

STUDY #: NIDA-CSP-1021

**DOUBLE-BLIND, PLACEBO-CONTROLLED MULTI-CENTER TRIAL
OF BACLOFEN FOR THE TREATMENT OF COCAINE DEPENDENCE**

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APPENDICES

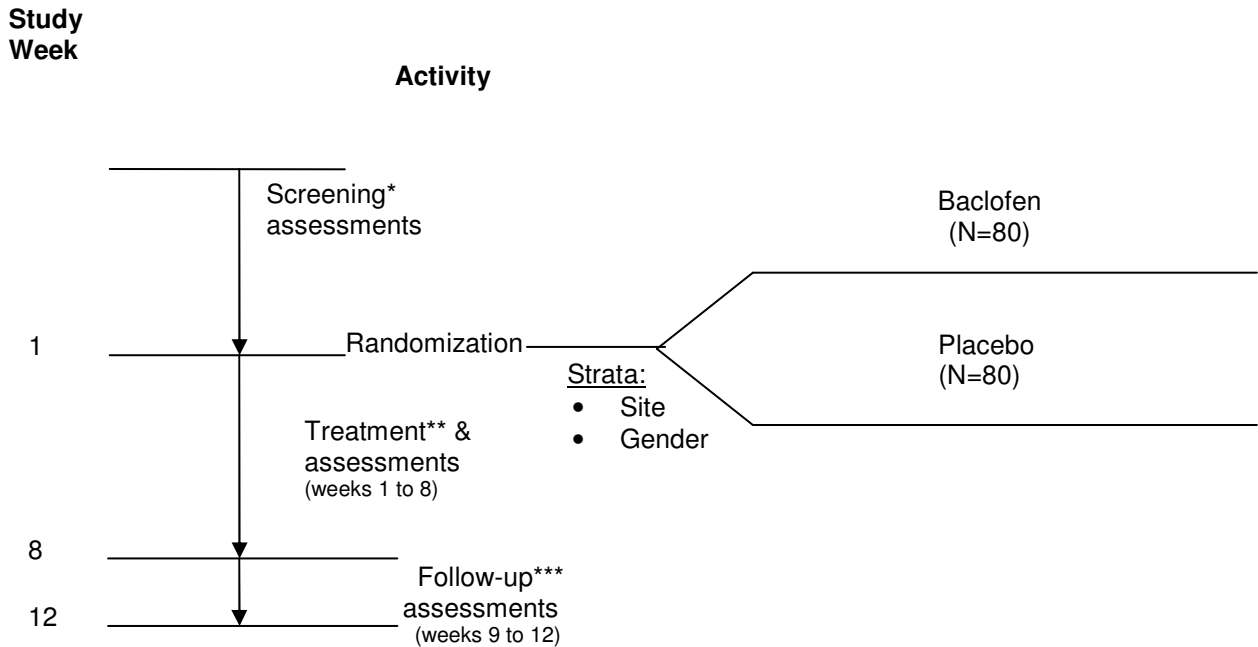
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1 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AIDS	acquired immune deficiency syndrome
ALP	alkaline phosphatase
ALT/SGPT	alanine aminotransferase/serum glutamic pyruvic transaminase
ASI-Lite	Addiction Severity Index-Lite
AST/SGOT	aspartate aminotransferase/serum glutamic oxaloacetic transaminase
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
CM	contingency management
CNS	central nervous system
CRF	Case Report Form
CPK	creatine phosphokinase
CSP	Cooperative Studies Program
CSPCC	Cooperative Studies Program Coordinating Center of the Department of Veterans Affairs (Perry Point, Maryland)
CSSA	Cocaine Selective Severity Assessment
CYP2D6	cytochrome P450 2D6 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
FDA	Food and Drug Administration
FTA-abs	fluorescent treponemal antibody absorption
GABA	gamma-aminobutyric acid
GGT	gamma glutamyltranspeptidase
HAM-D	Hamilton – Depression Rating Scale
HIV	human immunodeficiency virus
HR	heart rate

Abbreviation	Definition
HRBS	HIV Risk-taking Behavior Scale
IND	Investigational New Drug
IRB	Institutional Review Board
ITTRS	Interactive Touch Tone Randomization System
LAAM	levo-alpha-acetylmethadol
LDH	lactate dehydrogenase
MAO	monoamine oxidase
mg	milligrams
MHA-TP	microhemagglutination for <i>Treponema pallidum</i>
mL	milliliter
NET	norepinephrine transporter
NIDA	National Institute on Drug Abuse
OTC	over-the-counter
PCC	Pharmacy Coordinating Center
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
SMART	Site Mentoring Advice and Resource Team
SUR	substance use report
TPPA	<i>Treponema pallidum</i> particle agglutination
VACSP	Veterans Administration Cooperative Studies Program

2 STUDY SCHEMA



* Screening assessments occur over a 14-day period.

**Treatment period consists of:

- Dose escalation phase (week 1) with baclofen dose escalating from 10 mg to 60 mg daily or matched placebo.
- Maximal-dose phase (weeks 2 to 7) with 60 mg baclofen daily or matched placebo.
- Dose taper phase (week 8) with baclofen dose tapering off or matched placebo.

Note: Baclofen/placebo are administered orally in three divided daily doses at evenly spaced intervals with food, e.g., 2 tablets three times a day at 0700, 1500, and 2300 hours. Subjects will be provided with explicit instructions regarding an afternoon dosing window (1300 to 1700).

***Follow-up period consists of:

- Weekly assessments on weeks 9, 10 and 11.
- Final follow-up at week 12.

3 ABSTRACT

STUDY OBJECTIVES: To assess the efficacy and safety of baclofen in reducing cocaine use in subjects with cocaine dependence. It is hypothesized that baclofen treatment, compared to placebo, will be associated with fewer days of cocaine use as assessed by self-report confirmed with urine assays for benzoylecgonine (BE).

STUDY DESIGN: This is a double-blind, placebo-controlled, parallel design study in which, after a 14-day screening period, subjects will be randomly assigned to receive baclofen or matched placebo administered orally for 8 weeks with follow-up assessments for 4 weeks after treatment completion. The treatment period will consist of a dose escalation phase (week 1) with baclofen dose escalating from 10 mg to 60 mg daily or matched placebo, maximal-dose phase (weeks 2 to 7) with 60 mg baclofen daily or matched placebo and a dose taper phase (week 8) with baclofen dose tapering off or matched placebo. Follow-up will consist of assessments once each week during weeks 9, 10, 11 and 12. Adaptive randomization will be used to balance treatment groups based on clinical site and gender. All subjects will receive psychosocial therapy that will consist of weekly sessions of cognitive behavioral therapy (CBT) during the 8-week treatment period.

STUDY POPULATION: 160 subjects with Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria for cocaine dependence determined by structured clinical interview (SCID) will be randomized into one of two treatment groups (80 subjects per group). Subjects at least 18 years-of-age that provide 3 or more BE-positive urines during a 14-day screening period with the ability to understand and provide written informed consent that meet all of the study inclusion and do not meet any of the exclusion criteria may be randomized into the study.

TREATMENTS: During the 8 weeks of treatment, subjects will receive baclofen at a dose escalating from 10 mg to 60 mg daily or matched placebo during week 1, 60 mg baclofen daily or matched placebo during weeks 2 to 7 with baclofen dose tapering off or matched placebo during week 8. Baclofen/placebo are administered orally in three divided daily doses at evenly spaced intervals with food, e.g., 2 tablets three times a day at 0700, 1500, and 2300 hours. Subjects will be provided with explicit instructions regarding an afternoon dosing window (1300 to 1700). All subjects will receive CBT once a week during the 8 weeks of treatment. HIV counseling will be performed as a component of CBT.

SAFETY ASSESSMENTS: All candidates for study enrollment will have a physical examination, a 12-lead electrocardiogram (ECG) and clinical laboratory studies (blood chemistry, hematology, urinalysis, and pregnancy test, if female) completed during screening. Prior medication use will be assessed at screening and again on study day 1 prior to the administration of the 1st dose of study drug. A urine screen for other substances of abuse will be assessed weekly during screening, treatment and follow-up periods. Vital signs will be assessed at every clinic visit during screening (3 times a week) and once a week during treatment period.

A pregnancy test, if female, will be performed within 2 days prior to the first dose of investigational agent administration and at week 4; subjects will have clinical laboratory studies (blood chemistry, hematology, and urinalysis) at week 4. Adverse events (AEs) and concomitant medication use will be assessed at each study visit during the treatment period and recorded weekly on a case report form (CRF). At treatment week 8, or at the time of study discontinuation, all subjects will be evaluated for AEs, vital signs, physical examination, ECG, and clinical laboratory studies (including pregnancy test if female). AEs and concomitant medication use will be assessed weekly during the 4 weeks of follow-up.

EFFICACY ASSESSMENTS: The primary outcome variable for determining success in reduction of cocaine use will be weekly proportion of cocaine non-use days assessed by self report confirmed with urine assay for BE. Secondary assessments evaluating treatment effects on cocaine use include overall increases in the proportion of cocaine non-use days, increases in the proportion of successful subjects, weekly proportion of non-use days according to subject's self-report of use (SUR) without regard to BE levels, weekly non-use days of other drugs of abuse and increases in the largest number of consecutive cocaine non-use days. Severity of cocaine dependence will be assessed by comparing composite longitudinal scores of the Addiction Severity Index (ASI-Lite and ASI-Lite Follow-up), Brief Substance Craving Scale (BSCS), Cocaine Selective Severity Assessment (CSSA) and Clinical Global Impression as assessed by the subject (CGI-S) and an observer (CGI-O). The ASI-Lite will be performed at screening and ASI-Lite Follow-up at the first visit of weeks 4 and 8. The BSCS, CSSA, CGI-S, and CGI-O will be performed at each week during screening and at the first visit of each study week. Treatment effects on human immunodeficiency virus (HIV) risk-taking behavior hypothesized to be associated with drug use will be assessed by the HIV Risk-Taking Behavior Scale (HRBS). The HRBS will be conducted at screening and week 8. Another population descriptive variable to be used in covariate analysis includes the Hamilton Depression Rating Scale (HAM-D).

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. 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 who have completed the eight weeks of the double-blind treatment phase of the protocol. 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. As a secondary analysis, cocaine use in the last 30 days prior to informed consent (≤ 18 versus > 18), baseline severity of depression (HAM-D score ≤ 12 versus > 12) and their first-order interactions with treatment, clinical site, and gender will also be included in the model. It is hypothesized that baclofen treatment, compared to placebo, will be associated with a statistically significant change in cocaine use as assessed by weekly proportion of cocaine non-use days. 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, evaluable subjects, and for study completers. A summary will be prepared to show dropouts/retention over time in each treatment group and for study subpopulations. Weekly treatment retention will be summarized. All AEs will be reported in tabular form indicating the frequency of each type of event.

4 INTRODUCTION

4.1 COCAINE

Cocaine is a powerfully addictive stimulant. It was first extracted from the leaf of the *Erythroxylon coca* bush, which grows primarily in Peru and Bolivia, 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 (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 (Jansowski *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, 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.*, 2002a). 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).

The lack of success in finding an effective pharmacological treatment for cocaine abuse thus far, may in part, be 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). The

results of these monoamine transporter knockout studies also indicate that drugs (or drug combinations) acting on dopamine, serotonin and epinephrine brain systems may be needed to effectively combat cocaine addiction. Thus, drugs that block cocaine's uptake-inhibiting actions at DAT and SERT but allow it to continue to block uptake by NET could provide a possible means for cocaine antagonism at 'rewarding' transporters and continued cocaine action at its 'aversive sites' (Lin and Uhl, 2002; Uhl *et al.*, 2002).

However, despite intensive investment of resources and some promising data from a recent phase 2 placebo-controlled clinical trial with oral selegiline which has led 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. Investigators are increasingly looking for new families of investigational agents that may effectively alter the behavioral effects of cocaine. Conceptually, modulators of GABAergic system that exerts inhibitory control over DAergic system may have a therapeutic potential for the treatment of cocaine abuse.

GABA neurons are part of the mesolimbic dopamine system considered to be a major player in the brain reward and reinforcement circuitry and are known to dampen DA neurons via inhibitory GABA_B receptors (Bartholini, 1985; Bardo, 1998; Gong *et al.*, 1998). This finding that DAergic systems are under inhibitory control by GABAergic systems indicates that activation of GABAergic systems may reduce the activity of the mesolimbic DA system and thus lends support to the idea that GABA_B receptor agonists may have a therapeutic potential for the treatment of cocaine abuse (Dewey *et al.*, 1997,1998; Brebner *et al.*, 2002a; Cousins *et al.*, 2002). Increases in GABAergic activity induced by gamma-vinyl-GABA, an irreversible GABA transaminase inhibitor, have an attenuating effect on reward system and block cocaine self-administration in rats (Roberts *et al.*, 1996; Kushner *et al.*, 1999).

4.4 RATIONALE FOR STUDYING BACLOFEN

This study will investigate baclofen (Lioresal®), a GABA_B receptor agonist, as a potential medication for cocaine dependency. Baclofen (p-chlorophenyl GABA) is a GABA_B receptor agonist with skeletal muscle relaxant activities that is approved by FDA for treatment of spasticity caused by multiple sclerosis, spinal cord disease, and spinal cord injury.

Preclinical studies have demonstrated that baclofen prevents development of cocaine-induced behavioral sensitization and abolishes the motor stimulant actions of cocaine (Kalivas and Steward, 1991). In an extensive series of studies in rats, it has been also demonstrated that baclofen reduces intravenous cocaine self-administration (Roberts *et al.*, 1996; Brebner *et al.*, 2002a) and that this effect of baclofen is attenuated by GABA_B receptor antagonist CGP56433A (Brebner *et al.*, 2002b). Importantly, baclofen dose-dependently reduced cocaine-evoked DA release in the shell of rat nucleus accumbens confirming the ability of baclofen to modulate the mesolimbic DAergic transmission and indicating its potential as a candidate in the pharmacotherapy of cocaine abuse (Fadda *et al.*, 2003).

Human brain imaging studies indicate that baclofen blunts cocaine-induced changes in the limbic system. Thus, Brebner *et al.* (2002a) reported the results of imaging studies, wherein cocaine

addicts were given baclofen (10-20 mg twice daily by oral administration) for 7-10 days. When shown videotapes of drug paraphernalia, subjects treated with baclofen demonstrated elimination of limbic activation (orbital-frontal cortex, anterior cingulate, and amygdala) and reported reduced craving compared to cocaine addicts who were not given baclofen. A brain imaging study of a cocaine-dependent paraplegic patient chronically treated with baclofen was also conducted (Childress, 2002, personal communication). Following demonstration of videotapes of drug paraphernalia, no significant changes in relative regional blood flow were registered in this baclofen treated patient while in cocaine addicts who were not given baclofen regional cerebral flow increased.

