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DEPARTMENT OF VETERANS AFFAIRS
COOPERATIVE STUDIES PROGRAM STUDY # 1019**

**DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL
OF SELEGILINE TRANSDERMAL SYSTEM
FOR THE TREATMENT OF COCAINE DEPENDENCE**

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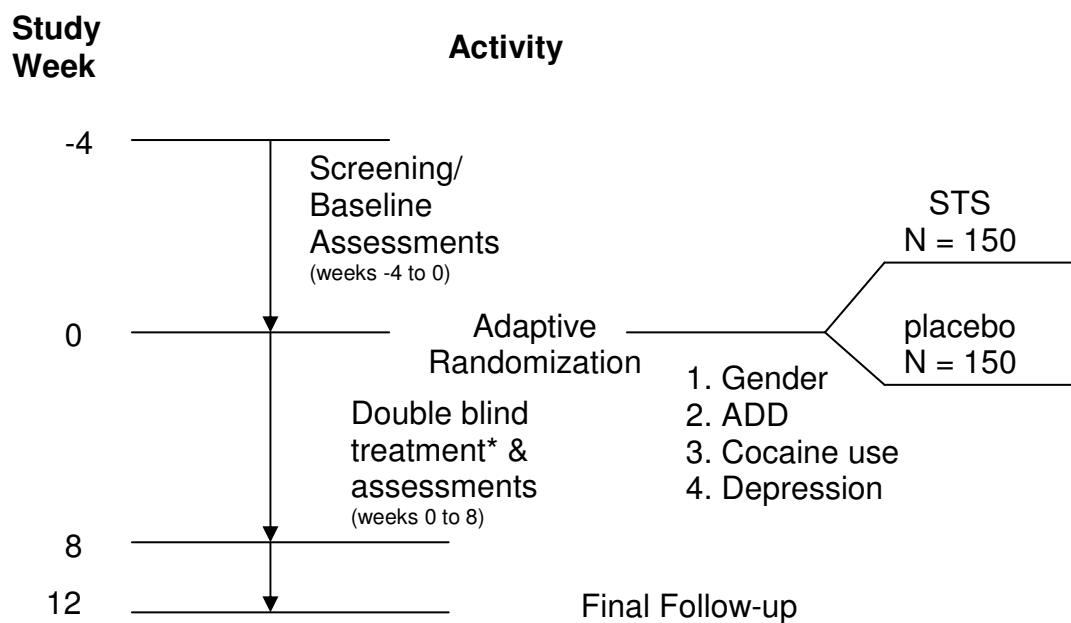
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1 LIST OF ABBREVIATIONS

Abbreviation	Definition
ADD	attention deficit disorder
ADHD	attention deficit hyperactivity disorder
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT/SGPT	alanine aminotransferase
ASI	Addiction Severity Index
AST/SGOT	aspartate aminotransferase
BE	benzoylecgonine
BSCS	Brief Substance Craving Scale
BUN	blood urea nitrogen
CCGI-O	Cocaine Clinical Global Impression Scale – Observer
CCGI-S	Cocaine Clinical Global Impression Scale – Self
CLIA	Clinical Laboratory Improvement Amendment of 1988
CRF	Case Report Form
CPK	creatine phosphokinase
CSPCC	Department of Veterans Affairs Cooperative Studies Program Coordinating Center (Perry Point, Maryland)
dL	deciliter
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
FEV ₁	forced expiratory volume in 1 second
FTA-abs	fluorescent treponemal antibody absorbant assay (confirmatory test for syphilis)
GGT	gamma glutamyltranspeptidase
HAM-D	Hamilton – Depression Rating Scale
HIV	human immunodeficiency virus
5-HT	serotonin
IM	intramuscularly
ITTRS	Interactive touch tone randomization system
kg	kilogram
LAAM	levomethadyl acetate (L-alpha acetylmethadol)
LDH	Lactic dehydrogenase
MAO-B	monoamine oxidase type B
mg	milligrams
MHA-TP	Microhemagglutination Assay-Treponema pallidum (confirmatory test for syphilis)
mL	milliliter

