatment period. After the AE assessment at the follow-up visit, only those AEs that are serious or clinically significant will be followed to resolution.

13.1   ASSESSMENT INSTRUMENTS

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

13.1.2   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.

13.1.3   Hematology
Blood will be collected in anticoagulant containing evacuated venous blood collection tubes (e.g., Vacutainer^{TM}) 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 locally. The laboratory performing these assessments should be either directly regulated by the College of American Pathologist (CAP) or the Clinical Laboratory Improvement Act of 1988 (CLIA) or indirectly according to CLIA guidelines. The laboratory will need to provide a copy of current certification.

13.1.4   Blood Chemistries
Blood will be collected in serum separation evacuated venous blood collection tubes (e.g., Vacutainer^{TM}) 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, alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), gamma-glutamyl transferase (GGT), total bilirubin, blood urea nitrogen (BUN). The laboratory performing these assessments should be either directly

regulated by CAP or CLIA or indirectly according to CLIA guidelines. The laboratory will need to provide a copy of current certification.

13.1.5　　　Infectious Disease Panel and Syphilis Tests

Blood will be collected in a serum separation evacuated venous blood collection tubes (e.g., Vacutainer^{TM}) 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 on all subjects and if positive a chest x-ray is required to assess active tuberculosis. If the subject reports that s/he has been previously positive for the PPD test or has been treated previously for TB, the PPD test will not be performed and only a chest x-ray will be required. A rapid plasma reagin (RPR) test for syphilis will be performed. If positive, a fluorescent treponemal antibody absorption (FTA-abs), a microhemagglutination for *Treponema pallidum* (MHA-TP), or a *Treponema pallidum* particle agglutination (TPPA) confirmatory test will be performed. If any tests are positive, the subject will be notified of the test results and referred to treatment.

13.1.6　　　HIV Test

All subjects will be offered the opportunity to have an HIV test performed. This test is not requisite for study participation. HIV test informed consent form must be obtained before collecting blood for this test. An HIV antibody test will be performed on a serum sample collected from the subject after the HIV test consent form is signed. All subjects will receive HIV counseling at baseline, week 12 and at the final follow-up (week 16).

13.1.7　　　Pregnancy Test

A urine pregnancy test designed to measure human chorionic gonodotropin will be used. All female subjects will be tested regardless of their childbearing capacity at screening, week 12 or early termination, and at followup. Female subjects will be tested every two weeks during treatment, unless there is documentation of a hysterectomy.

13.1.8　　　HAM-D

The HAM-D is an interviewer-administered assessment of the subject's level of depression. The 21-item version is being used, with three additional questions added by NIDA, which are associated with cocaine dependence (22. Helplessness, 23. Hopelessness, and 24. Worthlessness).

13.1.9　　　SCID

A Structured Clinical Interview for DSM-IV (SCID) (Spitzer *et al*., 1995) to assess the subject's cocaine-dependence, severity of depression, and Axis-I disorders will be conducted during screening.

13.1.10　　　ASI-Lite CF Version and ASI-Lite Follow-up

The ASI-Lite CF will be administered at baseline 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 assesses 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. ASI-Lite Follow-up will be administered at week 12; it eliminates demographic and other questions that do not change over time.

13.1.11   Urine Collection and Analyses
Urine will be collected for five types of analyses as follows:

1. Cocaine rapid test performed at the site during screening
2. BE and creatinine performed at a central laboratory
3. Urine Toxicology Screen (Qualitative Analysis of at least amphetamines, opiates, benzodiazepines and barbiturates) performed at a central laboratory.
4. Urinalysis performed at the local clinical laboratory
5. Pregnancy test

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

BE and Creatinine. Urine samples for BE and creatinine will be collected 3 times a week (generally Monday, Wednesday, and Friday, barring holidays and schedule conflicts). During baseline, three samples will be set aside, one for freezing and one for shipment to a central laboratory for analysis of BE plus creatinine. In addition, a third aliquot will be tested on-site for a rapid cocaine test result.

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

Urine Toxicology Screen (Qualitative Analysis of Substances of Abuse). The first sample of each week taken for BE and creatinine analysis will be analyzed additionally for at least amphetamines, opiates, benzodiazepines and barbiturates at the central laboratory. During the screening/baseline period, this weekly sample will be tested at the site for the above substances and then sent to the central laboratory for analysis.

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

13.1.12   Substance Use Inventory (SUI)
The SUI measures the subject's report of days of recent drug use and routes of administration. At each visit, participants are asked to report their substance use since their last visit. The information is elicited by study staff using a modified 'timeline follow back' method, which asks about most recent use, then use the prior day, then the day before that, recalling backwards until the day of the last visit. This method creates a record of a participant's report of substance use for each day of the study. The use of at least cocaine, alcohol, marijuana, amphetamines, opiates, benzodiazepines and barbiturates will be recorded.

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

13.1.14   Clinical Global Impression-Observer (CGI-O)
The CGI-O requires a trained observer to rate the global severity of the subject's cocaine dependence symptoms and to rate the improvement of the subject's cocaine dependence since baseline. The severity of the subject's cocaine dependence is rated first according to eight specific problem areas often associated with cocaine dependence. Then the global severity is rated, followed by the global improvement.

13.1.15   Clinical Global Impression-Self (CGI-S)
The CGI-Self is a self-administered assessment that asks the subject to rate the global severity of his or her cocaine dependence symptoms and to rate the improvement of his or her cocaine dependence symptoms since baseline.

13.1.16   Cocaine Selective Severity Assessment (CSSA)
The CSSA is administered by properly trained personnel. Questions relate to withdrawal symptoms of cocaine dependence. There are a total of 18 questions and subjects report their responses on a scale of 0 to 7 with 0 being no symptoms at all and 7 being the most extreme.