Two clinical studies, one open-label and another double-blind placebo-controlled assessing the effects of baclofen on cocaine use and craving in cocaine dependent subjects, suggest that baclofen shows promise in the treatment of cocaine dependence and warrant an expanded efficacy trial of baclofen (see the next section for details of the human clinical trials).

4.5 PREVIOUS HUMAN EXPERIENCE WITH BACLOFEN IN DRUG ABUSING POPULATIONS

4.5.1 Clinical Trials in Cocaine Dependent Populations

In an open-label pilot study, 10 cocaine-dependent subjects were treated with baclofen (20 mg t.i.d.), in conjunction with three times a week cognitive behavioral group counseling. The results of this study showed a trend towards reduced cocaine craving and self-reported cocaine use (verified by urine toxicology), during at least a portion of the 17-week treatment period (average of 5 weeks) in nine of the ten cocaine-dependent subjects (Gudelman *et al.*, 1996; Ling *et al.*, 1998).

In a double-blind placebo-controlled clinical study, cocaine-dependent subjects were treated for 16 weeks with baclofen (20 mg t.i.d.) (N=35) or placebo (N=35), in conjunction with three times a week cognitive behavioral counseling (Shoptaw *et al.*, 2003). The results of this study indicate that there were no statistically significant differences in craving and cocaine use in subjects receiving baclofen treatment compared to those receiving placebo. However, there was a trend (measured by a joint probability index) towards a reduction in cocaine use in baclofen-treated subjects during weeks 3-8 which, based on a *post hoc* analysis, was statistically significant ($p < 0.001$). This observation supported a possible treatment effect. Importantly, baclofen treatment was more effective in subjects with a higher incidence of BE-positive urines during the baseline period. This implies that subjects who have a more chronic and severe form of cocaine dependence are more likely to benefit from baclofen treatment. Unfortunately, the small sample size of this study limited the power to detect statistically significant differences between treatment groups but provided valuable data for the estimation of sample size that will be addressed in this larger clinical trial.

4.5.2 Clinical Trials for the Treatment of Opiate Withdrawal Symptoms

Baclofen seems to have potential in the treatment of opiate withdrawal symptoms. In a double-blind randomized controlled trial that compared the efficacies of baclofen (N=31) and clonidine (N=31) in the treatment of opiates withdrawal in opiate addicts, baclofen (40 mg daily given t.i.d. in divided doses for 14 days) was equally effective to clonidine (0.8 mg daily given t.i.d. in divided doses for 14 days) in treating physical symptoms of withdrawal (feeling sick, stomach cramps, muscle spasm/twitching, cold sensation, heart pounding, muscle tension, aches and pains, yawning, runny eyes, insomnia), but showed a significant superiority over clonidine in the management of mental symptoms of withdrawal, such as anxiety, agitation, irritability and craving (Akhondzadeh *et al.*, 2000).

4.5.3 Clinical Trials for the Treatment of Alcohol Dependence

The results of recently conducted double-blind placebo-controlled clinical study indicate efficacy of baclofen in reducing alcohol craving and intake (Addolorato *et al.*, 2002a). A total of 39 alcohol-dependent subjects were enrolled; 20 were treated with baclofen and 19 with placebo for 30 days in combination with weekly psychological counseling. Baclofen was administered orally at the dose of 15 mg/day for the first 3 days and at 30 mg/day for the subsequent 27 days, divided into three daily doses. Baclofen proved to be more effective than placebo in inducing and maintaining abstinence from alcohol (both in terms of number of subjects reaching complete abstinence and cumulative abstinence duration) and reducing craving for and consumption of alcohol. Thus, baclofen reduced craving for alcohol in all 17 subjects that completed the study and produced abstinence in 14 subjects (Addolorato *et al.*, 2002a). It is possible that subjects managed to achieve and maintain alcohol abstinence due to the previously reported suppressing effect of baclofen on alcohol withdrawal symptoms (Addolorato *et al.*, 2002b). Baclofen showed mild anxiolytic effects with a decrease in state anxiety found in the baclofen compared to the placebo group; no significant difference was found between the two groups in terms of current depression symptoms. Baclofen proved to be easily manageable and no subject discontinued due to AEs.

Efficacy of baclofen for treatment of anxiety and depression in alcoholic patients has been reported in a placebo-controlled trial, in which subjects (N=90) were divided into 4 treatment groups to receive orally baclofen (37.5 mg/day, N=29), diazepam (15 mg/day, N=20), amitriptyline (75 mg/day, N=18), or placebo (N=23) for 3 weeks (Krupitsky *et al.*, 1993). The results of clinical, psychological and electrophysiological assessments indicate that baclofen is an effective drug for secondary affective disturbances (anxiety, depression) in alcoholics, with efficacy superior to placebo and equal to diazepam and amitriptyline, but without the side effects and complications of the latter, such as symptoms of dependence. All in all, several studies suggest that baclofen may have positive mood altering sedative effects, including amelioration of dysphoria that often accompanies early abstinence, and thus may promote both sustenance of abstinence and greater engagement in behavioral therapy (Krupitsky *et al.*, 1993; Addolorato *et al.*, 2002a,b; Cousins *et al.*, 2002).

4.6 BACLOFEN PHARMACOKINETICS

Baclofen (Lioresal®) is rapidly and completely absorbed after oral administration and is capable of crossing the blood brain barrier in humans (Faigle and Keberle, 1972; Katzung, 1992). Its mean plasma half-life is about 7.0 hours (Wuis *et al.*, 1989; Shellenberger *et al.*, 1999). The time to peak plasma concentration is 2-3 hours (Wuis *et al.*, 1990); peak plasma concentration following a 40 mg single dose is 500-600 ng/mL; concentration remains above 100 ng/mL for 8 hours (Wuis *et al.*, 1989). Peak plasma concentration (C_{max}) after administration of 10 mg of baclofen t.i.d. for seven consecutive doses (steady state) is 211 ng/mL (Shellenberger *et al.*, 1999). Therapeutic plasma concentrations of baclofen for muscle spasms treatment is 80-400 ng/mL (Gerkin *et al.*, 1986). Single dose concentration curves (10, 20 and 40 mg of ^{14}C -baclofen, p.o.) administered to a healthy human volunteer indicate that daily amount of baclofen should not be given as one dose in 24 hourly interval as in such case the blood level of baclofen would fluctuate widely between high maximum initially and low values at the end of the interval (Faigle and Keberle, 1972; Package Insert for Lioresal®). These results are in good agreement with pharmacokinetic parameters of baclofen found in the study with spastic patients treated with multiple oral doses (Wuis *et al.*, 1990) and thus indicate that administration of baclofen should be done in partial doses three times daily to reduce these fluctuations.

Preclinical studies in rats indicate that baclofen crosses the blood brain barrier slowly; thus, 5 minutes after administration of ^{14}C -baclofen (10 mg/kg, i.v.), its concentration in the brain is approximately ten times lower than in plasma, and 6 hours after dosing its elimination from brain tissue is much slower than from plasma (Faigle and Keberle, 1972). The delayed clearance of baclofen from the brain is confirmed by the fact that CNS depression in a patient that took 2 gm of baclofen in a suicide attempt persisted even after plasma levels of baclofen returned to the therapeutic range (Gerkin *et al.*, 1986).

Whole-body autoradiography indicates a rapid distribution of baclofen (20 mg/kg, i.v.) through the mouse body with above-average concentrations in liver and kidneys and below-average concentrations in brain and spinal cord (Faigle and Keberle, 1972).

About 15% of baclofen is metabolized by the liver, mostly by deamination; the rest (85%) is excreted by the kidneys unchanged (Wuis *et al.*, 1989; Shellenberger *et al.*, 1999). Renal clearance of baclofen (approximately 121 mL/min) is similar to creatinine clearance suggesting that glomerular filtration is apparently the dominant renal excretory mechanism (Wuis *et al.*, 1989, 1990; Shellenberger *et al.*, 1999). Approximately 70-80% of the dose (40 mg, p.o., to a human volunteer) is excreted within 24 hours and almost 100% within 3 days (Faigle and Keberle, 1972). Baclofen absorption is not affected by food, but it should be taken with a meal to minimize stomach upset (Peterson *et al.*, 1985; Package Insert for Lioresal®).

4.7 BACLOFEN DOSE JUSTIFICATION

For the FDA approved indication to treat muscle spasms, dosing with baclofen (Lioresal®) usually starts at 15 mg daily, increasing, if tolerated, to as high as 80 mg daily (20 mg 4 times a day) (Drug Handbook, 2001; Package Insert for Lioresal®). Oral administration at the daily

dose proposed in this study (60 mg) has been previously investigated in outpatient clinical studies (Ling *et al.*, 1998; Addolorato *et al.*, 2002a; Shoptaw *et al.*, 2003). This dose of 60 mg divided into three daily doses administered orally at evenly spaced intervals (every 8 hours) appears to be safe for studies of healthy cocaine addicts with no preexisting cardiovascular disease. The 60 mg daily dose was used for 16 weeks in the randomized placebo controlled clinical trial reported by Shoptaw *et al.* (2003) that showed signs of efficacy and a good safety profile in cocaine dependent subjects in the outpatient setting.

Treatment in this study will start with low dose of baclofen (10 mg daily) being gradually escalated to maximal-dose level of 60 mg daily. At the end of treatment period in this study, the dose of baclofen will be tapered off as abrupt withdrawal-associated AEs have been described in patients treated with baclofen for muscle spasticity, including visual and auditory hallucinations, convulsions (status epilepticus), dyskinesia, confusion, psychotic, manic or paranoid states, anxiety with tachycardia and sweating, insomnia and worsening of spasticity (Package Insert for Lioresal®). Note: No withdrawal-associated AEs or SAEs were reported during clinical trials of baclofen for the treatment of cocaine, alcohol or opiate dependence that utilized up to 17 weeks of treatment without dose taper (Krupitsky *et al.*, 1993; Ling *et al.*, 1998; Ahmadi-Abhari *et al.*, 2001; Addolorato *et al.*, 2002a; Shoptaw *et al.*, 2003).

4.8 SAFETY OF BACLOFEN

4.8.1 Expected Adverse Events

Baclofen is a skeletal muscle relaxant that decreases the frequency and amplitude of muscle spasms and alleviates the accompanying pain.

The safety profile of baclofen is well established. The principal side effects of oral baclofen are mild and usually resolve after a few weeks of treatment. The most common side effects (Package Insert for Lioresal®) that have been also reported during clinical trials of baclofen for the treatment of cocaine, alcohol or opiate dependence include:

- Sleepiness or Drowsiness
- Dizziness or Lightheadedness
- Unusual weakness, especially muscle weakness
- Confusion
- Fatigue or Tiredness
- Headache
- Nausea
- Abdominal or stomach pain
- Trembling

rare AEs reported with baclofen use for treatment of signs and symptoms of muscle spasticity may be related to the underlying disease rather than baclofen therapy and include: hallucinations, nightmares, paresthesia, slurred speech, coordination disorder, ataxia, tremor, rigidity, dystonia, blurred vision, nystagmus, strabismus, miosis, mydriasis, diplopia, epileptic seizures, lowered

convulsion threshold, respiratory depression, urinary frequency, urinary retention, dysuria, instances of rash, pruritus (Package Insert for Lioresal®). Isolated cases of increased blood glucose concentrations have been reported with baclofen; dosage adjustments of antidiabetic agents (oral and insulin) may therefore be necessary with combined baclofen treatment. There are some reports that in individuals taking antihypertensive medications baclofen will cause further reductions in blood pressure; thus, dosage adjustments of antihypertensive medications may be necessary with combined baclofen treatment.

Clinical cases of baclofen overdose have been described; all of them were suicide attempts with ingested baclofen doses in the range of 0.45 gm to more than 2 gm (Gerkin *et al.*, 1986). The clinical picture of baclofen overdose is notable for CNS depression, muscle hypotonia, absence of deep tendon reflexes, respiratory depression, seizures, hypothermia, hypotension and cardiac arrhythmias. The plasma clearance of baclofen in overdosed patients was characterized by first-order elimination with a half-life of 8.6 hours. Importantly, CNS depression persisted after the return of plasma levels of baclofen to the therapeutic range indicative of delayed elimination of baclofen from CNS (Gerkin *et al.*, 1986) and thus in concordance with the results of preclinical studies (Faigle and Keberle, 1972). The treatment of overdose is symptomatic as there is no specific antidote.

Drinking alcohol may enhance the side effects of baclofen, such as drowsiness, dizziness, weakness, and fatigue (Olin *et al.*, 1993). Therefore, taking alcoholic beverages should be avoided in any subject where staying alert is necessary.

As baclofen may affect mental alertness and coordination, subjects must be warned that they should not drive or operate equipment or perform activities requiring mental alertness until their bodies have adjusted to the medication.

4.8.2 Safety in Pregnant and Lactating Women

Baclofen crosses the placental barrier and is assigned pregnancy “Category C” labeling by FDA. Studies of birth defects with baclofen have not been done in humans. Studies in animals have shown that baclofen, when given in doses several times higher than the amount given to humans (mg/kg), increases the incidence of abdominal hernias in fetuses, the chance of incomplete or slow development of bones in the fetus and lower birth weight. Baclofen passes into the breast milk of nursing mothers but has not been reported to cause problems in nursing infants (Kalb, 2000).

4.8.3 Safety of Baclofen in Cocaine Using Populations

4.8.3.1 Data from Outpatient Studies

The safety of baclofen was investigated in several clinical studies, both open-label and double-blind placebo-controlled. In an open-label pilot study, 10 cocaine-dependent subjects were treated with baclofen (20 mg t.i.d.), in conjunction with three times a week cognitive behavioral group counseling (Ling *et al.*, 1998). The side effects reported in this study were generally mild; the most frequent were nausea, nightmares, headache, sedation and dizziness (reported in 5

subjects). This study also provided preliminary data on the safety of baclofen in combination with cocaine. Thus, nine of the participants used cocaine at least once during treatment, but none reported lasting or deleterious effects attributable to cocaine/baclofen interaction. Of the 4 subjects who were asked, none experienced any subjective differences in their cocaine 'highs' while taking baclofen.