Abbreviation	Definition
ng	nanograms
NIDA	National Institute on Drug Abuse
OTC	over-the-counter
PEA	phenylethylamine
RPR	Rapid plasma reagin (test for syphilis)
RAB	Risk Assessment Battery
SAE	serious adverse event
SCID	structured clinical interview for DSM-IV
SUR	self use report
SSRI	selective serotonin reuptake inhibitor
STS	Selegiline Transdermal System
TP-PA	Treponema pallidum – particle agglutination assay (confirmatory test for syphilis)
VA	Veterans Administration
VACSP	Veterans Administration Cooperative Studies Program

2 STUDY SCHEMA



* Double blind treatment consists of daily application of STS or placebo patch and weekly psychotherapy

3 PROTOCOL SYNOPSIS

STUDY OBJECTIVES: To assess the efficacy and safety of the Selegiline Transdermal System (STS) in reducing cocaine use in subjects with cocaine dependence. It is hypothesized that selegiline 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-group design study in which, after screening, which includes a 14-day baseline assessment period, subjects will be randomly assigned to either placebo or STS patches for 8 weeks with a follow-up assessment 4 weeks later. Adaptive randomization will be applied to match groups on gender, diagnosis of attention-deficit disorder (ADD), self-reported cocaine use for the historical (30-day) period prior to providing informed consent, and severity of depression determined by a 24 question Hamilton – Depression Rating Scale (HAM-D).

STUDY POPULATION: Three hundred 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 (150 per group).

ELIGIBILITY CRITERIA: Males and females, at least 18 years-of-age, with a DSM-IV diagnosis of cocaine dependence and at least 3 urine BE positive specimens during the 14-day baseline period prior to randomization with the ability to understand and provide written informed consent will be included. Women of childbearing capacity will be required to use an acceptable method of birth control.

Subjects will be excluded if dependent on any psychoactive substance other than cocaine, alcohol, nicotine, or marijuana, have neurological or psychiatric disorders that require ongoing treatment or which would make medication compliance difficult, or have a past history of suicide attempts or suicidal ideation. Individuals with serious medical illnesses or cardiovascular abnormalities will also be excluded. Additional exclusions include, individuals mandated by the court to obtain treatment for cocaine-dependence, anticipating elective surgery within 14 weeks of signing the informed consent form, not seeking treatment for cocaine dependence, or who in the opinion of the investigator would not be expected to complete the study. Individuals with acquired immunodeficiency syndrome (AIDS), history of neuroleptic malignant syndrome, syphilis, known or suspected hypersensitivity to selegiline, any monoamine oxidase inhibitor, or phenylethylamine, known allergic or chronic dermatologic illness (e.g., psoriasis), which might interfere with the STS absorption, or Hymenoptera allergy will be excluded. Subjects on prior therapy with a medication that could interact adversely with selegiline (within defined periods before study enrollment) or who have participated in any experimental study within 8 weeks, or who have ever participated on a clinical trial utilizing the STS formulation will be excluded. Pregnant or lactating women, subjects with abnormal laboratory values, determined by the investigator to be clinically significant, or who have received electroconvulsive therapy within the past 90 days will be excluded. Subjects who have taken St. John's Wort, yohimbine, ginkgo biloba, or any other central nervous system active herbal preparations within 8 weeks of anticipated study entry or have received therapy with any opiate-substitutes (methadone, LAAM,

buprenorphine) within 6 months of enrollment will be excluded. Subjects with a diagnosis of adult asthma, including those with a history of acute asthma within the past two years, and those with current or recent (past 2 years) treatment with inhaled or oral beta-agonist or steroid therapy or actively using albuterol or other beta agonist medications, regardless of formal diagnosis of asthma, will be excluded.