13.1.17   Adverse Events (AEs)
AEs will be assessed starting at the first visit following completion of the informed consent process and at each subsequent study visit by study staff. If an AE requires medical attention, it should be reported to a study physician immediately. **A study physician must meet face to face with the subject once a week to assess all medical and psychiatric AEs since the previous physician visit, including those recorded by other study staff.** AEs will be assessed by asking the subject, "How have you been feeling since I saw you last?" After current AEs are assessed, the study physician must review with the subject and assess any AEs unresolved from the previous week. After each weekly AE assessment, the physician will record on the AE CRF, according to the procedures described in section 14.6, the type of AE, severity of each AE, and the relationship to the study agent. These categories are asking for the physician's best judgment

of the severity and relatedness of each AE; the 'unknown' category should be used only if no information exists upon which to base an opinion.

13.1.18   HIV Risk-Taking Behavior Scale (HRBS)

The HRBS is a brief 11-item interviewer-administered scale (Darke *et al.,* 1991), to which 12th item ("Have you ever been diagnosed with AIDS?") was added by NIDA. It measures two distinct HIV risk factors in the behavior of intravenous drug users: one related to injecting behaviors and the other to sexual behaviors.

13.1.19   ECG

Twelve-lead electrocardiograms will be performed according to standard procedures. Ventricular rate (bpm), PR (ms), QRS (ms) and QTc (ms) will be reported on the ECG readouts. The results will be reviewed for interpretation by the investigator/study physician or a licensed, institutionally credentialed provider. The investigator may consult a board-certified cardiologist, if necessary.

13.1.20   Prior Medications

All medications taken by the subject for the 30 days prior to screening will be documented on a Prior Medication CRF. Information will be obtained using the same modified timeline follow-back method described in section 13.1.12 (Substance Use Inventory). The reported medications will be reviewed and approved by the site principal investigator/study physician.

13.1.21`   Concomitant Medications

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

13.1.22   Treatment Compliance

Treatment compliance will account for and record the amount of investigational agent taken by each subject. Subjects may be requested to keep a medication diary and bring it to each visit. Treatment compliance will be monitored by pill count.   Compliance with psychosocial therapy during the study will be accounted for by recording the length of time the subject spent in attendance at scheduled CBT sessions.

13.1.23   Cocaine Craving Questionnaire (CCQ)

The CCQ is a 45 item self-administered questionnaire that asks the subject to rate his or her craving for cocaine (Tiffany, *etal*, 1993).

14   REGULATORY AND REPORTING REQUIREMENTS

14.1 GOOD CLINICAL PRACTICES

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

14.2 FDA FORM 1572

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

14.3 IRB APPROVAL

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

14.4 INFORMED CONSENT

All potential candidates for the study will be given a current copy of the Informed Consent Form to read. The investigator, study physician or other study staff may initially explain all aspects of the study in lay language and answer all of the candidate's questions. If the candidate desires to participate in the study, s/he will be asked to sign the Informed Consent and screening may commence. No study procedure will be performed prior to the candidate's signing the Informed Consent. Prior to randomization, the principal investigator or study physician must explain the study, answer questions and consent the candidate. Immediately prior to randomization, the candidate will be asked to re-initial the Informed Consent, indicating continued willingness to participate in the study. Subjects who refuse to participate or who withdraw from the study will be treated without prejudice. A separate consent form for HIV testing will be completed for those subjects who elect to have this test performed.

14.5 DRUG ACCOUNTABILITY

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

14.6 OUTSIDE MONITORING

Data and Safety Monitoring Board: Safety data will be reviewed by a Data and Safety Monitoring Board (DSMB) that is sponsored by NIDA's Division of Pharmacotherapies & Medical Consequenses of Drug Abuse. This Board holds Quarterly meetings by phone, e-mail, or in person, to continually review cumulative AEs and SAEs from all study sites. The Board will be blinded to subjects' actual treatment assignments, but may break the blind if safety

concerns arise. The DSMB may be responsible for review of data from an interim analysis for re-estimation of sample size. Summary reports of the Boards findings and recommendations will be provided to each site's PI for submission to all local IRBs.

Medical Monitor: The NIDA medical monitor will be responsible for establishing concurrence with the investigator and/or the DSMB 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 (Appendix III). The NIDA medical monitor will also be responsible for tracking and assessing trends in all AEs and SAEs, and submitting to the DSMB Annual and Final Safety Reports. These Reports will be suitable for submission to IRB, FDA or other annual review.

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

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

Routine monitoring visits by the data management center (BRCI) monitoring unit staff will be scheduled at appropriate intervals but more frequently at the beginning of the study. A monitoring visit soon after the first two subjects have been randomized is recommended. At these visits, the monitors will verify that the study is being conducted according to the protocol guidelines and review CRFs with source documentation, AEs, SAEs and drug accountability. At the end of the study, they will advise on storage of study records and return of unused study agents. All sites should anticipate visits by NIDA, their representatives, and the FDA.

14.7 ADVERSE EVENTS REPORTING

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

An AE is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial, whether or not the event is considered related to the investigational agent or

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

Each week, a study physician must interview each subject to assess AEs occurring since the last visit. All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed by study investigators until satisfactory resolution. AEs must be reported up to 4 weeks following completion of, or termination from treatment. At week 16 follow-up visit, AEs will be followed to resolution only if they are serious, or if the study physician assesses them to be clinically significant.

14.8 SERIOUS ADVERSE EVENTS

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

* results in death;

* is life-threatening; *(NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.)*

* requires inpatient hospitalization or prolongation of existing hospitalization;

* results in persistent or significant disability/incapacity; or

* is a congenital anomaly/birth defect.

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

Reporting of AEs and SAEs is described in Appendix III. 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 investigators in this study have the responsibility of promptly reporting all SAEs to NIDA in order that NIDA can comply with these reporting regulations. The site should inform their IRB and Cephalon of all SAEs as well.