Three serious adverse events (SAEs) were reported in the baclofen treatment group of a double-blind placebo-controlled clinical study, in which cocaine-dependent subjects were treated for 16 weeks with baclofen (20 mg t.i.d.) (N=35) or placebo (N=35), in conjunction with three times a week cognitive behavioral counseling; no SAEs were reported in the placebo group (Shoptaw *et al.*, 2003). All 3 SAEs involved worsening of the participants' cocaine problems and required overnight hospitalization and one of which required concomitant treatment for depression. Incidence of other adverse events (AEs), all rated as moderate in severity, were similar in baclofen and placebo treatment groups with the exception of headaches, which were reported more frequently in baclofen than in the placebo treatment group (32 *versus* 13), while flu/colds were reported 19 times in placebo compared to 10 times in the baclofen group. No clinically significant changes in physical examination, vital signs, cardiovascular function, and liver function tests were reported in either treatment group.

This study also explored a possible interaction between baclofen and cocaine by analysis of association between cardiovascular data and urinary BE values (Shoptaw *et al.*, 2003). Baclofen appears to have little effect on increase in heart rate (HR) subsequent to cocaine use as there was little to no increase in HR in subjects treated with baclofen as urinary BE levels increased; in contrast, subjects assigned to placebo demonstrated increases in HR that correlated with increase in urinary BE values (Figure 1). Baclofen appears to dampen the increase in systolic blood pressure (SBP) subsequent to cocaine use as a decrease in SBP was recorded in subjects treated with baclofen when urinary BE values increased (Figure 2). Analysis of diastolic blood pressure (DBP) as a function of the increase in urinary BE values did not reveal differences between baclofen and placebo groups (Figure 3). Thus, 3 subjects in each treatment group demonstrated urinary BE levels above 0 and DBP higher than 140 mm Hg with 7 occasions in the placebo *versus* 4 occasions in the baclofen group. Subjects treated with baclofen demonstrated lower respiration rates (RR) than those in the placebo group in general and especially when BE was detected in urine; thus, the RR exceeded 20 breaths per minute in 8 subjects in the baclofen group and in 20 subjects that received placebo when BE was detected in urine (Figure 4). Analysis of ECG data (graded as normal, borderline normal and abnormal) indicated that baclofen treatment may have mitigated cocaine-induced cardiovascular risks as subjects in baclofen group were statistically less likely to show abnormal or borderline ECGs as urinary BE levels increased than those taking placebo ($p=0.02$) (Figure 5).

Figure 1. Association Between Heart Rate and Urine BE Level by Assignment to Baclofen or Placebo

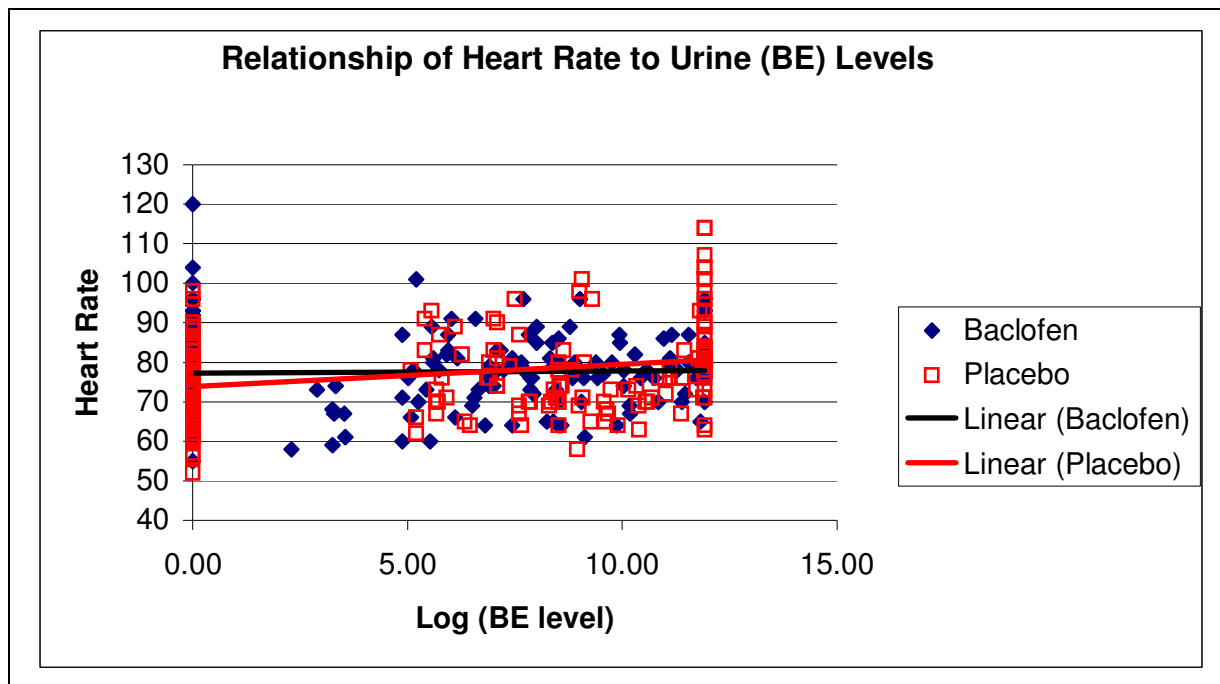


Figure 2. Association Between Systolic Blood Pressure and Urine BE Level by Assignment to Baclofen or Placebo

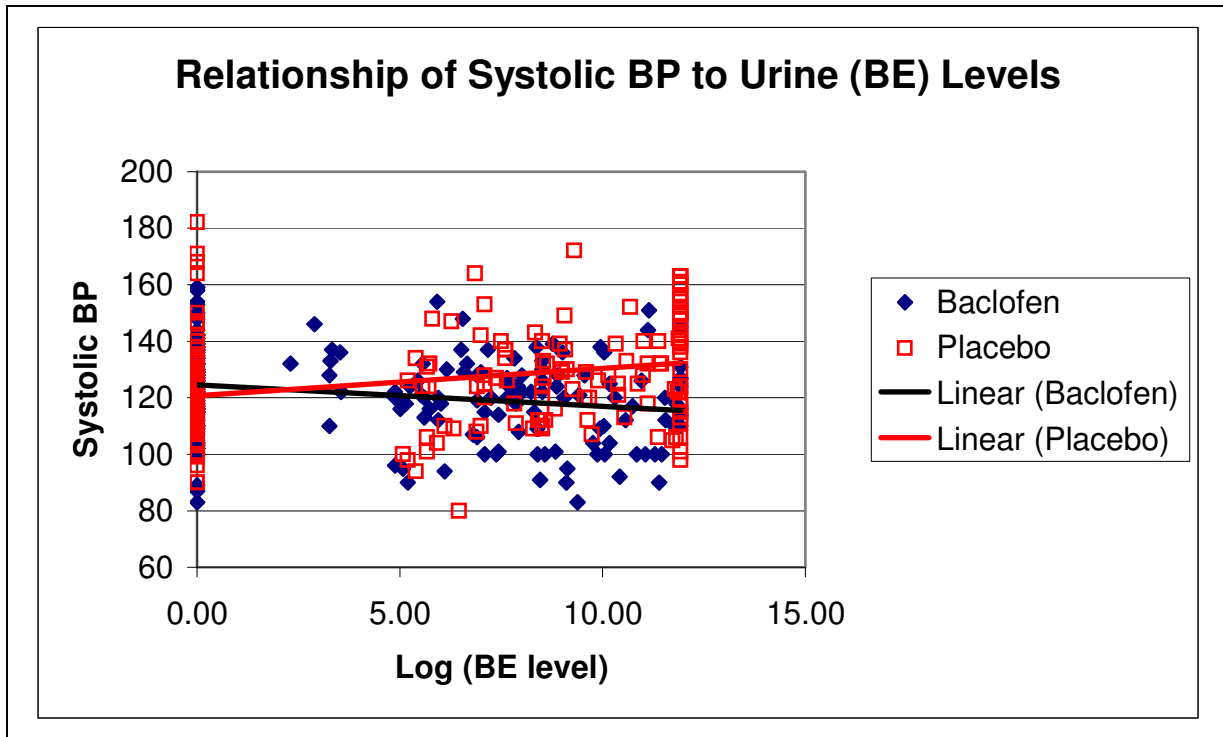


Figure 3. Association Between Diastolic Blood Pressure and Urine BE Level by Assignment to Baclofen or Placebo

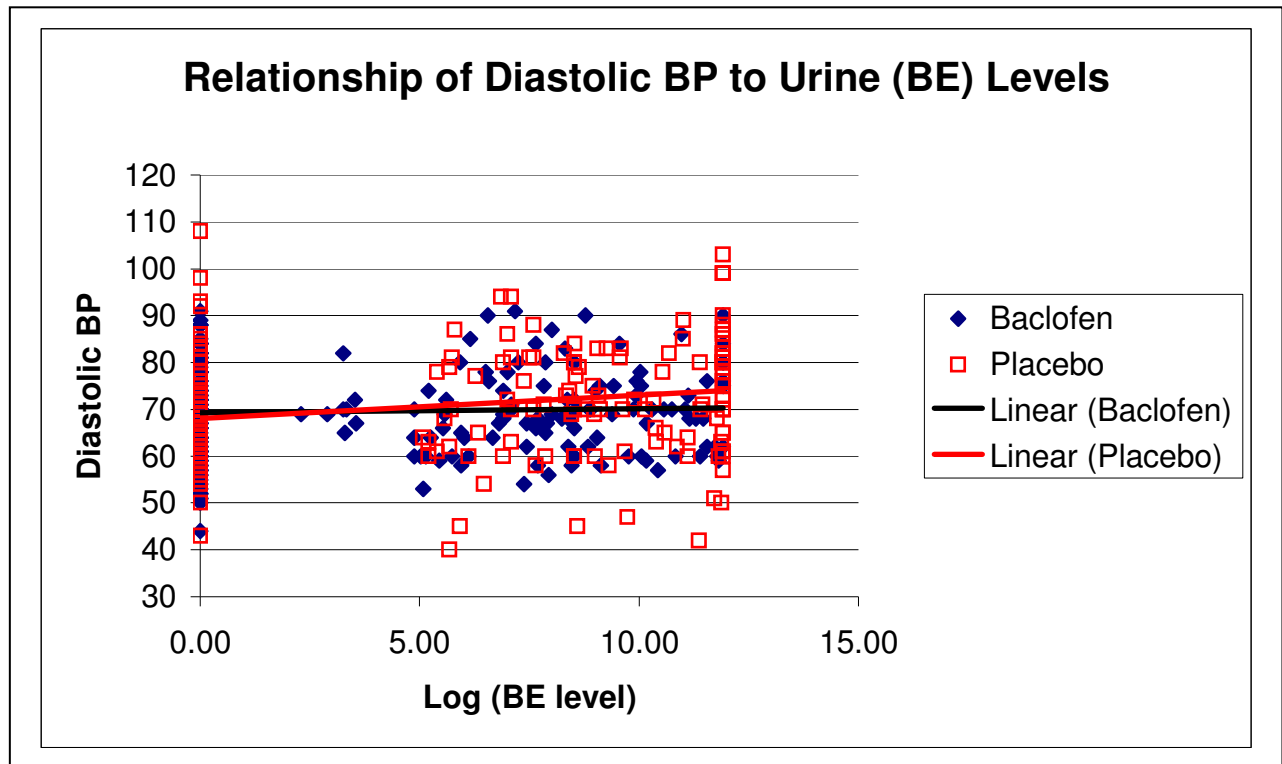


Figure 4. Association Between Respiration Rate and Urine BE level by Assignment to Baclofen or Placebo

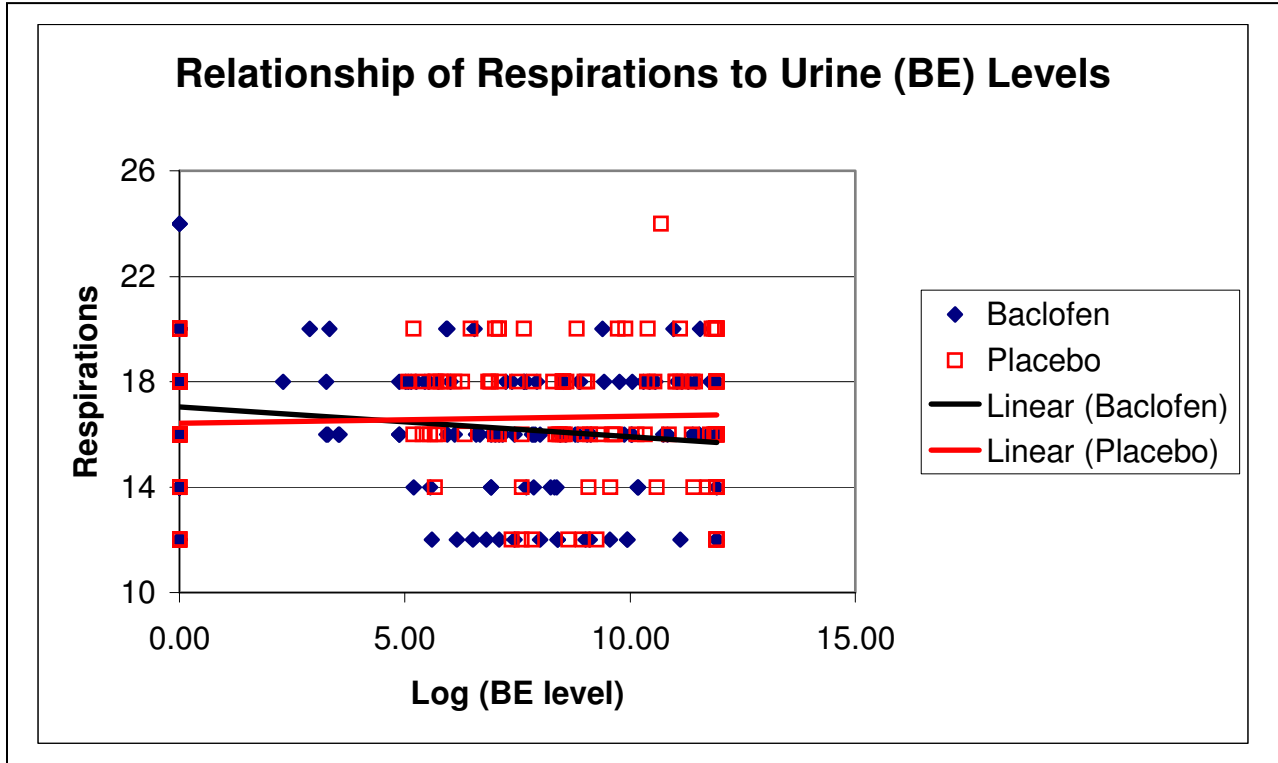
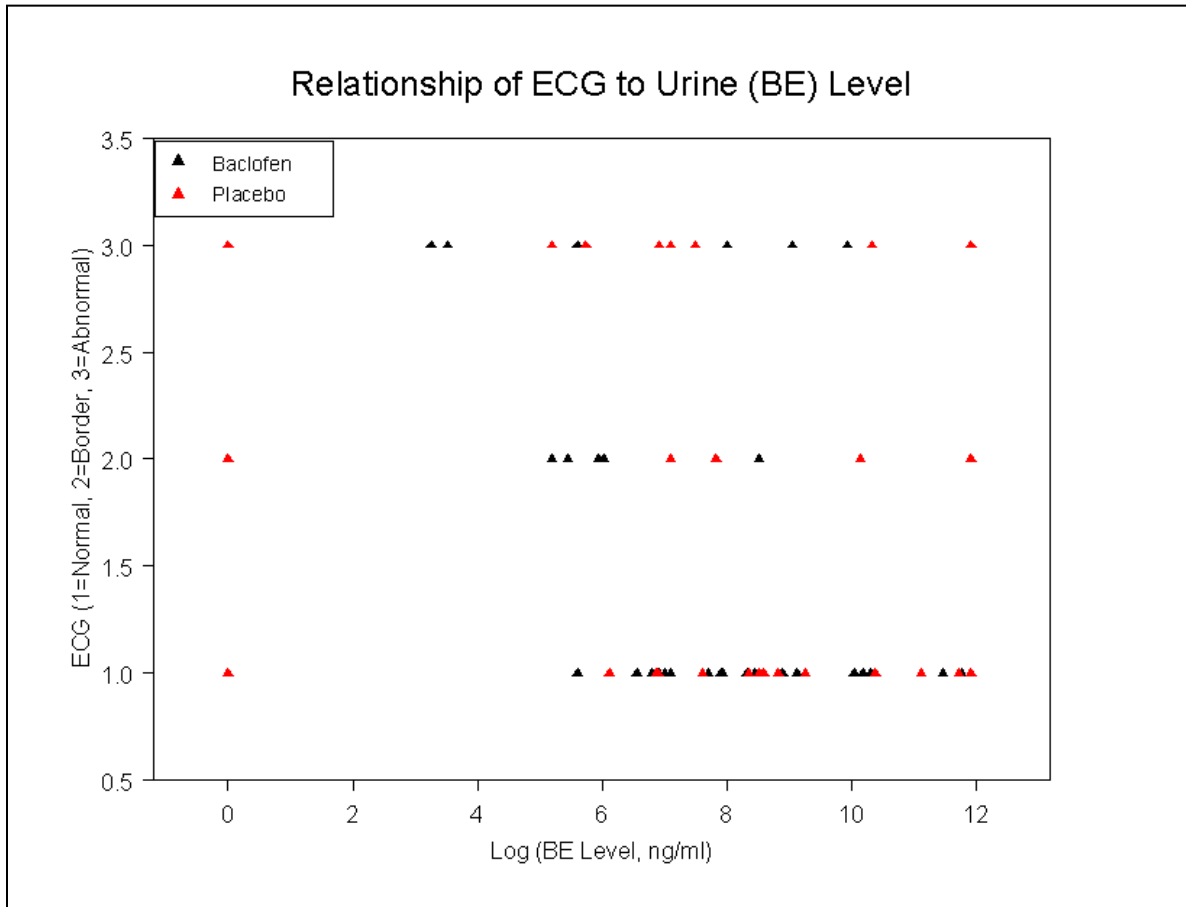