TREATMENTS: A STS patch (STS: 1.0 mg/cm² x 20 cm² patch) or matching placebo patch will be worn for 24 hours and replaced daily for the 8-week duration of the study. All subjects will receive manual-guided psychosocial therapy weekly during the 8 weeks of treatment.

DURATION OF THE STUDY: The total duration of study participation for each subject will be a maximum of 16 weeks consisting of: screening to be completed within 30 days prior to randomization including a 14-day baseline assessment period; double-blind medication (8 weeks); and, follow-up evaluation conducted 4 weeks following completion or termination from the study.

SAFETY ASSESSMENTS: All candidates for study enrollment will have a physical examination, a 12-lead ECG and clinical laboratory studies (blood chemistry, hematology, and urinalysis) performed during screening. During the treatment phase, vital signs will be taken at each visit for the first two weeks and weekly thereafter. Assessments of adverse events (AEs), concomitant medications, and a urine screen for other substances of abuse will be performed weekly. An HIV Risk Assessment Battery will be used to characterize the population HIV risk behaviors (screening and week 8). At treatment week 8, or at the time of study discontinuation, subjects will be evaluated by AE assessment, vital signs, physical examination, clinical laboratory studies, and ECG.

EFFICACY ASSESSMENTS: Success in reduction of cocaine use will be determined by comparing the weekly mean proportion of cocaine non-use days (self-report confirmed or disproved by urine BE level at each study visit) in both treatment groups. Secondary assessments include overall proportion of cocaine non-use days, proportion of successful subjects, the largest number of consecutive cocaine non-use days, weekly mean quantitative urine BE levels, Addiction Severity Index (ASI) score, HAM-D score, Brief Substance Craving Scale (BSCS) score, Clinical Global Impression scores as assessed by the subject (CGI-S) and an observer (CGI-O). ASI is performed during screening and at the first visit of week 5 and at the end of week 8. The BSCS, CGI-S, and CGI-O are performed weekly during the 14-day baseline assessment period and the first visit of each study week. The HAM-D is performed during screening and every two weeks during treatment.

TREATMENT COMPLIANCE: Treatment compliance will be determined by investigative staff recording patch use at each visit and assessing blood levels of selegiline/selegiline metabolites. Analysis of selegiline, N-desmethyloselegiline, L-amphetamine, and L-methamphetamine plasma concentration will be determined at screening and after 2 and 5 weeks of treatment by a central laboratory to maintain the study blind.

4 BACKGROUND AND RATIONALE

Cocaine dependence is a significant public health problem associated with serious medical, psychiatric, social, and economic consequences. Although many compounds have been evaluated for the treatment of cocaine dependence, none have been approved by the Food and Drug Administration (FDA) for this indication. Psychosocial and behavioral therapy are currently the treatments of choice for cocaine dependence. Unlike substitution treatment for heroin addiction, disulfiram or naltrexone for alcohol dependence, and nicotine or bupropion for cigarette smoking, there is no pharmacological agent currently approved for the treatment of cocaine dependence. It is the priority of NIDA to identify and/or develop pharmacological agents to treat cocaine dependence in conjunction with psychosocial interventions. Current strategies to treat cocaine dependence include: 1) blocking its effects, 2) restoration of central nervous system homeostasis, 3) reducing craving or enhancing the addict's ability to manage his/her response to craving, 4) treating underlying conditions (or consequences of use) that may predispose targeted subpopulations toward dependence. Several medications are presently under consideration for the treatment of cocaine dependence based on those mechanisms of action.