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, every attempt should be made to follow the subject until the problem prompting hospitalization has resolved. Every attempt should be made to obtain hospital records.

15   ANALYTICAL PLAN

15.1 STATISTICAL HYPOTHESES

15.1.1 Primary Efficacy Outcome
It is hypothesized that modafinil, as compared to placebo, will increase the weekly mean proportion of cocaine non-use days as determined by self-report of cocaine use confirmed with urine assays for BE.

15.1.2 Secondary Efficacy Outcomes
It is hypothesized that modafinil, as compared to placebo, will increase the proportion of successful subjects, the weekly mean proportion of cocaine non-use days according to self-report alone, the weekly mean proportion of other drug non-use days according to self-report and proportion of negative urines for other drugs use, and decrease the weekly median log of urine BE level. It is further hypothesized that modafinil will reduce the severity of cocaine dependence and craving as assessed by ASI-Lite, BSCS, CCQ, CGI-S, and CGI-O. It is also hypothesized that modafinil in combination with HIV counseling and psychosocial therapy (CBT) will reduce HIV risk-taking behavior (assessed by HRBS) hypothesized to be associated with cocaine use.

15.2   OUTCOME MEASURES

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

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

"The consensus of the group was that the best overall outcome measure was a composite index of abstinence derived from a combination of confidential patients self-report and objective biological testing (typically urinalysis testing). The recommendation was that this composite

index of abstinence be used to classify each day as abstinent or non-abstinent and that the primary outcome analysis be based on these classifications."

It is expected the exploratory analyses will be performed and that other outcome measures derived from the data will be used in these analyses to further understand cocaine dependency treatment effects.

Some data will be collected in this study for scientific use and not as primary or secondary outcome measures. Data from the CSSA are included in this category.

15.2.1 Primary Outcome Measure
The primary outcome variable is the weekly proportion of cocaine non-use days. Cocaine use and non-use days will be defined by subject self-report of use, confirmed or disproved by quantification of urine BE. For the primary efficacy response, each day of the 12-week study will be coded as either a use or a non-use day based on the self-reports and on the urine BE data. Three urine collection days are scheduled per calendar week. The first day of week 1 and the last day of week 12 that the subject receives the investigational agent will not be scored as use or non-use days because of the scoring rules. Thus, each subject has a maximum of 82 study days over the 12 weeks of the study.

Because of the pharmacokinetics of cocaine and BE, carryover from previous cocaine use may be difficult to distinguish in the laboratory from new use. The rules enunciated by Preston *et al*. (1997) and modified to meet the conditions of this study (Rules 1-5 below) will facilitate classification of each assessment day as use or no-use (Appendix V). Specifically, the Preston rules were modified to delete reference to previous urine specimen collected at least 48 hours earlier as assessment days may be less than 48 hours apart in this study.

The following will indicate "new use":

RULE 0:   Subject reports new use.
           The subject self report claims no new use but any of the following applies:

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

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

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

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

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

The following will assign study day as a "use" or "non-use day":

Self-report gives preliminary determination of each day as a use or non-use day. Self-reports of use are accepted in all cases, and every day in the study that subjects report use is scored as a use day (whether confirmed or disproved by urine BE). Self reports of non-use days are confirmed or disproved by the urine BE data as follows:

1.   Subject reports no new use since last urine BE or within the preceding 72 hours (whichever is the shorter time frame) but urine BE shows new use, then score the preceding day as a use day.

2.   Self-report days of non-use will be considered as missing if not followed by a urine BE assessment within 7 days.

The following will reevaluate the assignment of study day as a "use" or "non-use day":

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

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

For subjects with concordance rate <70%, the assignment of study days as use or non-use days should be reevaluated (the concordance rate of < 70% was established based on a survey of data sets from recently completed NIDA studies that showed that mean concordance rates ranged from 70-90%). Specifically, "self report days of non-use will be considered as missing if not followed by a urine BE assessment within 7 days" (see criterion in #2 immediately above) will be expanded to state that "If the concordance rate between self report and urine BE for the individual is < 70%, self report days of non-use will be considered as missing even in the case of obtaining urine within 7 days".

15.2.2 Secondary Outcome Measures

Measured reductions in cocaine and other drug use over 12-week treatment period

A.   The proportion of successful subjects. A successful subject is one who reduces the overall proportion of cocaine use days to 75% or less of his/her baseline rate.

B.   The proportion of successful subjects. A successful subject is one who reduces the overall proportion of cocaine use days to 50% or less of his/her baseline rate.

C.   The proportion of successful subjects. A successful subject is one who reduces use days to 75% of his/her baseline level according to subject self report without regard to BE levels.

D.   The proportion of successful subjects. A successful subject is one who reduces use days to 50% of his/her baseline level according to subject self report without regard to BE levels.

E.   The proportion of successful subjects. A successful subject is one who achieves 3 consecutive weeks of abstinence at any time during the treatment phase – self-report confirmed by urine BE.

F.   The proportion of successful subjects. A successful subject is one who achieves 3 consecutive weeks of abstinence at any time during the treatment phase and stays abstinent through the remainder of the treatment phase – self-report confirmed by urine BE.

G.   Weekly proportion of non-use days according to subject self report without regard to BE levels.

H.   Weekly proportion of non-use days of other drug use, by other drug according to SUI.

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

J.   Weekly median of the log of urine BE level.

K.   Overall proportion of cocaine non-use days during the 12-week treatment period (non-use days divided by non-missing study days).

L.   The maximum number of consecutive cocaine non-use days.

Reduction in the severity of cocaine dependence and craving

M.   CGI-O scores.

N.   CGI-S scores.

O.   ASI-Lite scores.

P.   BSCS scores.

Q.   CCQ scores.

Reduction in HIV Risk-taking Behavior

R.   Change in HRBS scores since baseline.

Safety of modafinil

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

15.3 SUBJECT POPULATIONS (INTENT-TO-TREAT, EVALUABLE AND COMPLETERS)

The intent-to-treat population is defined as the subjects who were properly qualified to participate in the study in accordance with the inclusion and exclusion criteria, were randomized to treatment, and received the first dose of study agent.