Figure 5. Association Between Level of ECG Results (Normal, Borderline Normal, or Abnormal) and Urine BE Level by Assignment to Baclofen or Placebo



No serious systemic or single-organ event leading to drug cessation was reported in a recent double-blind placebo-controlled clinical study of baclofen for the treatment of alcohol dependence (Addolorato *et al.*, 2002a). Baclofen was administered orally at the dose of 15 mg/day for the first 3 days and at 30 mg/day for the subsequent 27 days, divided into three daily doses. The most common AEs in the baclofen group, as previously reported in an open label trial of baclofen for alcohol dependence (Addolorato *et al.*, 2000), were sleepiness (2), tiredness (1) and vertigo (1), which resolved within 1-2 weeks of treatment and did not recur. Baclofen did not seem to have misuse liability as no patient reported euphoria or other pleasant effects after taking baclofen and no subject showed craving for baclofen or consumed baclofen above

the prescribed dose. At baclofen discontinuation, neither drug withdrawal syndrome nor side effects due to drug suspension were observed.

The results of another placebo-controlled clinical study of baclofen for the treatment of affective disorders in alcohol-dependent subjects indicate that baclofen administration (37.5 mg/day for 3 weeks) is not accompanied by any side effects and does not lead to development of dependence (Krupitsky *et al.*, 1993).

The safety of baclofen was also investigated in a double-blind randomized controlled trial that compared the efficacies of baclofen (N=31) and clonidine (N=31) in the treatment of opiates withdrawal in opiate addicts (Ahmadi-Abhari *et al.*, 2001). Subjects were treated with baclofen (40 mg daily given t.i.d. in divided doses) or clonidine (0.8 mg daily given t.i.d. in divided doses) for 14 days. Headache (9), nausea (9) and vomiting (7) were more frequently observed in the baclofen group while significantly more problems relating to orthostatic hypotension were encountered with subjects receiving clonidine than baclofen (11 *versus* 1).

4.8.3.2 Data from Inpatient Studies on Interactions of Baclofen and Cocaine

A possible interaction between baclofen and cocaine is being investigated in an ongoing phase 1 double-blind placebo-controlled study (T. Newton, personal communication, 2002). The goal of this study is to determine whether pretreatment with baclofen (30 mg t.i.d.) plus amantadine (100 mg t.i.d.), compared to pretreatment with placebo, will alter the cardiovascular changes produced by experimentally administered cocaine. Data collected from the subjects who were treated with baclofen orally (30 mg t.i.d.) (N=2) for 5 days and then challenged with cocaine (40 mg i.v.) were compared to those from subjects treated with placebo (N=2). Vital signs, e.g., systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), and ECG were recorded on the day of cocaine infusion session prior to and up to 180 minutes after administration of cocaine 40 mg intravenously over 1 minute (Table 1). Subjects continued to be monitored and under continuous observation for 6 hours post cocaine administration. An ECG was also obtained at screening and on the morning of cocaine infusion session.

Subjects treated with baclofen had normal ECGs at pre-dose and post-dose conditions for both baclofen and cocaine with no arrhythmias or changes in conduction intervals. Table 1 summarizes the vital signs recorded during 43 minutes after cocaine infusion. At time-points immediately after cocaine infusion, both subjects who received baclofen (subjects #1 and #2) demonstrated mild changes in systemic blood pressure and heart rate that returned to pre-infusion levels in 25 minutes. Subject #4, a placebo recipient, experienced elevation of SBP by approximately 30 mm Hg 5 minutes after cocaine infusion, but elevation of DBP by <5 mm Hg, and an elevation of heart rate that returned to pre-infusion levels in 10 minutes. These data indicate that there is no clinically significant cardiovascular interaction between oral baclofen after steady state conditions have been reached and acute exposure to cocaine administered intravenously (T. Newton, personal communication, 2002).

Table 1. Effect of Cocaine/Baclofen Interaction on Systolic Blood Pressure, Diastolic Blood Pressure and Heart Rate (T. Newton, personal communication, 2002)

	Subject #1			Subject #2			Subject #3			Subject #4		
	SBP	DBP	HR	SBP	DBP	HR	SBP	DBP	HR	SBP	DBP	HR
Days 1 to 5	Baclofen 30 mg t.i.d.			Baclofen 30 mg t.i.d.			Placebo			Placebo		
Day 6: min												
-15	106	66	67	105	69	76	111	70	73	106	70	68
0: Cocaine Infusion												
1	125	88	81	129	69	84	133	86	73	121	86	100
2	116	85	76	114	71	86	133	86	73	121	81	98
3	119	78	77	114	69	88	125	78	82	121	74	107
4	121	81	77	123	75	93	134	82	73	136	74	121
5	120	75	75	117	72	74	131	89	84	130	82	104
6	115	77	75	112	69	87	118	71	80	117	78	101
7	122	78	83	110	70	85	117	79	83	112	74	99
8	110	78	73	113	71	83	117	74	72	116	76	93
9	110	78	70	113	69	77	118	71	87	98	61	88
10	112	77	72	106	65	83	117	79	83	108	73	79
15	109	76	71	107	68	77	116	74	74	110	74	82
20	96	77	63	99	65	73	101	71	82	107	71	75
25	123	83	75	117	75	89	107	73	75	116	75	106
30	126	82	70	116	67	88	117	72	76	115	71	93
35	120	82	68	98	67	84	109	72	76	108	70	83
40	103	79	71	99	66	77	100	68	72	106	74	81
43	104	84	78	100	66	74	93	68	78	109	77	79

Another safety study was conducted to evaluate the potential for interaction between the cardiovascular effects of cocaine administered by the intravenous route and oral baclofen. Five (5) adult cocaine experienced volunteers were admitted to the University of Pennsylvania Treatment Research Center. Subjects were assigned to receive baclofen 20 mg b.i.d. orally (N=3) or placebo (N=2) in a randomized double-blind fashion. Subjects #1 and #4 received placebo, while subjects #2, #3, and #5 received baclofen. All subjects were challenged with cocaine (30 mg i.v.) twice: one day prior to administration of baclofen (day 2) and following two days of baclofen or placebo administration (steady state, day 5). Vital signs (HR, SBP, DBP) and ECG were monitored by continuous real-time non-invasive techniques, and recorded on the day of each cocaine infusion session at the following time points for subjects #1, 2 and 3: -150, -120, -10, +5, +15, +30, +45, +60, +90, +120, +180, and +240 minutes, where (-) and (+) time is expressed relative to administration of cocaine 30 mg intravenously over 1 minute. For subjects #4 and #5, the time-points were changed to: -125, -95, -6, +1, +10, +25, +45, +54, +90,

+115, +180, +240 minutes. Subjects continued to be monitored and under continuous observation for 6 hours post cocaine administration. An ECG was also obtained at screening and on each morning of a cocaine infusion session.

All subjects had normal ECGs at pre-dose and post-dose conditions for both baclofen and cocaine. There were no arrhythmias or changes in conduction intervals on any ECGs as measured by standard 12-lead tracings and rhythm strips of Leads II, V₁, and V₅.

Table 2 summarizes the vital signs results. Only one subject, #5 (baclofen), experienced clinically significant increases in systemic blood pressure and heart rate at time-points +1 and +10 minutes after cocaine infusion on day 5; these changes reverted to normal by time-point +25 minutes. Comparing the cardiovascular response in this subject when on baclofen (184/100 mm Hg post-cocaine *versus* 140/78 mm Hg pre-cocaine with a change of 44 in SBP) to his responses at baseline (150/94 mm Hg post-cocaine *versus* 106/87 mm Hg pre-cocaine with a change of 44 in SBP), it appears that no exacerbation can be ascribed to the addition of baclofen. Another two subjects who received baclofen demonstrated mild changes in systemic blood pressure and heart rate at time-points immediately after cocaine infusion on day 5. Subject #1, a placebo recipient, experienced elevation of SBP by approximately 20 mm Hg 5 minutes after cocaine infusion, but elevation of DBP by <10 mm Hg, and mild elevation of heart rate that returned to pre-infusion levels by +45 minutes. The data set demonstrates that there is no clinically significant cardiovascular interaction between oral baclofen after steady state conditions have been reached and acute exposure to cocaine administered intravenously (A.R. Childress, personal communication, 2002).

Table 2. Effect of Cocaine/Baclofen Interaction on Systolic Blood Pressure, Diastolic Blood Pressure and Heart Rate (A.R. Childress, personal communication, 2002)

	Subject #1			Subject #2			Subject #3				Subject #4			Subject #5		
	SBP	DBP	HR	SBP	DBP	HR	SBP	DBP	HR		SBP	DBP	HR	SBP	DBP	HR
Day 2: min										Day 2: min						
-150	108	72	73	ND	ND	ND	ND	ND	ND	-125	123	79	ND	118	68	66
-120	122	70	74	120	56	54	120	66	76	-95	88	64	ND	116	72	66
-10	132	90	65	124	76	58	ND	ND	ND	-6	106	65	ND	106	87	74
<u>0: Cocaine Infusion</u>										<u>0: Cocaine Infusion</u>						
5	154	90	89	136	66	77	142	76	93	1	110	67	ND	150	94	93
15	138	86	85	146	64	70	134	78	81	10	135	85	ND	156	100	104
30	122	86	83	126	66	65	126	66	71	25	118	73	ND	130	88	79
45	122	82	65	124	58	56	120	60	69	45	117	74	ND	134	84	74
60	118	80	81	119	60	58	110	64	64	54	107	63	ND	126	80	71
90	120	78	65	116	60	53	118	62	64	90	ND	ND	ND	128	74	77
120	128	76	70	120	62	53	122	62	61	115	112	66	ND	121	75	74
180	126	84	85	134	56	70	130	70	71	180	118	76	ND	130	80	77
240	124	66	89	132	62	73	128	72	89	240	ND	ND	ND	146	90	76
Days 3 and 4	Placebo			Baclofen (20 mg b.i.d.)			Baclofen (20 mg b.i.d.)				Placebo			Baclofen (20 mg b.i.d.)		
Day 5: min										Day 5: min						
-150	110	62	69	122	62	59	ND	ND	ND	-125	122	79	52	139	73	70
-120	108	68	69	154	66	58	146	60	82	-95	119	78	57	129	80	73
-10	114	74	62	152	80	61	130	66	64	-6	114	68	53	140	78	79
<u>0: Cocaine Infusion</u>										<u>0: Cocaine Infusion</u>						
5	138	86	91	138	62	66	154	82	89	1	124	86	73	184	100	107
15	144	72	96	130	72	71	144	74	91	10	128	68	79	168	100	114
30	130	72	85	140	66	76	146	72	77	25	121	74	61	130	80	89
45	124	82	74	122	70	58	142	70	66	45	116	72	55	136	84	76
60	120	72	81	134	60	61	130	64	69	54	118	72	56	134	78	76
90	126	82	85	134	66	53	130	68	69	90	108	58	55	116	72	76
120	110	74	73	124	56	59	136	70	69	115	100	66	66	122	72	83
180	138	80	101	136	58	59	168	84	76	180	114	71	65	134	74	76
240	126	72	89	122	66	55	174	80	70	240	ND	ND	ND	ND	ND	ND

5 STUDY OBJECTIVES

5.1 PRIMARY OBJECTIVE

The primary objective of this study is to assess the efficacy of baclofen in reducing cocaine use in subjects with cocaine dependence (DSM-IV criteria). The hypothesis is that baclofen will reduce cocaine use over the treatment period as compared to placebo as determined by self-report confirmed with urine assays for BE.