The investigational drug to be investigated in this study is Selegiline. Selegiline is an irreversible selective inhibitor of monoamine oxidase type B (MAO-B). It is hypothesized that selegiline may affect cocaine addiction through several potential mechanisms of action. Inhibition of MAO-B increases concentrations of dopamine and other neurotransmitters, which may help restore normal levels in subjects whose use of cocaine has disrupted levels of these neurotransmitters. Another hypothesis is that selegiline metabolites may provide a low, but sustained therapeutically effective level of substitution for the stimulating effects of cocaine. There is no evidence that selegiline causes euphoria or dependence. The high degree of MAO-B inhibition achieved is associated with functional increases in dopamine concentrations. Dopamine is thought to be central to the reinforcing effects of cocaine. While dopamine depletion has been associated with chronic cocaine use and withdrawal symptomatology, it is widely accepted that euphoria associated with cocaine use is a result of action at reward pathways via antagonist properties at the dopamine transporter site. Cocaine also inhibits re-uptake of the neurotransmitters serotonin and norepinephrine. These actions are thought to underlie cocaine's potent reinforcing properties. With prolonged use, cocaine may deplete these neurotransmitters, affect postsynaptic receptor density, and elicit an overall dysregulation of these neurotransmitter systems. These long-term consequences may account for the post-cocaine dysphoria thought to contribute to relapse.^{1, 2, 3}

Pharmacology laboratory studies in humans and animals suggests that selegiline blunts the reinforcing effect of cocaine, while a pilot outpatient clinical trial, with a sustained release oral selegiline, reduced cocaine use.⁴

Selegiline was first tested for cocaine dependence using a sustained-release oral dosage formulation. Initial, protocol-specified analyses of a phase 2, double-blind, placebo-controlled clinical trial showed a trend toward decreased cocaine use. However, subsequent analysis according to FDA's recommendations showed a statistically significant effect of selegiline over placebo. Currently, this is the strongest positive treatment signal seen in clinical trials for cocaine dependence.⁴ However, sustained-release selegiline is no longer available.

The rationale for using the transdermal patch in lieu of the IR oral capsule is due to possible favorable differences in the pharmacokinetic and metabolic profiles. Compared to the oral capsule, the STS provides a continuous release of selegiline over a 24-hour period and avoids first-pass metabolism allowing for higher and more sustained plasma levels of selegiline, while reducing the levels of the main metabolites, R(-)-N-desmethylnelgiline, R(-)-amphetamine, and R(-)-methamphetamine. Transdermal delivery of selegiline also minimizes direct, high concentration contact with the MAO system of the gut and liver, reducing the probability for drug and food interactions, most notably tyramine. The STS 20 mg/20 cm² dose was chosen for study in the present trial based on data supporting the safety and efficacy in depression and the positive results of tyramine interaction studies (see below).

Somerset Pharmaceuticals, Inc. has performed numerous studies to evaluate the tyramine sensitivity of subjects administered the selegiline transdermal system (STS) and has subsequently eliminated dietary tyramine restrictions normally associated with MAO inhibitor treatment from all clinical study protocols involving the STS. Tyramine challenge studies evaluate the potential of tyramine-induced hypertensive episodes secondary to treatment with MAO inhibitors under controlled clinical conditions. An increase in systolic blood pressure (SBP) of > 30 mm Hg above a baseline value is typically used to define tyramine sensitivity.

Results of a study to assess blood pressure response produced by the natural administration of tyramine during an “enriched” meal (consisting of large quantities of aged cheese) following administration of the STS showed no evidence of significant changes in blood pressure between the baseline and active phases of the trial. In a study of healthy male volunteers who received single doses of up to 18 mg of selegiline as STS, oral tyramine doses up to 200 mg (given as concentrated solution) were tolerated without apparent increase in sensitivity. Multiple dose studies with 15, 20, or 30 mg selegiline, administered via the STS once daily for 21 days, showed a dose-dependent response. In these studies, a mean of 350, 256, and 107 mg of tyramine were needed to produce a SBP increase of 30 mm Hg in subjects administered the 15, 20, and 30 mg STS, respectively. Tyramine content of most meals, including those of red wine and cheese are appreciably below 100 mg.