The evaluable population is defined as the subjects who were randomized, took study medication at least 3 weeks, and who contributed at least four (4) usable on-study-treatment urine samples and 21 days of self-report while on medication. This requirement can be satisfied any time during treatment, from Week 3 onward. Administrative study dropouts are defined as subjects who missed 7 consecutive study visits after randomization, were removed for other administrative or medical reasons (Sec. 12.8.1), or voluntarily discontinued participation in the study.

Study completers are subjects who: 1) continued to receive study medication (i.e., medication was not discontinued); 2) did not meet administrative drop-out criteria; and 3) provided a self-report of cocaine use/non-use covering at least one of the seven days of Week 12, which was confirmed or disproved by a urine collected which conformed to the primary outcome measure rules specified in Sec. 15.2.1.

15.4 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 site, gender, and frequency of cocaine use in the last 30 days ($\leq$ 18 *versus* >18). 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. Randomized treatment assignment will be performed by the VA Cooperative Studies Program, Perry Point, MD.

15.5 ANALYSIS PLAN

15.5.1 Efficacy Assessments

Each primary and secondary efficacy outcome measure will be analyzed for the intent-to-treat, evaluable population, and for study completers. 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.

It is hypothesized that modafinil treatment, compared to placebo, will be associated with fewer days of cocaine use as assessed by self-report confirmed with urine assays for BE. All statistical tests will be two-sided at a 5% Type I error rate. Confidence intervals will be two-sided with a 95% confidence coefficient.

Primary Efficacy Outcome

The primary outcome variable for each subject is the weekly proportion of cocaine non-use days. Each subject's weekly proportion is equal to the number of his/her cocaine non-use days divided by the number of his/her non-missing study days during that week (a maximum of 6 days for week 1 and 12 and 7 days for weeks 2 through 11). There is interest in attempting to estimate the actual number of cocaine "use" or "non-use" days by combining the self-reported patterns of use confirmed or disproved by the presence of urinary BE. For this outcome measure, each day of treatment will be coded as either a use or non-use day based on the self-reports and on the urine BE data. Three urine collections are scheduled per calendar week. The first day of week 1 and the last day of week 12 will not be scored as use or non-use days because of the scoring rules. Thus there would be a maximum of 82 days over 12 weeks of the study treatment for each subject.

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

1. It can be used to analyze different types of outcomes such as continuous, binary, or count.

2. It can be used to analyze an unbalanced design caused by either differing numbers of observations per person or by observations taken at different times.

3. The parameter estimates are consistent even if assumptions about the variance structure are not completely accurate.

As a secondary analysis, baseline severity of depression (HAM-D score $\leq$ 12 *versus* > 12) and its first-order interaction with treatment, site, gender and frequency of cocaine use in the last 30 days ($\leq$ 18 *versus* >18) will also be included in the model. Presentation will include the full model with all terms and a reduced model containing only significant terms.

Secondary Efficacy Outcomes

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

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

2. Weekly mean proportion of cocaine non-use days, other drug non-use days, and log of weekly median urine BE levels (measures G, H and J) by GEE.

3. The proportion of negative urines for other drug use, and the proportion of cocaine non-use days on study (measures I and K) will be assessed by generalized linear model.

4. The maximum number of consecutive cocaine non-use days will be assessed by Wilcoxon test (measure L).

5. Weekly CGI-O, CGI-S, and BSCS scores (measures M, N, P) will be assessed by GEE (the CGI-O, CGI-S, and BSCS scores obtained on the first visit of treatment week one before study agent administration will be also included in the baseline mean score calculations).

6. The change in the CCQ, HRBS and ASI Lite Followup scores (measures O, Q, R) from baseline to week 12 will be assessed by t-test or appropriate non-parametric test

15.5.2 Descriptive Statistics
Summaries of the characteristics of the subject population in both study groups at baseline will be prepared for the intent-to-treat, evaluable subjects, and study completers. A summary will be prepared to show dropouts/retention over time in each group and for *a priori* defined subgroups. The number of missing observations will be compared between treatments and for *a priori* defined subgroups. Weekly treatment compliance of each group will be summarized. All AEs will be reported in tabular form indicating the frequency and severity of each type of event. The frequencies of AEs by type will be compared between study groups using Chi-square analysis. Laboratory data, physical exams, and vital signs will be reported in tabular form.

15.6   SAMPLE SIZE CALCULATION

No formal power analysis was performed for this study's primary outcome of weekly mean proportion of cocaine non-use by GEE because there is little available information to determine the effect of modafinil on the study population and because in the previous pilot study of 17 patients the qualitative urine BE level was the outcome measure (C. Dackis, 2002, personal communication).

The study sample size is 70 subjects in each treatment arm. The number of 70 in each arm was selected based on other NIDA studies of substance abuse as a number that is sufficient to provide an estimate of treatment effect, which can then be used in planning a future, pivotal trial should it be warranted.

15.7   EXPLORATORY ANALYSES

The following lists some of the exploratory analyses that may be performed:

1.   Determine if the effects of modafinil treatment are more pronounced in the subgroup of subjects who are more motivated to stop using cocaine (≤ 18 *versus* >18 in the last 30 days prior to the study).
2.   Determine if modafinil treatment will increase treatment retention.
3.   Determine if modafinil treatment is more effective in the subgroup of subjects that demonstrated greater compliance with psychosocial therapy.