5.2 SECONDARY OBJECTIVES

Secondary objectives include determining baclofen's:

1. Safety in the study population.
2. Efficacy in reducing the proportion of cocaine use-days.
3. Efficacy in increasing the proportion of subjects who achieve measured reductions in cocaine use.
4. Efficacy in the reduction in the severity of cocaine dependence (assessed by longitudinal changes in ASI-Lite and ASI-Lite Follow-up, CSSA and Self and Observer scored CGI and craving (assessed by BSCS scores).
5. Efficacy in reducing the proportion of use-days of other substances of abuse (alcohol, marijuana, amphetamines, opiates, and benzodiazepines) as determined by self-report and the percentage of urines positive for other drugs of abuse (amphetamines, opiates, and benzodiazepines).
6. Efficacy in reduction of HIV risk-taking behaviors (assessed by HRBS).

6 STUDY SPONSOR

This study will be conducted under an Investigational New Drug (IND) application held by NIDA.

7 STUDY SITES

This study will be conducted at 8 clinical sites, both at Veterans Administration (VA) and non-VA institutions. Each clinical site will enroll at least 20 subjects, with a maximum of 30 subjects. Enrollment of more than 20 subjects at one site needs approval from the NIDA Project Manager. All participating institutions will be geographically located within the United States. Based on the enrollment rate of the previous double-blind placebo-controlled phase 2 study of baclofen to treat cocaine dependence (Shoptaw *et al.*, 2003), it is anticipated that clinical sites will enroll approximately 2 subjects per month. With a total of 8 clinical sites, it is estimated that enrollment will take about 10 to 15 months to complete.

8 STUDY DESIGN

This is a double-blind, placebo-controlled, parallel design study in which, after a 14-day screening period, subjects will be randomly assigned to receive baclofen or matched placebo administered orally for 8 weeks with follow-up assessments for 4 weeks after treatment completion. The treatment period will consist of a dose escalation phase (week 1) with baclofen dose escalating from 10 mg to 60 mg daily or matched placebo, maximal-dose phase (weeks 2 to 7) with 60 mg baclofen daily or matched placebo and a dose taper phase (week 8) with baclofen dose tapering off or matched placebo. Follow-up will consist of assessments once each week during weeks 9, 10, 11 and 12. Adaptive randomization will be used to balance treatment groups based on clinical site and gender. All subjects will receive psychosocial therapy that will consist of weekly sessions of CBT during the 8-week treatment period.

9 SUBJECT SELECTION

160 male and female subjects with cocaine dependence will be enrolled in the study (80 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 and word of mouth among subjects themselves also seeking treatment; additional subjects will be recruited from the community by means of advertising in local media. Recruitment advertisements will be approved by each site's Institutional Review Board (IRB) and NIDA.

9.1 INCLUSION CRITERIA

Potential subjects must:

1. Be at least 18 years-of-age.
2. Have a DSM-IV diagnosis of cocaine dependence as determined by SCID.
3. Be seeking treatment for cocaine dependence.
4. Have provided at least 4 urine samples during the 14-day screening period, of which 3 or more are BE-positive (>300 ng/mL).
5. Be able to verbalize understanding of consent form, able to provide written informed consent, and verbalize willingness to complete study procedures.
6. If female and of child bearing potential, agree to use of one of the following methods of birth control or be surgically sterile:
 - a. oral contraceptives
 - b. patch
 - c. barrier (diaphragm or condom)

- d. intrauterine contraceptive system
 - e. levonorgestrel implant
 - f. medroxyprogesterone acetate contraceptive injection
 - g. complete abstinence from sexual intercourse
 - h. hormonal vaginal contraceptive ring
7. Have completed all other psychological assessments (ASI-Lite, HRBS, CGI-S, CGI-O, BSCS, CSSA, HAM-D) during the 14-day screening period.

9.2 EXCLUSION CRITERIA

Potential subjects must not:

1. Have current dependence, defined by DSM-IV criteria, on any psychoactive substance other than cocaine, alcohol, nicotine, or marijuana or physiological dependence on alcohol requiring medical detoxification.
2. Be mandated by the court to obtain treatment for cocaine-dependence.
3. 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.
4. Have a psychiatric disorder, as assessed by the SCID, or a neurological disorder including but not limited to epilepsy and absence seizures, 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.
5. Have had electroconvulsive therapy within the past 3 months preceding screening.
6. Have current suicidal ideation or plan (within the past 30 days) as assessed by the SCID.
7. Be pregnant or lactating.
8. 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
9. Have clinically significant abnormal laboratory values, per Appendix I.

10. Have AIDS according to the current CDC criteria for AIDS – MMWR 1999; 48 (No. RR-13: 29-31).
11. Have active syphilis that has not been treated or refuse treatment for syphilis (see note below).
12. Have active tuberculosis (positive tuberculin test and confirmatory diagnostic chest x-ray).
13. 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).
14. 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.
15. Have received medication that could interact adversely with baclofen, 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; or
 - B) Two weeks; or
 - C) Interval recommended by other medication's product labeling.

Medications that fall into this category include:

- Muscle relaxants (including tricyclic antidepressants)
- Antiseizure medication
- CNS depressants (tranquilizers, sleeping pills)
- MAO inhibitors

Note: Isolated cases of increased blood glucose concentrations have been reported with baclofen; dosage adjustments of antidiabetic agents (oral and insulin) may therefore be necessary with combined baclofen treatment. There are some reports that in individuals taking antihypertensive medications baclofen will cause further reductions in blood pressure; thus, dosage adjustments of antihypertensive medications may be necessary with combined baclofen treatment. Subjects are cautioned not to use alcohol and antihistamines because these agents may enhance the side effects of baclofen, such as drowsiness and somnolence.

16. Have participated in any behavioral and/or pharmacological intervention study within 2 months preceding the beginning of screening.
17. Have known or suspected hypersensitivity to baclofen.
18. Be taking baclofen for any reason currently or during the past year.
19. Have tested positive twice for benzodiazepines during the 14-day screening period.

Notes on inclusion/exclusion criterion: Although AIDS is an exclusion criterion, a positive antibody titer to HIV is not. Potential subjects will be offered HIV testing during screening but may not have the test performed until after enrollment. This testing, along with HIV education, will be offered as a courtesy to the subjects. Subjects will be asked, but will not be required, to provide the results of the testing in order to better characterize the subject population.

Potential subjects who are positive for syphilis by the RPR test will have a fluorescent treponemal antibody absorption assay (FTA-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 tests are positive, the subject will be notified of the test results and referred to treatment.

10 INVESTIGATIONAL AGENTS

10.1 BACLOFEN

Baclofen (Lioresal®) is a white odorless compound with a molecular weight of 213.66. Its chemical name is (+/-)-beta(Aminomethyl)-4-chlorobenzenepropanoic acid and chemical formula is C₁₀H₁₂ClNO₂.

Baclofen will be supplied by Murty Pharmaceuticals (Lexington, KY) as white 10 mg round tablets for oral administration.

Baclofen 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 Murty Pharmaceuticals (Lexington, KY) as an exact match of baclofen.

Investigational agents will be distributed through the Department of Veterans Affairs (DVA) Pharmacy Coordinating Center (PCC) as described.

10.3 DISPENSING INVESTIGATIONAL AGENTS

The PCC at DVA Cooperative Studies Program (Albuquerque, NM) will prepare investigational agents for each subject based on the treatment assignment on the list of subject numbers for each participating center; Cooperative Studies Program Coordinating Center (CSPCC) at the DVA (Perry Point, Maryland) will provide the list.

A ten-day blinded supply of baclofen 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 for dispensing to the subject. Subjects should be instructed to take investigational agents with food three times a day at evenly spaced intervals (each 8 hours); suggested schedule is 0700, 1500 and 2300 hours. On the first day of treatment, subjects will be given only two doses of study agent (at 1500 and 2300) as they will come to the clinic later than 0700 (Table 3).

Note: Subjects will be provided with explicit instructions regarding an afternoon dosing window (1300 to 1700). Subjects should be instructed to take the missed dose as soon as they remember. However, if it is within 2 hours of the time to take the next dose, they should skip the missed dose and continue their regular dosing schedule. Subjects should not take a double dose to make up for a missed one.

When a subject is at the clinic, dosing will be observed by a clinical staff member if close to the timing for a dose. The subject will be asked to bring his/her investigational agents to the clinic with them. If they do not have investigational agents with them, the pharmacy will supply replacement investigational agent for the subject for that dose.

As baclofen may affect mental alertness and coordination, subjects must be warned that they should not drive a car or operate machinery or perform other activities requiring mental alertness until their bodies have adjusted to the investigational agent. They should also avoid alcohol consumption while on the study as alcohol potentiates baclofen's side effects.

Note: Subjects who want to drop out of the study should be switched to week 8 dosing regimen of study agent.

10.4 BLINDING PLAN

The investigational agents, baclofen and placebo, will be packaged in child-resistant amber blister packs of matched appearance and labeling. The same number of blister packs per day will be dispensed to subjects in both treatment groups (baclofen and placebo). The daily combinations of tablets in the blister packs will differ for dose escalation, dose taper, and maximal-dose phases (see Table 3 in Section 11.1).

10.5 LABELING

The investigational agents, baclofen and placebo, will be supplied by a research pharmacist in blister packs. The blister packs will be labeled with a product label and a subject label. The product label will include the protocol number, study week number, the number of blisters in the blister pack and the following statement – “Caution: New Drug – Limited by Federal Law to Investigational Use” and “Keep Out of the Reach of Children.” The subject label, supplied by the study site, will include the subject name, study physician’s name, number of blisters dispensed, directions for use and will be labeled “Baclofen or Placebo”, thus identifying the drug but preserving the blind. It will also contain the name and address of the dispensing institution.

10.6 STORAGE

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

10.7 RECORD OF ADMINISTRATION

Accurate recording of all investigational agents received, dispensed, administered and returned will be maintained.

10.8 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.

10.9 CONTRAINDICATIONS

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

- Muscle relaxants (including tricyclic antidepressants) – may cause muscle hypotonia
- Antiseizure medication - may cause changes in seizure control
- CNS depressants (tranquilizers, sleeping pills) – increased CNS depression
- MAO inhibitors

Note: Isolated cases of increased blood glucose concentrations have been reported with baclofen; dosage adjustments of antidiabetic agents (oral and insulin) may therefore be necessary with combined baclofen treatment. There are some reports that in individuals taking antihypertensive medications baclofen will cause further reductions in blood pressure; thus, dosage adjustments of antihypertensive medications may be necessary with combined baclofen treatment. Subjects are cautioned not to use alcohol and antihistamines because these agents may enhance the side effects of baclofen, such as drowsiness and somnolence.

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 the treatment group assignment, subjects will receive either baclofen or matched placebo for 8 weeks. The treatment period will consist of a dose escalation phase (week 1) with baclofen dose escalating from 10 mg to 60 mg daily or matched placebo, maximal-dose phase (weeks 2 to 7) with 60 mg baclofen daily or matched placebo and a dose taper phase (week 8) with baclofen dose tapering off or matched placebo (see Table 3). Dose escalation and taper are performed in order to minimize side effects. Subjects will take investigational agents in three divided daily doses at evenly spaced intervals with food, e.g., 2 tablets three times a day at 0700, 1500, and 2300 hours. Subjects will be provided with explicit instructions regarding an afternoon dosing window (1300 to 1700).

Table 3 shows the number of 10-mg baclofen tablets or identical appearing placebo that are to be taken three times a day during the 8 weeks of treatment period by subjects in the baclofen treatment group; subjects in placebo treatment group will receive 2 tablets of placebo three times a day during all 8 weeks of treatment. On the first day of treatment, subjects will be given only two doses of study agent (at 1500 and 2300) as they will come to the clinic later than 0700 (Table 3) and will be sent home with sufficient amount of investigational agents for study week 1, plus enough additional investigational agents for an extra 3 days of dosing at the same level as dosing on day 6 of week 1, which is maximal-dose level. The subjects will be instructed on how to take investigational agents during the upcoming days and asked to bring back empty cards or any unused tablets during the first clinic visit of study week 2. Ideally, subjects will receive investigational agents during the first clinic visits of study weeks 2 to 7. During the study weeks 2 to 6 the subjects will receive investigational agents for the 7 days of the week plus additional amount for an extra 3 days; during the first visit of study week 7, subjects will receive investigational agents for the 7 days of the week only. Subjects will preferably receive investigational agents for study week 8 during the last visit of study week 7.

As baclofen may affect mental alertness and coordination, subjects must be warned that they should not drive a car or operate machinery or perform other activities requiring mental alertness until they have a chance to determine how they are responding to the investigational agent.

Week	Day	Daily dose	0700	1500	2300	Week	Day	Daily dose	0700	1500	2300
1	1	10 mg	none	10 mg & P**	2P	8	1	50 mg	2x10 mg	2x10mg	10 mg & P
1	2	20 mg	10 mg & P	10 mg & P	2P	8	2	40 mg	2x10 mg	10mg & P	10 mg & P
1	3	30 mg	10 mg & P	10 mg & P	10 mg & P	8	3	30 mg	10 mg & P	10mg & P	10 mg & P
1	4	40 mg	2x10 mg	10 mg & P	10 mg & P	8	4	20 mg	10 mg & P	10mg & P	2P
1	5	50 mg	2x10 mg	2x10 mg	10 mg & P	8	5	10 mg	10 mg & P	2P	2P
1	6	60 mg	2x10 mg	2x10 mg	2x10 mg	8	6	0 mg	2P	2P	2P
1	7	60 mg	2x10 mg	2x10 mg	2x10 mg	8	7	0 mg	2P	2P	2P
2 to 7	1-7	60 mg	2x10 mg	2x10 mg	2x10 mg						

*Subjects will take 2 tablets three times a day for all 8 weeks of treatment except day 1; on day 1 they will miss the morning dose as they will come to clinic to receive the weekly supply of study agent later than 0700.

**P=placebo

11.2 PSYCHOSOCIAL THERAPY

The efficacy of pharmacological treatment of cocaine dependence is often critically dependent upon a behavioral platform that enhances patient's compliance. Overall, long-term outcome at one year is substantially enhanced by the use of psychotherapy in combination with pharmacotherapy. Behavioral treatments, contingency management (CM) and cognitive behavioral therapy (CBT) in particular, have been utilized for managing cocaine- and amphetamine-dependent individuals and appear to be most useful for abstinence initiation (Carroll *et al.*, 1994; McLellan *et al.*, 1994; Simpson *et al.*, 1997; Sevarino *et al.*, 2000). A 12-week clinical trial conducted among methadone-maintained cocaine abusers indicated that the contingency group achieved significantly longer duration of sustained cocaine abstinence, relative to controls (Silverman *et al.*, 1996). Comparison of these 2 psychosocial approaches, CM and CBT, during methadone maintenance treatment for cocaine dependence (subjects were treated for 16 weeks with follow-ups at 17, 26 and 52 weeks) indicates that both CM and CBT are efficacious and although the effect of CM is significantly greater during treatment, CBT appears to produce comparable long-term outcomes (Rawson *et al.*, 2002). During the 8-week treatment period, weekly sessions of CBT will be conducted. HIV counseling will be performed as a component of CBT.