Comparisons of different MAO inhibitors are accomplished by determining a tyramine sensitivity factor (TSF). The TSF is the ratio of doses of tyramine required to produce a predetermined increase in SBP in the absence (during placebo treatment) and presence (during active treatment) of MAO-inhibitors. For example, non-selective MAO inhibitors known to cause hypertensive reactions, such as Nardil® and Parnate®, can increase the TSF 13 to 55-fold. Previous studies in the literature have demonstrated that administration of 10 mg /day of oral selegiline produces a TSF of 3.7 in depressed patients and 1.5 in healthy subjects. Oral selegiline (Eldepryl®) has been used safely in clinical practice for the adjunctive treatment of Parkinson’s disease for over ten years and can be safely taken without dietary restrictions at the recommended dose of 10 mg/day.

Cross-over studies to directly compare the blood pressure effects of the 20 mg STS, 10 mg/day IR oral capsule, and 30 mg/day Parnate® have demonstrated TSFs of 1.82, 1.62, and > 40 for the STS, IR oral capsule, and Parnate®, respectively. No subjects administered the 20 mg STS (n = 47) demonstrated a SBP response when given up to 200 mg of tyramine orally. All subjects

administered Parnate® 30 mg/day (n = 10) demonstrated a SBP increase of > 30 mm Hg when given 10 mg of tyramine resulting in at least a 20-fold difference between the STS and Parnate®.

4.1 PHARMACOLOGY OF SELEGILINE

Selegiline is a potent, irreversible selective inhibitor of monoamine oxidase (MAO) type B.⁵ Achievement of greater than 95% enzyme inhibition is obtained after 3 days of oral dosing at 10 mg/day. At oral doses greater than 10 mg/day, selegiline starts to lose MAO-B selectivity. The precise dose at which selegiline becomes a non-selective inhibitor of all MAO is unknown, but may be in the range of 30 to 40 mg orally per day. Inhibition of MAO-B is associated with functional increases in available dopamine concentrations. Dopamine is thought to be central to the reinforcing effects of cocaine and depletion of dopamine is believed to be associated with chronic cocaine use and/or withdrawal states. Increases in dopamine would therefore be potentially therapeutic for cocaine-dependent subjects engaged in treatment to stop or reduce cocaine use.

Selegiline hydrochloride (Eldepryl®) has been approved for use throughout Europe and the U.S. in doses of 5 mg b.i.d. for oral administration to late-stage Parkinson's disease subjects who demonstrate a deteriorating response to carbidopa/levodopa therapy. Previous human use in the treatment of Parkinson's disease has demonstrated the safety of oral selegiline. The most common treatment-emergent adverse effects are nausea, dizziness, lightheadedness, and fainting (Eldepryl® package insert, 1998).

Selegiline has been investigated for efficacy in treating other disorders, some of which have direct clinical relevance to cocaine-dependence pharmacotherapy. The STS is currently being studied in Parkinson's disease, social phobia, major depressive disorder, and ADHD.

A four site, sixty-four subject placebo-controlled trial of selegiline 5 mg b.i.d. (Eldepryl®) for cocaine dependence is ongoing. It is designed to test various outcome measures for future studies. As of April 20, 2000, no serious AEs have been reported. In the first study with sustained-release oral selegiline, five of 134 subjects were terminated due to AEs, one on selegiline and four on placebo. One selegiline-treated subject attempted suicide as did one placebo-treated subject. The total number of AEs was comparable in the two groups.

4.2 PRECLINICAL PHARMACOLOGY

MAO-B selectivity of selegiline HCl in striatal or whole brain was evident in acute *in vivo* experiments at parenteral doses of 1 mg/kg in rats^{1,2,3} and at a single oral dose of 10 mg/kg.⁶ In chronic treatment regimens, selectivity was evident at 0.1 mg/kg, while increasing selegiline HCl doses to 10 mg/kg completely inhibited both MAO-B and MAO-A in the brain and liver.⁷ In mice, specific MAO-B inhibition was demonstrated with a single treatment of 2.5 mg/kg.⁶ These doses are similar to those used to treat Parkinson's disease in humans (10 mg/70 kg, or 0.14 mg/kg). Higher doses are likely to be associated with decreasing selectivity.