16   DATA MANAGEMENT AND CASE REPORT FORMS (CRF)

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

16.1 DATA COLLECTION

Data will be collected at the study sites on source documents, which will be entered at the site onto CRFs or into an electronic data capture system. The CRFs will be supplied by the data management center. CRFs 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. CRFs should be completed according to the instructions in the study operations manual.   Completed CRF information will be submitted on a regular basis to the data management center.   The site principal investigator is responsible for maintaining accurate, complete and up-to-date records for each subject. The site principal investigator is also responsible for maintaining any source documentation related to the study, including any films, ECG tracings, computer discs or tapes.

16.2 DATA EDITING AND CONTROL

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

Site investigators agree to routine data audits by the staff of the data management center as well as by NIDA. Data management center monitors will routinely visit each site to assure that data submitted to the data center are in agreement with source documents at the sites. They will also verify that investigational agents have been properly stored and accounted for, subject informed consent for study participation has been obtained and documented in the patient's progress notes, 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 will be made using established data management center procedures.

16.3 DATA ENTRY, PROCESSING AND ANALYSES

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 BRCI and NIDA in accordance with the analytical plan section of this protocol. Periodically during the investigation, data sets will be submitted to the NIDA DTR&D central data repository according to procedures specified in the study operations manual.

16.4 STUDY DOCUMENTATION AND RECORDS RETENTION

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

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Accordingly, source documents include, but are not limited to, laboratory reports, ECG tracings, X-rays, radiologist reports, subject diaries, biopsy reports, ultrasound photographs, subject progress notes, hospital charts or pharmacy records and any other similar reports or records of any procedure performed in accordance with the protocol. Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original document.

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

16.5 CONFIDENTIALITY

16.5.1 Confidentiality of Data

Particular attention is drawn to the regulations promulgated by the FDA 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 FDA 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, NIDA program officials and the IRB will have

access to the records. Subject information will not be released without written permission, except as necessary for monitoring by the FDA, the data management center (BRCI), NIDA or the IRB. Upon approval of the study by an IRB, an application will be filed with NIDA for a certificate of confidentiality. Subjects may be entered into the study upon receipt of the Certificate.

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

18   SIGNATURES

NIDA REPRESENTATIVES

Typed Name	Signature	Date
Ann Anderson, M.D. Principal Investigator	_____	_____
Ahmed Elkashef, M.D. Principal Investigator	_____	_____
Roberta Kahn, M.D. Medical Monitor	_____	_____
Edwina Smith, RN,BC, M.S. Project Director	_____	_____
Jurij Mojsiak, M.S. Project Officer	_____	_____

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
Domenic Ciraulo, MD Principal Investigator Boston Site	_____	_____
Ihsan M. Salloum, M.D., MPH Principal Investigator Pittsburgh Site	_____	_____
Eugene Somoza, MD Principal Investigator Cincinnati Site	_____	_____
John Roache, MD Principal Investigator San Antonio Site	_____	_____

Harold Urschel, MD _____ _____
Principal Investigator
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Malcolm Reid, PhD _____ _____
Principal Investigator
New York Site

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

Blood Chemistry and Hematology

Analyte	Values	
Fasting Glucose (mg/dL)	<40	>140
Non-fasting Glucose (mg/dL)		>200
AST (SGOT)		> 3X ULN*
ALT (SGPT)		> 3X ULN
Alkaline Phosphatase		> 3X ULN
Lactate Dehydrogenase		> 3X ULN
Gamma Glutamyltranspeptidase		> 3X ULN
Creatinine (mg/dL)		>1.7
Bilirubin (total) (mg/dL)		>1.5
Hemoglobin (g/dL)		
Male	<11.0	
Female	< 9.5	
Red Blood Cells (mill/mm^3)	<3.5	
White Blood Cells (per mm^3)	<2,800	>16,000
Neutrophils (%)	<35	>80
Eosinophils (%)		>10
Basophils (%)		>5
Lymphocytes (%)	<10	>50
Monocytes (%)		>15
Platelet Count (per mm^3)	<75,000	>700,000

*ULN = upper limit of normal

APPENDIX II: HIV/AIDS Education

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

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

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

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

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

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

A. GENERAL INSTRUCTIONS

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

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

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

4. Report the relatedness of the event to the study agent administration according to the guidance in section C.

B. DEFINITIONS – SEVERITY OF EVENTS

Mild: Awareness of symptom, but easily tolerated.

Moderate: Discomfort enough to cause interference with usual activity.

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

C. DEFINITIONS – RELATEDNESS OF EVENTS

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

•   *Exposure:* Is there evidence that the subject was actually exposed to the drug/placebo?

•   *Timing of the study drug/placebo:* Did the AE/SAE follow in a reasonable temporal sequence from administration of the drug test?

•   *Consistency with study drug profile:* Known pharmacology and toxicology of the study drug in animals and man; reaction of similar nature having been previously described with the study drug.

•   *Alternative explanations* for the adverse event such as concomitant medications, concurrent illness, non-medicinal therapies, diagnostic tests, procedures or other confounding findings.

•   *Response to discontinuation* of the study drug/placebo.

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

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

- *Definitely Not Related:*
  The subject did not receive the test drug, the temporal sequence of the AE/SAE onset relative to administration of the test drug is not reasonable, or there is another obvious cause of the AE/SAE.

- *Remotely Related:*
  There is evidence of exposure to the test drug or there is another more likely cause of the AE/SAE.

- *Possibly Related:*
  There is evidence of exposure to the test drug, the temporal sequence of the AE/SAE onset relative to administration of the test drug is reasonable, but the AE/SAE could have been due to another equally likely cause.

- *Probably Related:*
  There is evidence of exposure to the test drug, the temporal sequence of the AE/SAE onset relative to administration of the test drug is reasonable, and the AE/SAE is more likely explained by the test drug than by any other cause.