The CBT manual to be provided in the study operations manual is the 2003 version of the Boston Cognitive Behavioral Therapy Manual. During psychosocial therapy sessions, emergency counseling and referral services will be provided. Additional emergency crisis management sessions will be available up to a maximum of four. These visits will be documented. Subjects should not be discouraged from seeking additional forms of psychosocial therapy.

The goal of behavioral treatment interventions is to increase protocol compliance and educate the subject about his/her dependence and factors associated with drug use, and assist study subjects in achieving abstinence from cocaine without obscuring the impact of the pharmacological treatment. Given the high rate of dropouts in this population, psychosocial therapy also helps to keep subjects in treatment. There will be no negative consequences based on urine toxicology results or patient revelations regarding use of illicit substances; the results of the urine tests will be blinded during both screening and treatment periods. The primary purpose of using a manual-guided procedure for therapists is to achieve consistency of theoretical orientation, therapeutic style, and behavioral intervention across subjects and sites. Each therapy session should be audiotaped to monitor drift and assure adherence to manual-guided therapy. A separate consent form will be used to obtain informed consent from the subject to audiotape therapy sessions. Original tapes are to be maintained at the site. The Boston Behavioral Treatment Training Center will select a random proportion of these tapes for review. The psychotherapy manual has the procedure for submission and review of tapes. It is expected that at least one session per month will be rated by the training center. These tapes will be used only by selected study researchers and will be destroyed when the study is over.

12 STUDY PROCEDURES

12.1 SUBJECT RECRUITMENT

Interested candidates, who responded to recruitment materials and are available to come to the clinic for 14 weeks will be scheduled to meet with a qualified investigative staff member and receive an explanation of the study purpose and requirements in lay language. During the initial interview, the interviewer should not ask questions in a manner that reveals the eligibility criteria for study entry.

If still interested after receiving an explanation of the study, candidates will be given an opportunity to review, inquire about, and sign the study informed consent form. The subject will then be given a copy of the signed consent form. After that, individuals will be given a screening number and proceed to the screening phase of the study. Screening assessments must be completed within a 14-day time period and randomization should be performed on the next calendar clinic visit day. Subjects can not be randomized until day 15 and no later than day 19 after completion of the 14-day screening period. At no time during the screening process should individuals be given information regarding inclusion or exclusion criteria. When individuals are evaluated, questions should be asked in a way that the criteria are not discernable.

Any participant who has difficulty understanding the information contained in the consent form will reread the misunderstood portion(s) of the consent and discuss with a research staff member

until s/he shows complete understanding of the information discussed in the consent form, and may thus give full consent. Research staff will work closely with the participant in an effort to help them understand the requirements of their participation. Subjects 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. Subjects who are excluded, or who decline participation, will be given referrals to other resources in the area. Subjects who refuse to participate or who withdraw from the study will be treated without prejudice.

12.2 SCREENING ASSESSMENTS

Screening assessments will be conducted as shown in Table 4. The screening period will last 14 days during which the candidates must satisfy the eligibility criteria, provide 3 or more BE-positive urines and complete all other psychological assessments (ASI-Lite, HRBS, CGI-S, CGI-O, BSCS, HAM-D, CSSA).

12.3 SUBJECT ENROLLMENT AND RANDOMIZATION

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.

The investigator or study coordinator will call the Interactive Touch Tone Randomization System (ITTRS) of the Cooperative Studies Program Coordinating Center (CSPCC) at the DVA (Perry Point, Maryland) that will serve as the data coordinating center and review the eligibility criteria and provide information such that adaptive randomization procedures can be followed including:

- Clinical site
- Gender

The ITTRS will provide the caller with a non-sequential subject number. Non-sequential subject numbers will be assigned to ensure that investigators cannot start a subject on medication without first contacting the CSPCC. CSPCC will also develop and maintain randomization codes for subject treatment assignments; randomization will be accomplished by assigning subjects to precoded medication supplies. The randomization list will be submitted to the pharmacy coordinating center (PCC) at DVA Cooperative Studies Program (Albuquerque, NM), which will then prepare medication supplies for each subject based on the treatment assignment on the list.

The investigator or study coordinator will arrange for investigational agent to be dispensed and arrange for the first visit of the subject to initiate treatment. Subjects will be dosed as soon as possible after receiving the subject number. If a subject does not actually receive any investigational agent after s/he has been randomized, s/he is considered to be an intent-to-treat population. The CSP should be notified of any irregularities that occurred during randomization.

12.4 TREATMENT PHASE

Subjects will be scheduled for assessments three times per week usually on a Monday, Wednesday, and Friday for 8 weeks. Treatment may start any day of the week. Two consecutive days may be scheduled around holidays or other schedule conflicts. All subjects will be offered an opportunity for HIV testing and HIV/AIDS education (Appendix II). All subjects will be provided with CBT once a week during the 8 weeks of treatment; HIV counseling will be performed as a component of CBT. Clinical evaluations are described in detail in section 13.0.

12.5 FOLLOW-UP

After the end of the 8 weeks of treatment, subjects will be asked to come to the clinic for follow-up visits once each week during weeks 9, 10, 11 and 12. The subject will be asked to provide a urine specimen for BE/creatinine and urine toxicology screen, list of concomitant medications, self-report for cocaine, alcohol, marijuana, amphetamines, opiates, and benzodiazepines use, and report any AEs. The subject will be asked to list any current treatments for drug or alcohol abuse and to give an overall impression of the study agent at the final follow-up visit. If it is not possible to arrange for the subject to return to the clinic, the subject will be telephoned and asked to provide a current self-reported cocaine and other drug use, current treatment for drug or alcohol abuse, and an impression of the study agent. If a subject cannot be contacted directly, attempts will be made to reach the individual(s) previously identified by the subject as a contact source.

12.6 MAINTAINING AND BREAKING STUDY BLIND

The decision to break the study blind for an individual subject should be made by the site principal investigator (PI) or the medically responsible physician at the site if the PI is not a physician. The NIDA medical monitor should be part of the process if the time permits. The decision to break the study blind should be resorted to only in cases of life-threatening emergency when knowledge of the treatment arm investigational agent will influence clinical management.

12.7 SUBJECT REIMBURSEMENT

Subjects will be compensated for their time and inconvenience (e.g., gasoline, public transportation, etc.), at a rate of \$10 per clinic visit. During the screening phase of the study, subjects will be paid \$10 for each clinic visit at which a urine specimen is provided. During the treatment phase of the study, subjects will be paid \$10 for each day that they attend a scheduled clinic visit and complete the required tests and questionnaires. Subjects will also be paid \$10 on each of the 4 weekly follow-up visits after they stop taking the study medication. The maximum payment is \$340. Subjects will be compensated regardless of whether they continue to receive study medication. Subject reimbursement may be made by cash or vouchers in accordance with local site policies (decided by IRB). Subjects (or potential subjects as is the case during screening) should be paid on a daily or weekly basis, whichever format is most convenient/acceptable locally.

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 reason, including the following:

- 1) significant side effects from the investigational agents
- 2) serious AEs
- 3) inability to comply with the study protocol
- 4) protocol violation
- 5) serious intercurrent illness

A subject may withdraw from the study anytime s/he wishes. A subject who is discontinued from receiving the investigational agent, will be allowed to continue psychosocial therapy with the approval of the investigator and complete the assessments.

Any subject who discontinues prematurely, regardless of the reason (missed 7 consecutive study visits after randomization, was removed for medical reasons or voluntarily discontinued participation in the study), will be requested to return for a final visit to perform the necessary procedures listed in section 13 and to obtain data for end of study/early termination.

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

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

12.8.2 Trial Discontinuation

The study sponsor (NIDA) 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. Baclofen should not be administered concurrently with:

- Muscle relaxants (including tricyclic antidepressants), e.g., amitriptyline (Elavil), desipramine (Norpramin), imipramine (Tofranil), protriptyline (Vivactil), bupropion (Wellbutrin), nefazodone (Serzone)
- Antiseizure medication, e.g., phenytoin (Dilantin), carbamazepine (Tegretol), valproic acid (Depakene)
- CNS depressants (tranquilizers, sleeping pills), e.g., secobarbital (Seconal), zolpidem (Ambien), temazepam (Restoril)
- MAO inhibitors, e.g., phenelzine (Nardil), tranylcypromine (Parnate), selegiline (Eldepryl)

Note: Isolated cases of increased blood glucose concentrations have been reported with baclofen; dosage adjustments of antidiabetic agents (oral and insulin) may therefore be necessary with combined baclofen treatment. There are some reports that in individuals taking antihypertensive medications baclofen will cause further reductions in blood pressure; thus, dosage adjustments of antihypertensive medications may be necessary with combined baclofen treatment. Subjects are cautioned not to use alcohol and antihistamines because these agents may enhance the side effects of baclofen, such as drowsiness and somnolence.

13 CLINICAL EVALUATIONS

Table 4 provides an overview of the schedule of assessments to be conducted over the course of the study.

Table 4. Overview of Study Assessments

Assessment	Screening*		Treatment					Follow-up	
			1	2-3	4	5-7	8	9-11	12
Study Week									
Screening									
Informed consent	X								
SCID/Psychiatric evaluation	X								
Medical history	X								
Prior medications	X								
Infectious disease panel/ syphilis test	X								
Safety									
Physical exam	X					X ^b			
Vital signs	3X/week		X ^a	X ^a	X ^a	X ^a	X ^b		
Hematology	X				X ^a		X ^b		
Blood chemistries	X				X ^a		X ^b		
Medical urinalysis	X				X ^a		X ^b		
Pregnancy test	X				X ^a		X ^b		
ECG	X						X ^b		
Adverse events			X ^c	X ^c	X ^c	X ^c	X ^{b,c}	X	X
Concomitant medications			X ^c	X ^c	X ^c	X ^c	X ^{b,c}	X	X
Efficacy									
ASI-Lite	X								
ASI-Lite Follow-up					X ^a		X ^b		
CSSA	Weekly		X ^a	X ^a	X ^a	X ^a	X ^b		X
HRBS	X						X ^b		
HAM-D	X				X ^a		X ^b		
BSCS	Weekly		X ^a	X ^a	X ^a	X ^a	X ^b		
CGI-S	Weekly		X ^a	X ^a	X ^a	X ^a	X ^b		
CGI-O	Weekly		X ^a	X ^a	X ^a	X ^a	X ^b		
SUR	3X/week		X ^c	X ^c	X ^c	X ^c	X ^{b,c}	X	X
Urine test for cocaine and other drugs of abuse	3X/week								
Urine BE and creatinine	3X/week		X ^c	X ^c	X ^c	X ^c	X ^{b,c}	X	X
Urine tox screen	Weekly		X ^a	X ^a	X ^a	X ^a	X ^b	X	X
Treatment compliance – Drugs			X ^c	X ^c	X ^c	X ^c	X ^{b,c}		
Treatment compliance - Psychosocial therapy			X	X	X	X	X		
Follow-up interview									X

* During the 14-day screening period candidates must provide 3 or more cocaine-positive urines as well as satisfy other screening measures. ** Urine test for cocaine will be performed 3 times a week during screening period.
X^a - Once a week at the beginning of weeks 1-8. X^b - At the beginning of week 8 or if the subject discontinues prematurely.
X^c - Three times a week.

13.1 SCREENING ASSESSMENTS

Prior to enrollment on the study, subjects will be screened to determine if they meet eligibility requirements. During the 14-day screening period each urine specimen (collected on Monday, Wednesday and Friday) will be tested at the site via urine test for cocaine and other drugs of abuse (methamphetamine, THC, benzodiazepines and morphine), then sent to the central laboratory to determine BE and other drugs of abuse (amphetamines, opiates and benzodiazepines). During the screening period the candidates must satisfy the eligibility criteria (Table 4) and complete the assessments listed below.

Screening assessments that will occur over a 14-day period include the following:

1. Three-times weekly urine BE plus creatinine measurements for 14 days. Ideally, 3 of the specimens will be obtained in one 7-day period and 3 in the next 7-day period. No more than 4 of the specimens may be obtained in one 7-day period of the 14-day screening period and no more than two specimens can be collected on consecutive days. Subjects must provide at least 4 urine specimens in a consecutive 14-day period.
2. The following will be obtained weekly:
 - a. BSCS
 - b. CGI-S
 - c. CGI-O
 - d. CSSA
 - e. Urine toxicology screen
3. Daily report of cocaine, alcohol, amphetamines, marijuana, opiates, and benzodiazepines use will be recorded at each visit on a SUR CRF.
4. ASI-Lite, HAM-D and HRBS should be assessed once.
5. Pregnancy test within 2 days prior to the first dose of the study agent administration.
6. Prior medication use will be assessed once during the screening period and again before the administration of the first dose of study agent.

Note: Only subjects that provided 3 or more BE-positive urine samples and completed all other psychological assessments (ASI-Lite, HRBS, CGI-S, CGI-O, BSCS, CSSA, HAM-D) during the 14-day screening will be randomized. Subjects with a benzodiazepine-positive urine sample will be cautioned against further use; those that tested positive twice during the 14-day screening period will be excluded from study participation.

13.2 ASSESSMENTS DURING TREATMENT

Over the 8-week period of treatment, subjects will 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 (Table 4).

13.3 ASSESSMENTS AT THE END OF TREATMENT OR EARLY TERMINATION

Concomitant medications, AEs, urine BE and creatinine, SUR and treatment compliance are to be assessed three times during week 8. All other assessments scheduled for study week 8 (Table 4) should ideally be completed at the first week 8 visit or if the subject discontinues prematurely, regardless of the reason (request that the subject returns for final assessments).

13.4 ASSESSMENTS AT FOLLOW-UP (WEEKS 9, 10, 11 and 12)

The follow-up assessments are presented in Table 4.

13.5 ASSESSMENT METHODS

13.5.1 Vital Signs

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

13.5.2 Physical Exam

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.

13.5.3 Hematology

Blood will be collected in anticoagulant containing evacuated venous blood collection tubes (e.g., Vacutainer™) for hematologic assessments. Complete blood counts (CBC) with differentials and platelet count will be performed. Quantitative analyses for hemoglobin, hematocrit, red blood cells, platelets, total white blood cells, and percentage of neutrophils, lymphocytes, monocytes, eosinophils, and basophils will be performed. Analyses will be performed in the institution's clinical laboratory. For this multi-site study, the laboratory performing these assessments should be directly accredited by the College of American Pathologist (CAP) and licensed by the Clinical Laboratory Improvement Act of 1988 (CLIA); both certification and accreditation must be renewed every 2 years. The laboratory will need to provide a copy of current certification, and each laboratory should provide the Laboratory Normals for their laboratory values to determine the upper limit of normal (ULN) (Appendix I).