As mentioned previously, dopamine is strongly implicated in mediating the reinforcing effects of cocaine. In addition to increasing dopamine levels through MAO inhibition, selegiline may also affect dopamine through a selective increase in endogenous phenylethylamine (PEA).⁸ PEA is a substrate for MAO-B, a potent releaser of neuronal dopamine, and a strong inhibitor of neuronal

dopamine reuptake. Increases in PEA are also associated with a functional down regulation and decrease in the density of beta₁ adrenoreceptors⁹, an effect observed for some antidepressant medications (Somerset Pharmaceuticals, Investigator's Brochure).

Animal studies indicate that delivery of selegiline by routes of administration which avoid first pass metabolism are capable of inhibiting both MAO-A and MAO-B in brain tissue while maintaining MAO activity at peripheral sites. This tissue selective inhibitory profile is desirable in that it retains central clinical effects while potentially avoiding hypertensive reactions ("cheese effects") that are seen with oral MAO inhibitory medications.

4.3 SELEGILINE EFFECTS IN COCAINE TRAINED RHESUS MONKEYS:

Selegiline has been evaluated in rhesus monkeys trained to discriminate cocaine (IM, 0.4 mg/kg) from saline. [NIDA contract with McLean Hospital/Harvard Medical School (Belmont, MA)]. When given with a short pretreatment time (15 min) in a substitution test, selegiline produced cocaine-like subjective effects in 4 of 4 monkeys; at doses of 10 to 32 mg/kg selegiline (IM), all monkeys responded exclusively on the cocaine-appropriate key while working for their food. These findings are consistent with previously published cocaine drug discrimination studies in rats and pigeons but they contrast with the clinical experience with selegiline. Selegiline has not been reported to produce cocaine-like subjective effects in man and, despite widespread use, is not subject to abuse.

Subsequent antagonism studies in the same drug discrimination monkeys showed that selegiline, when given with a longer pretreatment time (24 hours), did not produce cocaine-like subjective effects but actually antagonized (blocked) the subjective effects of cocaine. Following 24-hour pretreatment with 3.2 to 10 mg/kg selegiline (IM), monkeys responded on the saline-key for their food despite having received injections of cocaine. The interpretation is that the cocaine injections were recognized as saline-like. Thus, while high doses of selegiline may produce some immediate cocaine-like subjective effects in monkeys, these effects are short-lived and a delayed-onset, long-lasting antagonism (blockade) of cocaine endures. The observed blockade of cocaine subjective effects in monkeys is consonant with a recently published clinical study in which selegiline significantly reduced the rating of how "high" subjects felt following cocaine.

In a second (same NIDA contract) study, selegiline was evaluated in 4 rhesus monkeys trained to self-administer intravenous cocaine (0.01 mg/kg/injection). To mimic the pharmacokinetics of the STS, selegiline was administered by constant intravenous infusion and each dosing rate was maintained for a minimum of 3 days or until rates of responding for both cocaine and food were stable. Responding for cocaine was essentially eliminated at a selegiline infusion rate of 0.13 to 0.23 mg/kg/hour in 3 of 4 monkeys. This decrease in cocaine self-administration persisted for several days after discontinuation of the selegiline infusion.

4.4 THE SELEGILINE TRANSDERMAL SYSTEM (STS) – CLINICAL EXPERIENCE

Transdermal delivery of selegiline avoids the first pass effect providing greater and more prolonged levels of unmetabolized selegiline. The transdermal delivery system provides greater consistency of medication delivery and may improve clinical effectiveness while reducing the levels of the three major metabolites. Continuous sustained levels of selegiline may lead to a faster onset of action.