- *Definitely Related:*
  There is evidence of exposure to the test drug, the temporal sequence of the AE/SAE onset relative to administration of the test drug is reasonable, the AE/SAE is more likely explained by the test drug than by any other cause, and the AE/SAE shows a pattern consistent with previous knowledge of the test drug or test drug class.

D. SPECIFIC INSTRUCTIONS – LABORATORY/ECG ADVERSE EVENT

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

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

E. SERIOUS ADVERSE EVENT AND UNEXPECTED ADVERSE EVENT REPORTING

24 hour Reporting Requirements

Any serious adverse event, including death due to any cause, which occurs to any subject from the time of admission through discharge whether or not related to the study drug/placebo, must be reported *within 24 hours* to the NIDA Medical Monitor, the NIDA Project Director, and at least one of the principal investigators.

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

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

3-day Supporting Documentation Requirements

Written documentation for all SAEs/unexpected AEs must be received by the NIDA Medical Monitor/Alternate and the NIDA Project Director, and at least one of the principal investigators within 3 days of reporting the event. Required documents that must be submitted include the following:

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

Follow-Up of All Adverse Events/Serious Adverse Events

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

additional follow-up must be recorded in the source document. All serious and unexpected adverse events occurring 30 days after administration of the last dose of study drug/placebo must be reported. All follow-up week 16 AEs will be recorded and followed to resolution only if they are serious, or if the study physician assesses them to be clinically significant.

The investigator is required to provide the Medical Monitor/Alternate and the NIDA Project Director, and at least one of the principal investigators with all relevant follow-up information necessary to facilitate a thorough understanding of the event and judgment regarding the relationship to the study drug/placebo.

Reporting to the FDA

The IND sponsor is required to report SAEs to the FDA:

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

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

- in an annual report in all other cases.

APPENDIX IV: Procedure for Applying for a Certificate of Confidentiality

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

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

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

Applying for a Certificate of Confidentiality

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

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

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

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

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

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

> Ms. Jacqueline R. Porter
> NIDA Certificate of Confidentiality Coordinator
>   or
> Ms. Sandra Solomon,
> Certificate of Confidentiality Assistant
>
> Office of Extramural Affairs
> 6001 Executive Boulevard, Room 3158, MSC 9547
> Bethesda, Maryland 20852-9547
> Rockville, MD 20852 (courier or express mail)
> TEL: 301-443-2755
> FAX: 301-443-0538
> E-MAIL: jporter@nida.nih.gov   or   ssolomo1@nida.nih.gov

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

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

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

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

or

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

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

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

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

APPENDIX V: Guidance Document for Scoring Use and Non-Use Days for NIDA Clinical Trials of Cocaine Dependence

**NOTE: THE FOLLOWING EXAMPLE OF SCORING USE AND NON-USE DAYS IS BASED ON AN 8-WEEK TREATMENT PERIOD, BUT THE METHOD OF SCORING IS THE SAME ONE TO BE USED FOR A TWELVE WEEK TREATMENT PERIOD.

The following are the logical steps in the sequence of scoring cocaine use and non-use days. Note: This guidance document assumes that the study design included a 2-week baseline assessment period and an 8-week treatment period.

1.   Use the following modified Preston rules to determine if a urine sample is considered positive or negative for new use (the Preston rules take carryover of BE into account) as follows:

The following rules indicate that a sample is positive for new use:

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

Note: It does not matter how long before the preceding sample was collected. If the concentration of the current specimen is greater than the preceding specimen, there was new use in the interim.

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

Note: The concept here is that due to the excretion rate of BE in the urine that concentrations greater than half the concentration of the preceding sample are only possible if there is new use. Although it does not matter how long before the preceding sample was collected as long as samples were collected, at least one-day apart, this rule really applies to samples collected two days apart as RULE 4 applies to cases where samples are greater than two days apart.

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

Note: Because there is no earlier specimen, this sample, by default, is considered positive because carryover cannot be determined.

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

Note: Because there is no sample within two days, there is no way to establish if a carryover effect has occurred, these sample are *de facto* considered positive.

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

Note: Creatinine concentrations less than 20 mg/mL suggest that the urine sample is not physiologic and has been diluted in some manner.

EXAMPLE:

Study Day	-7	-6	-5	-4	-3	-2	-1	1	2	3	4	5
Weekday	M	T	W	T	F	S	S	M	T	W	T	F
BE ng/mL	800		399		275			325		800		625
BE +/-	+		-		-			+		+		+

Note: Every urine sample collected during the study between the start of the two-week baseline (shown as negative study days) and day 57 is scored as positive or negative for new use based on urine BE.

Study day –7 is positive per rule 3. (in the example above the study starts on day –7, this is not typically the case but is presented this way due to space layout constraints)
Study day –5 is negative per rule 2.
Study day –3 is negative because it is not considered positive by any rule.
Study day 1 is positive due to rule 4.
Study day 3 is positive due to rule 1.
Study day 5 is positive due to rule 2.

2.   *Use the subject's self-report of use in combination with the urine BE positive/negative scores from above to assign each study day as a use or non-use day without taking into consideration concordance rates as follows:*

a.   Self reports of use are accepted in all cases.

   Note: For every day in the study that the subject reports that they have used cocaine, score that day as a use day ignoring the urine BE levels. Remember, use and non-use days are also scored for each baseline measurement day of the study because some of the outcome measures will be compared to baseline use. Urine collected on the first day of the study before medication is given may be used to assess the preceding days as a use or a non-use day during baseline, if self-reports are given for these days.

b.   Subject reports no new use since last urine BE or within the preceding 72 hours (whichever is the shorter time frame) but urine BE shows new use, then score the preceding day as a use day.

c.   The first day of investigational agent administration is scored as missing.

d. Study days after day 56 are not scored; however, urine collected on day 57 may be used to assign a score to day 56.

e. If there is no urine after the last sample to confirm or disprove use, the subject's self report will be used to score that last study day. However, this may be overruled after calculating the concordance rate, if the concordance rate is <70%.