13.5.4 Blood Chemistries

Blood will be collected in serum separation evacuated venous blood collection tubes (e.g., Vacutainer™) and serum separated according to standard procedures. Quantitative analysis will be performed for the following analytes: sodium, potassium, chloride, carbon dioxide, glucose, creatinine, albumin, total protein, calcium, cholesterol, triglycerides, phosphorous, alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), gamma glutamyltranspeptidase (GGT), total bilirubin, lactate dehydrogenase (LDH), creatine phosphokinase (CPK), alkaline phosphatase (ALP), blood urea nitrogen (BUN), and uric acid. The laboratory performing these assessments should be either directly regulated by CAP or CLIA or indirectly according to CLIA guidelines. The laboratory will need to provide a copy of current certification.

13.5.5 Infectious Disease Panel and Syphilis Tests

Blood will be collected in a serum separation evacuated venous blood collection tubes (e.g., Vacutainer™) and serum separated according to standard procedures. Qualitative analysis reporting positive/negative results will be performed for the following analytes: Hepatitis B surface antigen, Hepatitis B surface antibody, Hepatitis B core antibody, and Hepatitis C virus antibody. A purified protein derivative (PPD) skin test for tuberculosis will be performed 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, 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. Subjects will continue to be screened even if the tests are positive if they could produce evidence of prior treatment or if they started treatment during screening. If any tests are positive without evidence of treatment, the subject will be notified of the test results and referred to treatment.

13.5.6 HIV Test

All subjects will be offered the opportunity to have an HIV test performed. This test is not requisite for study participation. Subjects may be referred to a clinic for HIV testing. The clinic will use its own HIV consent form. Subjects will be asked, but will not be required, to provide the results of the testing in order to better characterize the subject population.

13.5.7 Pregnancy Test

Sites are encouraged to use any FDA approved urine pregnancy test in the clinic. All female subjects will be tested regardless of their child-bearing capacity.

13.5.8 HAM-D

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

13.5.9 SCID

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

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

The ASI-Lite CF will be administered at screening by a research staff member having at least a bachelor's degree in the social sciences or equivalent training and experience as determined by the site's investigator. The ASI-Lite is the interviewer's estimate of the severity of the subject's status in seven areas (medical, employment, drug use, alcohol use, legal, family/social, and psychological). Composite scores will be calculated according to the procedures described by McGahan *et al.* (1982) and Carroll *et al.* (1994). The Lite version is a shorter version of the ASI that still retains all questions used to calculate the ASI composite scores. ASI-Lite Follow-up will be administered at weeks 4 and 8; it eliminates demographic and other questions that do not change over time.

13.5.11 Urine Collection and Analyses

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

1. Test for cocaine and other drugs of abuse, methamphetamine, THC, benzodiazepines and morphine, performed at the site during screening
2. BE and creatinine performed at a central laboratory
3. Urine Toxicology Screen (Qualitative Analysis of amphetamines, opiates and benzodiazepines) performed at a central laboratory
4. Medical 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 (cocaine rapid tests, urinalysis and pregnancy test samples) will be sent directly to the appropriate laboratory for analysis. Samples to be tested for drugs of abuse and creatinine will be sent to a central laboratory and tested using a validated method. Specimens will be collected and tested as follows:

BE and Creatinine. Urine samples will be collected 3 times a week (generally Monday, Wednesday, and Friday, barring holidays and schedule conflicts). During screening, one sample

will be tested on-site for a rapid cocaine test result, another will be shipped to a central laboratory for analysis of BE plus creatinine (do not freeze if shipping within 10 days) and the third one will be frozen as a back-up on site until verification is received from the data coordinating center that the backup can be destroyed.

Only samples from subjects randomized into the study will be sent to the central laboratory. Urine samples collected during treatment and follow-up will be sent to a central laboratory to be analyzed for BE and creatinine (do not freeze if shipping within 10 days) or frozen for back-up. The back-up sample retained at the site will be stored frozen until the data coordinating center has notified the site that it can be disposed. Results will not be provided to the site during the study, and the site is prohibited from analyzing samples locally.

Urine Toxicology Screen (Qualitative Analysis of Substances of Abuse). The first sample of each week taken for BE and creatinine analysis will be analyzed additionally for amphetamines, opiates, and benzodiazepines. The sample collected for BE plus creatinine analysis will be tested for these drugs at the central laboratory.

Medical Urinalysis. Urine will be collected and analyzed for specific gravity, pH, blood, protein, glucose, ketones, leukocytes, and nitrite at a local laboratory.

13.5.12 Substance Use Report (SUR)

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

13.5.13 BSCS

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

13.5.14 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 the beginning of the study. The severity of the subject's cocaine dependence is rated according to eight specific problem areas often associated with cocaine dependence. The severity of each of the eight specific problem areas is to be rated first; the global severity is rated second; and the global improvement is rated last.

13.5.15 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 the beginning of the study.

13.5.16 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.

13.5.17 Adverse Events (AEs)

AEs will be assessed starting at the double-blind treatment phase of the protocol at each 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 14.7, 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.

13.5.18 HIV Risk-Taking Behavior Scale (HRBS)

The HRBS is a brief 11-item interviewer-administered scale (Darke *et al.*, 1991), to which a 12th item "Have you had an HIV test come back positive?" and 13th item "Date of most recent HIV test?" were added by NIDA. HRBS measures two distinct HIV risk factors in the behavior of intravenous drug users: one related to injecting behaviors and the other to sexual behaviors. Although AIDS is an exclusion criterion, a positive antibody titer to HIV is not. Potential subjects will be offered HIV testing during screening but may not have the test performed until after enrollment. This test is offered as a courtesy to the prospective subject along with HIV education and counseling.

13.5.19 ECG

Twelve-lead electrocardiograms will be performed according to standard procedures. The results will be reviewed by a study physician who will consult a board-certified cardiologist, if needed.

13.5.20 Prior Medications

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

13.5.21 Concomitant Medications

All medications taken by the subject during the 8-week treatment period and during follow-up must be pre-approved by the study physician whenever possible to avoid interactions with study drug. All medications will be recorded once per week on a concomitant medications CRF.

13.5.22 Treatment Compliance

Compliance with pharmacotherapy during the 8 weeks of treatment will be monitored by tablet count. Subjects will be instructed to bring their investigational agent card to each clinic visit.

Compliance with psychosocial therapy during the study will be accounted for by recording the length of time the subject spent in attendance at scheduled therapy sessions.

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. The monitoring of the sites participating in the trial will be executed according to Cooperative Studies Program (CSP) guidelines. A GCP reviewer from the Site Mentoring Advice and Resource Team (SMART) may visit the centers during the course of the study. The purpose of these visits is to encourage and assess compliance with GCP requirements. Reviewers will examine subjects' study files including source documents in both the clinic files and subjects' official medical records and will also review regulatory/essential documents such as correspondence with the IRB and the Sponsor (NIDA). Areas of particular concern will be subject informed consent issues, protocol adherence, safety monitoring, IRB reviews and approvals, regulatory documents, subject records, study agents accountability and principal investigator supervision and involvement in the trial. Reports will be prepared following the visit and forwarded to the principal investigator and CSPCC director.

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. In addition, the CSPCC IRB will also be required to approve the protocol and informed consent form. 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 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, sub-investigators, or study physician at each site will explain all aspects of the study in lay language and answer all of the candidate's questions regarding the study. If the candidate desires to participate in the study, s/he will be asked to sign the Informed Consent. No study procedure will be performed prior to signing Informed Consent, which should be signed prior to screening. Subjects who refuse to participate or who withdraw from the study will be treated without prejudice. One additional consent form will be used for consent to allow psychosocial therapy sessions to be audiotaped. The clinic, which subjects will be referred to for HIV testing, will use its own HIV consent form.

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 Pharmacy Coordinating Center.

14.6 OUTSIDE MONITORING

Data and Safety Monitoring Board: Safety and efficacy data will be reviewed by a Data and Safety Monitoring Board (DSMB) that will meet annually. The board will be blinded to subjects' actual treatment assignments.

Medical Monitor: The NIDA medical monitor will be responsible for establishing concurrence with the investigator on the severity of any AEs and 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 the SAEs reported.

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, the sponsor, with the opportunity to evaluate the progress of the study and to 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 Practices guidelines, confirm receipt of study supplies, and assure that acceptable facilities are available to conduct the study.

Routine monitoring visits by the Veterans Administration Cooperative Studies Program (VACSP) monitoring unit staff will be scheduled at appropriate intervals but more frequently at the beginning of the study. At these visits, the monitors will verify that study procedures are being conducted according to the protocol guidelines and review AEs and SAEs. 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 double-blind treatment phase of the protocol at each study visit and the AE CRF will be completed weekly.

An AE is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial, whether or not the event is considered related to the investigational agent or clinically significant. For this study, AEs will include events reported by the subject, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant clinical laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. Stable chronic conditions, such as arthritis, which are present prior to clinical trial entry and do not worsen are not considered AEs. All AEs must be recorded on the AE CRF. The AE CRF is also used to record follow-up information for unresolved events reported on previous visits.

Each week, a study investigator must review the AE CRF completed for the previous week for any events that were reported as continuing. All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed by study investigators until satisfactory resolution. AEs must be reported up to 4 weeks following completion of, or termination from treatment. At the week 12 follow-up visit, AEs will be recorded and 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 Code of Federal Regulations Title 21 part 312.32 and 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 a serious adverse event (SAE) or serious adverse drug experience as any untoward medical occurrence at any dose that:

- 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 within 24 hours.

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 including, if necessary, hospitalization.

15 ANALYTICAL PLAN

15.1 STATISTICAL HYPOTHESES

15.1.1 Primary Efficacy Outcome

It is hypothesized that baclofen treatment, compared to placebo, will increase the weekly proportion of cocaine non-use days. The weekly mean proportion of cocaine non-use days on the study will be compared between treatment groups using generalized estimating equations (GEE).

15.1.2 Secondary Efficacy Outcomes

It is hypothesized that baclofen as compared to placebo will increase the proportion of successful subjects, the weekly other drug non-use days according to self-report and proportion of negative urines for other drugs use. It is further hypothesized that baclofen will reduce the severity of cocaine dependence and craving as assessed by ASI-Lite, CGI-S, CGI-O, CSSA and BSCS. It is also hypothesized that baclofen in combination with HIV counseling and psychosocial therapy (CBT) will reduce HIV risk-taking behaviors (assessed by HRBS) associated with drug 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 activity of the study agent. Some of the secondary outcome variables add a measure of clinical relevance to the reduction of use by evaluating use on a daily basis by incorporating the results of self report of use in combination with urine BE results, 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.

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.

15.2.1 Primary Outcome Measure

The primary outcome variable will be the weekly proportion of cocaine non-use days. Cocaine use and non-use days will be defined by data from both subject self-reports and confirmatory urine testing utilizing BE concentrations (see rules for defining "new use" below). Three urine collection days are scheduled per calendar week. Because of the pharmacokinetics of cocaine and BE, carryover from previous cocaine use may be difficult to distinguish from new use. The rules described by Preston (Preston *et al.*, 1997), modified to meet the conditions of this study, will be used to classify study days as use or non-use days. The first study day (day of randomization) will be scored as missing.

The following will indicate "new use":

RULE 0: Subject reports new use.

If 1) the subject self-report indicates no new use, or 2) the subject self-report of use is missing, an affirmative finding of any of the following will be indicative of new cocaine use.

- RULE 1: An increase in cocaine metabolite concentration over the 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 concentration is greater than 300 ng/mL in the first urine sample collected during baseline.
- RULE 4: If the previous urine specimen was collected more than 2 calendar days before, urine specimen with cocaine metabolite concentration greater than 300 ng/mL.
- RULE 5: Creatinine concentration less than 20 mg/dL and cocaine metabolite/creatinine ratio is increased compared to that of previous specimen. (The cocaine metabolite concentration 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:

$\% \text{ non-concordant} = \# \text{ non-concordant use days} / \text{total urine samples analyzed} \times 100\%$, thus
 $\% \text{ concordant} = 100 - \% \text{ non-concordant}$.

For subjects with concordance rate <70%, the assignment of study days as use or non-use days should be reevaluated (the concordance rate cutoff of < 70% was established based on a survey of data sets from recently completed NIDA studies that indicated that mean concordance rates

ranged from 70 to 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 3 days” (Appendix V).

15.2.2 Secondary Outcome Measures

Secondary Outcome Measures will include:

Measured reductions in cocaine and other drug use over 8-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.** Weekly proportion of non-use days according to subject self report without regard to BE levels.
- E.** Weekly non-use days of other drug use, by other drug according to both SUR and urine toxicology results.
- F.** Weekly mean urine BE level.
- G.** Proportion of cocaine non-use days during the 8-week treatment period (non-use days divided by non-missing study days).
- H.** The maximum number of consecutive cocaine non-use days.

Reduction in the severity of cocaine dependence and craving

- I.** CGI-O scores.
- J.** CGI-S scores.
- K.** ASI scores.
- L.** BSCS scores.

M. CSSA scores.

Reduction in HIV risk-taking behavior

N. Change in HRBS score at week 8 compared to baseline.

Safety of baclofen

O. 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 are randomized to treatment. 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.

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. Study completers are the intent-to-treat subjects who have completed the eight weeks of the double-blind treatment phase of the protocol.

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 clinical site and gender. 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 (Efron, 1971). The randomization process will be performed by computer at CSPCC.

Clinical site was selected as a stratum due to the possible influence of the clinician providing the behavioral therapy component of the treatment. It is also appropriate to balance groups in the present study with respect to gender as the results from the double-blind placebo-controlled trials for cocaine dependence indicate a higher long-term abstinence in women users compared to men users.

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 baclofen treatment, compared to placebo, will be associated with a reduction of cocaine use. 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 7 days for weeks 2 through 8).

The weekly mean proportion of cocaine non-use days on study will be compared between treatment groups using Generalized Estimating Equations (GEE). GEE procedure is a model-based, regression methodology that is applicable to the analysis of the correlated binary outcomes (cocaine use and non-use days as determined from the modified Preston rules described above) that will result from this repeated-measures longitudinal study. GEE will be used to compare slopes of the use/non-use response between treatment groups over the active-treatment period of the study.