EXAMPLE:

Study Day	-7	-6	-5	-4	-3	-2	-1	1	2	3	4	5
Weekday	M	T	W	T	F	S	S	M	T	W	T	F
SUI	0	0	0	0	0	0	0	1	0	0	0	0
BE +/-	+		-		-			+		+		+
Score	0	0	0	0	0	0	1	M	0	0	1	0

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

Notes:
Day –7 is scored as no new use because the subject reported no use and there is no day –6 urine to overrule this.
Day –1 was scored as new use even though the subject reported no new use because the day 1 urine specimen was positive.
Day 1 was scored as missing because this is the first day of investigational agent administration and by default is not scored.
Day 2 was scored as no new use even though the day 3 urine specimen was positive because the subject did report use on day 1 which could account for the positive urine on day 3.

3. How to handle missing data. The examples above show complete data sets. However, participants in substance abuse studies frequently miss visits. The following rules apply to missing data.

a. If there is no self-report for a day, the day will be scored as missing, unless there is a urine specimen the following day that is positive. In this case, the day will be scored as a use day unless the subject reported use since the last urine specimen or within the preceding 72 hours.

b. Self report days of non-use will be considered as missing if not followed by a urine BE assessment within 7 days.

Note: This rule does not apply to the last day of the study (day 56 or earlier if the subject terminated the study earlier). If the subject reports new use, then this last day is scored as new use (standard rule from above). However, if the subject reported no new use on this day and a urine specimen is available for the next day, this urine sample will be used to score the last day of treatment. Alternatively, if the subject reports no new use and <u>no</u> urine specimen is available

for the next day, the day will be scored as no new use unless the concordance rate is < 70%, in which case it will be scored as missing.

EXAMPLE:

Study Day	3	4	5	6	7	8	9	10	11	12	13	14
Weekday	M	T	W	T	F	S	S	M	T	W	T	F
SUI	0	1	1	0	0	0	0	1	0	0	0	0
BE +/-	-		+									+
Score	0	1	1	M	0	0	0	1	0	0	1	0

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

Note: In this example, the self report of use/non-use on study day 6, is not followed by a urine sample until 8 days later on study day 14. Self-report of use/non-use is on study day 7 through 13 are followed by a urine result on day 14 and are thus not considered missing.

4.   *Determine concordance rate for each subject.*

Once a complete data set has been collected for a subject (this could be for an interim or final analysis) and the use and non-use days determined, the concordance rates can be calculated for the subject as follows (note that data for the interim analysis will be from a frozen locked dataset; however, it is not expected that the data is fully cleaned, thus, these data may change at the final analysis):

Percentage non-concordance between self-report of use and urine BE data will be calculated for each study subject as the percentage of the number of days that were scored as use days based on urine BE data overruling self-report divided by the total number of urine samples that were used to evaluate concordance, as follows:

% non-concordant = # non-concordant use days/total urine samples used to evaluate concordance * 100%, thus

% concordant = 100 - % non-concordant.

Notes:

Baseline scores will be used in the calculations of concordance regardless of whether the baseline period is two weeks-long or less. Baseline may not be followed immediately by treatment. If treatment does not immediately follow baseline, the first consecutive 14 day period used to establish baseline requirements for urine specimens (six total specimens over a consecutive two week period, three of which must be positive for BE and no more than 4 specimens collected in one week) will be considered the baseline period. If the number of baseline days is less than 14 for a participant, this will need to be considered in the statistical analysis.

Day 57 urine will be used to evaluate the last treatment day (Day 56) as use or non-use day and will be included in the denominator of % non-concordance calculation. Day 57 is the cut-off day and urines after Day 57 will not be used.

On-site cocaine test cups are used for screening but only the results if quantitative assay will be used for scoring purposes.

There may be a delay between the date of randomization and the date of treatment. The date of randomization is considered study day 1. These gaps between the start of treatment will need to be considered in the statistical analysis.

If the patient dropped out, the last clinic visit is considered to be the last study day.

EXAMPLE:

Study Day	3	4	5	6	7	8	9	10	11	12	13	14
Weekday	M	T	W	T	F	S	S	M	T	W	T	F
SUI	0	1	1	0	0	0	0	1	0	0	0	0
BE +/-	-		+									+
Score	0	1	1	M	0	0	0	1	0	0	1	0

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

Notes: Although this is not a complete data set, it serves the purpose of providing an example of the concordance rate calculation. In the above example, there is 1 discordant result on day 13. Thus, 1 is the numerator of the discordant rate calculation. There are 2 urine specimens used to establish concordance, the specimens on study days 5 and 14. Thus, 2 is the denominator of the discordant rate calculation. Therefore:

% non-concordant = 1 non-concordant use days/2 total urine samples used to evaluate concordance * 100% = 50%

% concordant = 100 – 50 % non-concordant = 50 % concordant

5.   *For subjects whose concordance rates are < 70%, the non-use days must be re-evaluated.*

Rule: When the concordance rate between self report and urine BE for the individual is < 70 %, non-use day scores will be considered as missing, if not followed by a urine specimen in 3 days.

EXAMPLE 1:

Original Scores:

Study Day	3	4	5	6	7	8	9	10	11	12	13	14
Weekday	M	T	W	T	F	S	S	M	T	W	T	F
SUI	0	1	1	0	0	0	0	0	0	0	0	0
BE +/-	-		+									+
Score	0	1	1	M	0	0	0	0	0	0	1	0

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

Notes: The concordance rate for this dataset is 50% and there is a longer than 3 day gap between urine specimens, thus the dataset will be re-scored as follows:

Re-scored:

Study Day	3	4	5	6	7	8	9	10	11	12	13	14
Weekday	M	T	W	T	F	S	S	M	T	W	T	F
SUI	0	1	1	0	0	0	0	0	0	0	0	0
BE +/-	-		+									+
Score	0	1	1	M	M	M	M	M	0	0	1	0

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

Notes:

Day 6 stays as missing because it was not followed by a urine result within 7-days.
Days 7, 8, 9, and 10 are re-scored as missing because there is no urine result in the next 3 days.
Days 11, 12, and 13 scores do not change because there is a urine result within the next 3 days (day 14).

EXAMPLE 2:
Original Scores:

Study Day	3	4	5	6	7	8	9	10	11	12	13	14
Weekday	M	T	W	T	F	S	S	M	T	W	T	F
SUI	0	1	1	0	0	0	0	0	0	0	0	0
BE +/-	-		+					+				+
Score	0	1	1	0	0	0	1	0	0	0	1	0

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

Notes: The concordance rate for this dataset is 33.3% and there is a longer than 3 day gap between urine specimens, thus the dataset will be re-scored as follows:

Re-scored:

Study Day	3	4	5	6	7	8	9	10	11	12	13	14
Weekday	M	T	W	T	F	S	S	M	T	W	T	F
SUI	0	1	1	0	0	0	0	0	0	0	0	0
BE +/-	-		+					+				+
Score	0	1	1	M	0	0	1	0	0	0	1	0

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

Notes:

Day 6 is re-scored as missing because there is no urine specimen in the next 3 days.

The following is an example of the scoring of a complete dataset for an individual:

Study Day	SUI	BE +/-	Score	Study Day	SUI	BE +/-	Score
-14	1	+	1	22	0	+	0
-13	0	+	0	23	0		1
-12	0		0	24	1	+	1
-11	1	-	1	25	0		0
-10	0		M	26	0		0
-9	0		0	27	0	+	M
-8	0		0	28	0		0
-7	0		1	29	0		0
-6	1	+	1	30	0		1
-5	1	+	1	31	1	+	1
-4	1	+	1	32	0		0
-3	0		0	33	0		0
-2	0		0	34	1	+	1
-1	1		1	35	0		0
1	0	+	M	36	1	+	1
2	0		0	37	0		0
3	1	-	1	38	1	+	1
4	0		0	39	0		0
5	0		0	40	0		0
6	0	+	M	41	0	+	0
7	0		M	42	0		1
8	0		M	43	0	+	0
9	1		1	44	0		1
10	0		M	45	0	+	M
11	0		M	46	0		0
12	0		0	47	1		1
13	0		0	48	0		0
14	0		1	49	1	+	1
15	1	+	1	50	0	+	0
16	1		1	51	0		0
17	0		0	52	0	-	0
18	0		0	53	0		0
19	0		1	54	0		1
20	0	+	0	55	0	+	M
21	1		1	56	0		M

Concordance rate = 66.7 %; no urine specimen is available on day 57; day 1 is the first day of investigational agent administration.

APPENDIX VI: Preliminary Report on Phase I Safety Evaluation of Cocaine Treatment Medication, Modafinil: Interaction with Intravenous Cocaine

APPENDIX VII: Substrates of CYP 1A2, 2B6, 2C9, 2C19, and 3A4 which should be used cautiously with modafinil.

1A2	2B6	2C19	2C9	3A4,5,7	
amitriptyline	bupropion	Proton Pump	NSAIDs:	Macrolide	HMG CoA
caffeine	cyclophosphamide	Inhibitors:	diclofenac	antibiotics:	Reductase
clomipramine	efavirenz	lansoprazole	ibuprofen	clarithromycin	Inhibitors:
clozapine	ifosfamide	omeprazole	**Error!**	erythromycin (not	atorvastatin
cyclobenzaprine	methadone	pantoprazole	**Hyperlink**	3A5)	cerivastatin
estradiol			**reference not**	NOT azithromycin	lovastatin
fluvoxamine		Anti-epileptics:	**valid.**		NOT pravastatin
haloperidol		diazepam	naproxen	Anti-arrhythmics:	simvastatin
imipramine		phenytoin	piroxicam	quinidine=>3-OH	
mexiletine		S-mephenytoin	suprofen	(not 3A5)	Steroid 6beta-OH:
naproxen					estradiol
ondansetron		amitriptyline	Oral	Benzodiazepines:	hydrocortisone
acetaminophen		carisoprodol	Hypoglycemic	alprazolam	progesterone
propranolol		citalopram	Agents:	diazepam=>3OH	testosterone
riluzole		clomipramine	tolbutamide	midazolam	
ropivacaine		cyclophosphamide	glipizide	triazolam	Miscellaneous:
tacrine		hexobarbital			buspirone
theophylline		imipramine	Angiotensin II	Immune	cafergot
verapamil		indomethacin	Blockers:	Modulators:	caffeine
(R)warfarin		mephobarbital	losartan	cyclosporine	cocaine
zileuton		nelfinavir	irbesartan	tacrolimus	dapsone
zolmitriptan		nilutamide			codeine- N-
		primidone	amitriptyline	HIV Antivirals:	demethylation
		progesterone	celecoxib	indinavir	dextromethorphan
		proguanil	fluoxetine	nelfinavir	eplerenone
		propranolol	fluvastatin	ritonavir	fentanyl finasteride
		teniposide	glyburide	saquinavir	gleevec
		(R)warfarin	phenytoin		haloperidol
			rosiglitazone	Antihistamines:	irinotecan
			tamoxifen	chlorpheniramine	LAAM
			torsemide		lidocaine
			S-warfarin		methadone
				Calcium Channel	odanestron
				Blockers:	pimozide
				amlodipine	propranolol
				diltiazem	quinine
				felodipine	salmeterol
				nifedipine	sildenafil
				nisoldipine	sirolimus
				verapamil	tamoxifen
					taxol
					terfenadine
					trazodone
					vincristine
					zaleplon
					zolpidem