The GEE procedure (Liang and Zeger, 1986; Zeger and Liang, 1986) has several useful features:

1. It can be used to analyze different types of outcomes such as continuous, binary, or count.
2. It can be used to analyze an unbalanced design caused by either differing numbers of observations per person or by observations taken at different times.
3. The parameter estimates are consistent even if assumptions about the variance structure are not completely accurate.

Secondary Efficacy Outcomes

As a secondary analysis, the baseline proportion of cocaine non-use days, site, gender, severity of depression during screening, and their first-order interactions with treatment will also be included in the model. Presentation will include the full model with all terms and a reduced model containing only significant terms.

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, and C) will be assessed by Chi-square tests.

2. Weekly mean proportion of cocaine non-use days and urine BE levels, and weekly other drug non-use days (measures D, F, and E) will be assessed by GEE.
3. The proportion of cocaine non-use days on study and the maximum number of consecutive cocaine non-use days and proportion of cocaine non-use days (measures G and H) will be assessed by t-test.
4. 4. Change in CGI-S, CGI-O, ASI-Lite, BSCS and CSSA scores (measures I, J, K, L and M) will be assessed by GEE.
5. Change in HRBS scores (baseline to 8 weeks) (measure N) will be assessed by t test or non-parametric equivalent.

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 subpopulations. 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. Laboratory data, physical exams, and vital signs will be reported in tabular form.

15.5.3 Missing-Value Strategies

Every attempt will be made to maximize data capture. However, a plan has been developed to address missing data.

Assessing Potential for Differential Bias. Non-ignorable missing values can generate bias in parameter estimates. Of greatest concern for this planned trial is differential bias between the baclofen and placebo treatment groups, as these could cause analysis to underestimate or exaggerate true treatment differences. Two methods will be employed to examine possible differential bias:

- 1) **Retention analysis.** Appropriate survival-analytic methods (e.g., Cox proportional hazards) will be used to model time until dropout as a function of treatment (baclofen *versus* placebo) as well as some ancillary covariates (e.g., prior duration of cocaine use, baseline cocaine usage level, etc.).
- 2) **Missing as an Outcome.** Appropriate longitudinal logistic modeling tools (e.g., GEE) will be used to model missingness coded dichotomously (missing = 1 *versus* present = 0) as a function of treatment (baclofen *versus* placebo). Additional ancillary covariates of gender, age, ethnicity, days elapsed since randomization, and baseline cocaine-usage level will be included as well.

Corrective Measures. Two methods will be employed to achieve some correction in parameters' estimates due to missing values:

- 1) **Exchangeable Covariance.** An exchangeable covariance structure gives relatively less weight to longer sequences of repeated measurements than do other commonly used covariance structures, so that estimates primarily reflect results obtained over the earlier stages of treatment when the most complete data are available. Weighting mechanisms that give equal or greater weight to data obtained later in the trial (e.g., first-order autoregressive) prove highly sensitive to the leverage exerted by the few observations obtained at end of trial, which can exaggerate any non-ignorable bias existing in the empirical distribution of those later data.
- 2) **Weighting by Dropout Probabilities.** Methods will be explored using estimating equations weighted by dropout probabilities, which assume that data are missing at random (Fitzmaurice *et al.*, 1995) or non-ignorable (Rotnitzky *et al.*, 1998).

Missing-Value Strategies. Two approaches will be taken to address missing values. These approaches will be applied as appropriate to the analysis of the primary and secondary outcome measures. Both Stratification on Missing Value Patterns and Multiple Imputations will be used for the analysis of the primary outcome measures. Stratification on Missing Value Patterns only will be used for the analysis of the secondary outcome measures.

- 1) **Stratification on Missing Value Patterns.** In the spirit of Dawson (1994), missing-value patterns will be used to stratify observations. Indicators for these strata and their interactions with group will be added to elapsed time and elapsed time by group as predictors to the model. This will permit assessment of group differences for each separate missing value pattern. Strata will be formed in the following way. Each subject's data consists of a sequence of 8 weeks. If any data are missing in a given week, that week will receive a value of zero; whereas if no data are missing for that week, that week will receive a value of one. Thus each subject will have a vector of eight binary (0/1) outcomes. A divisive clustering algorithm (Kaufman and Rousseeuw, 1990) employing Euclidean distance will be used to identify 3 to 5 strata of missing-value patterns.
- 2) **Multiple Imputation.** This method assumes data are missing at random. For each visit v and within each group, two subsets of subjects will be identified: a) those with observations at visits v and $v - 1$ and b) those with a missing value at v and an observation at visit $v - 1$. Each of these two groups will then be partitioned into those with urine BE > 300 ng/mL ("dirty") at visit $v - 1$ versus those with urine BE ≤ 300 ng/mL ("clean") at visit $v - 1$. For each subject in (a), the difference d in urine BE between v and $v - 1$ will be computed. Then for each subject in (b) with a dirty urine at $v - 1$, a value of d will be randomly selected with replacement from all subjects in

(b) with dirty urines at $v - 1$. Likewise, for each subject in (b) with a clean urine at $v - 1$, a value of d will be randomly selected with replacement from all subjects in (b) with clean urines at $v - 1$. Once this process is completed for all subjects in (a), this process will be repeated anew for the next pair of sequential visits $\{v, v + 1\}$. The algorithm will sweep forward through the data in this fashion until all missing data are imputed. In making this sweep, none of the imputed values from a prior step will be used to make imputations in a subsequent step. After the sweep is completed, GEE will be used to fit the common intercept model to the data. This sweep and fit algorithm will be repeated at least 250 times to obtain at least 250 imputations. Because imputations are statistically independent, the variance in the estimate of β_2 will be taken to be the sum of the average of the variances in $\hat{\beta}_2$ plus the variance in the $\hat{\beta}_2$ across the 250 imputations.

15.6 SAMPLE SIZE CALCULATION

The primary outcome measure is weekly proportion of cocaine non-use days over the 8-week treatment period. The treatment groups will be compared on this measure using GEE. As only subjects who provide 3 or more BE-positive urine samples during the screening phase will be eligible to enroll in the study, the sample size calculation necessary for the power analysis was based on the results of the recent study of Shoptaw *et al.*, 2003 (*in press*). That study enrolled 28 subjects with 3 or more BE-positive urines, utilized the same primary outcome measure of weekly proportion of cocaine non-use days over 8-week treatment period after post-baseline randomization, and the treatment groups were compared using the GEE measure proposed for this study.

Model and GEE fit for the study of Shoptaw *et al.*, 2003 (*in press*).

GEE fit adjusted for data missing at random

Parameter	Estimate	Standard Error	p-value
Intercept	0.2155	0.0650	0.0009
Group	0.1335	0.1018	0.1895
Week	0.0069	0.0230	0.7629
Week \times Group	0.0371	0.0255	0.1457

The "Group" term is the difference in outcome just prior to randomization. "Week" is the slope over time for the placebo arm, which is estimated at a 0.69% increase in non-use per week. The "Week \times Group" term is the treatment effect adjusted for differences at baseline. From this, we estimate that the slope over time for the baclofen arm is 0.69% + 3.71% = 4.40% increase in non-use per week. Based on these estimates, change over time is approximately six times larger (4.40/0.69) for baclofen than placebo.

Sample Size Estimate: For Type I error α and power $1 - \gamma$, the quantity of subjects m required for the study is

$$m \approx \frac{(z_{\alpha/2} + z_{\gamma})^2 (m_p \hat{\sigma}^2)}{(\hat{\beta})^2}$$

where $\hat{\beta}$ is the point estimate of the week by group interaction ~~obtained~~ via GEE, parameter estimate's corresponding estimate of the standard error, m_p is the sample size of the pilot study, and z_{ξ} is the upper $(1 - \xi)^{\text{th}}$ percentile of the standard-normal distribution. The treatment effect size is $\hat{\beta}/(\hat{\sigma} \sqrt{m_p})$. Note that this treatment effect size accounts for all design constraints as well as the data's covariance structure because $\hat{\sigma}$ is obtained from the fit of the desired model to the pilot study data.

Suppose we wish to protect the ability to detect a treatment effect of 3.71% with 80% power at the 5% level of significance. Using the method outlined here with $\hat{\beta} = 0.0371$, we obtain a sample-size estimate of 104. Assuming 35% attrition, the attrition-adjusted sample-size estimate is $104/0.65 \approx 160$.

As we are not aware of standard methods for adjusting sample size based on potential site differences in multicenter trials, we decided to evaluate the potential effects of site differences based on the results of a previous trial (VACSP 1019), which had a very similar study design to the present one, and which included some of the sites expected to participate in the present trial. The group x week effect, its standard error, and the estimate of the scale parameter changed very little between the model that includes site effects and the model that does not. To what extent these analyses have implications for the current baclofen protocol cannot be exactly determined, but we don't believe that the modest differences observed make a clear argument for an upward adjustment of the sample size based on potential site differences.

Based on the above considerations, the study will be conducted at 8 sites with each site enrolling 20 subjects (total $m = 160$).

15.7 EXPLORATORY ANALYSES

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

1. Determine if baclofen treatment will increase treatment retention.
2. Determine if baclofen 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 CSPCC at the DVA in Perry Point, MD.

16.1 DATA COLLECTION

Data will be collected at the study sites on source documents, which will be entered at the site into CRFs. The CRFs will be supplied by CSPCC. 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 CRFs will be submitted on a regular basis to CSPCC. 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 CSPCC 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 CSPCC. 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 CSPCC.

Site investigators agree to routine data audits by the staff of the Veterans Administration Cooperative Studies Program (VACSP) monitoring unit, as well as by NIDA. VACSP monitors will routinely visit each site to assure that data submitted on the appropriate forms are in agreement with source documents at the sites. They will also verify that 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 to the data forms will be made using established CSPCC procedures.

16.3 DATA ENTRY, PROCESSING AND ANALYSES

Data will be collected at the study sites on source documents, which will be entered into CRFs. When the study is completed and all data have been entered into the clinical database and the database has been checked by Quality Assurance and is locked, statistical analysis of the data will be performed by the CSPCC statisticians in accordance with the Analytical Plan section of this protocol. Periodically, during the investigation, CSPCC will also prepare summary reports of the data so that progress of the study can be monitored. Various reports will be prepared for NIDA DTR&D central data repository according to procedures specified in the study operations manual, the DSMB, and others, as appropriate.

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) and finalization of all marketing strategies. In all instances you must get permission from NIDA prior to disposition of any study documentation and materials.

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

16.5.2 Confidentiality of Patient Records

To maintain subject confidentiality, all laboratory specimens, CRFs, reports and other records will be coded using alpha-numeric identifiers only. Only research and clinical records will be stored in a locked cabinet. Only research staff and NIDA program officials will have access to the records. Subject information will not be released without written permission, except as necessary for monitoring by the FDA, the VACSP monitoring unit, or NIDA. NIDA will file for a certificate of confidentiality that will cover all sites participating in the study.

By participating in this 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 baclofen for the treatment for cocaine dependence may not be submitted for publication until the main findings of the study have been published or in press and this study has been accepted by the FDA for filing to the IND or NDA. Review of manuscripts resulting from this study or from data generated during this study must occur according to the NIDA DTR&D Publications Policy prior to submission for publication. Authorship shall be consistent with NIDA and DTR&D policies.

18 SIGNATURES

NIDA REPRESENTATIVES

Typed Name	Signature	Date
<u>Ahmed Elkashef, M.D.</u> Study Co-chairman	_____	_____
<u>Roberta Kahn, M.D.</u> NIDA Principal Investigator	_____	_____
<u>Ivan Montoya, M.D.</u> Medical Monitor	_____	_____
<u>Liza Gorgon, M.A.</u> Project Manager	_____	_____

VA REPRESENTATIVE

<u>Paul Fudala, Ph.D.</u> Study Co-chairman	_____	_____
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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
- **Outside referrals may be offered for HIV testing.**

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

A. GENERAL INSTRUCTIONS

1. The Adverse Events (AEs) must be assessed at each visit during the treatment period of the study, recorded on AE CRF weekly and reviewed weekly by a study physician.
2. Record AEs during the treatment period of the study.
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 test drug?
- **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:

- ***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.
- ***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

Any abnormal laboratory value or ECG reading that occurs during the course of the study is considered an AE. The AE may be the first manifestation or the worsening of a previous condition, whether or not considered to be study agent related. For each AE, 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.

Laboratory values that can be abnormal due to lower or higher than range of normal values should be specified as an increased or decreased test result (e.g., “increased blood glucose,” “decreased blood potassium,” “increased heart rate”) or as a term that implies an abnormality (e.g., hyperglycemia, hypokalemia, or bradycardia).

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 Project Manager.

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

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

3-day Supporting Documentation Requirements

Written documentation for all SAEs must be received by the NIDA Project Manager 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 NIDA Project Manager.

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 12 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 NIDA Project Manager 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:

- verbally within 7 calendar 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 within an additional 8 calendar days;
- in 15 calendar 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.

NIDA will apply for a Certificate of Confidentiality for all 8 participating sites.

This 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).

This certificate is necessary for investigators 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 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

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 14-day screening 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 concentration is greater than 300 ng/ml in the first urine sample collected during screening.

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 concentration 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 samples are *de facto* considered positive.

RULE 5: Creatinine concentration less than 20 mg/dL and cocaine metabolite/creatinine ratio is increased compared to that of previous specimen. (Cocaine metabolite concentration 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 14-day screening period (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 because it is not considered positive by any rule.

Study day -3 is negative because it is not considered positive by any rule.

Study day 1 is positive due to rules 1 and 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 screening measurement day of the study because some of the outcome measures will be compared to screening 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 screening, 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 study day (day of randomization) will be 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. For study days on and after the last on-study urine specimen, the subject's self report will be used to score each day as a use or non-use day.

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.

Day 4 was scored as a new use day because the day 5 urine specimen was positive and the subject did not report any use since the last urine specimen.

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, except during screening and after the last on-study urine specimen.

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 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 (all urines with non-missing self report data for the previous study day), as follows:

$\% \text{ non-concordant} = \# \text{ non-concordant use days} / \text{total urine samples used to evaluate concordance} \times 100\%$, thus $\% \text{ concordant} = 100 - \% \text{ non-concordant}$.

Notes:

Screening scores will be used in the calculations of concordance.

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 $\% \text{ non-concordance}$ 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 of the quantitative assays 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 on study clinic visit is considered to be the last study day (not including any later termination or follow-up visits).

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:

$\% \text{ non-concordant} = 1 \text{ non-concordant use days} / 2 \text{ total urine samples used to evaluate concordance} \times 100\% = 50\%$

$\% \text{ concordant} = 100 - 50 \% \text{ non-concordant} = 50 \% \text{ concordant}$

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. (This applies to all study days, including the baseline period and any study days after the last on-study urine specimen.)

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