Multiple Phase 1 clinical studies evaluating the safety, tolerance, and pharmacokinetics of selegiline administered as a transdermal dosage form have been conducted in healthy, young and elderly, male and female, volunteers. These studies have included dose-proportionality, age and gender analysis, in single and multiple dose paradigms. Results have shown that the STS reliably delivers sustained quantities of selegiline, which reach steady-state levels in 5 to 7 days, with no significant age or gender differences. All subjects completed these trials without serious AEs or significant laboratory changes (Somerset Pharmaceuticals, Investigator's Brochure for STS).

Somerset Pharmaceuticals recently completed a Phase 3 clinical trial demonstrating the efficacy and safety of STS in the treatment of major depression. Significant improvement was seen after 6 weeks of treatment in the clinical endpoints (HAM-D₁₋₁₇, HAM-D₁₋₂₈, HAM-D depressed mood item, CGI, and Montgomery-Asberg Depression Rating Scale) (Somerset Pharmaceuticals, Personal Communication).

In studies in normal volunteers and subjects with major depression, Parkinson's disease, and Alzheimer's disease, transdermal selegiline (STS) has been well tolerated. AEs leading to discontinuation of STS treatment included application site reaction, contact dermatitis, tachycardia, and orthostatic hypotension.

4.5 CLINICAL PHARMACOLOGY OF STS IN COCAINE DEPENDENCE

Two clinical pharmacology studies to investigate the potential interaction between cocaine and STS in subjects experienced in cocaine use were initiated. In both studies, the subjects received a daily dose of 20 mg STS for a period of 10 days. Challenge doses of cocaine were administered intravenously prior to and during STS treatment.

The first study, in which the challenge dose of cocaine consisted of a loading dose of 0.5 mg/kg infused over 10 minutes followed by a slow 4-hour infusion of 2 mg/kg, was completed in 12 subjects. Preliminary data suggest that a one-week exposure to STS did not affect the cardiovascular effects (heart rate, systolic and diastolic blood pressure) of cocaine. AEs reported were transient nausea, vomiting, and anxiety. These AEs were attributed to a vasovagal reflex secondary to the i.v. cocaine infusion. One episode of mild transient erectile dysfunction was also reported. No serious adverse events (SAEs) occurred.

The second study involves the administration of challenge doses of cocaine, 20 mg and 40 mg, rapidly over a one-minute duration. This study is ongoing. To date, 9 subjects have completed this study with no SAEs reported.

5 STUDY OBJECTIVES

The primary objective of this randomized controlled trial is the assessment of the efficacy of STS in reducing cocaine use in subjects with cocaine dependence (DSM-IV criteria). The hypothesis is that STS will reduce the weekly mean proportion of cocaine non-use days relative to placebo as determined by self report of use confirmed with urine assays for BE.

Secondary objectives include assessing the reduction in the overall proportion of non-use days and the proportion of subjects that achieve measured reductions in cocaine and other drugs use, the reduction in the severity of cocaine dependence and craving, and severity of depression (HAM-D), and the safety of STS in the study population.

6 STUDY SPONSOR

Somerset Pharmaceuticals, Inc. is the study sponsor. This study will be conducted under a Cooperative Research and Development Agreement (CRADA) between Somerset Pharmaceuticals and NIDA under IND # 57,052 held by Somerset Pharmaceuticals, Inc.

7 STUDY SITES AND ENROLLMENT RATE

The study will be conducted at approximately 16 sites, both at Veterans Administration (VA) and non-VA institutions. All participating institutions will be geographically located within the United States. Based on the enrollment rate of the phase 2 study of oral selegiline, it is anticipated that sites will enroll approximately 2 subjects per month. With a total of 16 sites, it is estimated that enrollment will take 12 months to complete.

8 STUDY DESIGN

This is a double-blind, placebo-controlled, two arm study with a parallel-group design in which, after screening (which includes a 14-day baseline assessment period), subjects will be randomly assigned to either placebo or STS patches daily for 8 weeks. All subjects will receive weekly psychosocial treatment. Adaptive randomization will be applied to match groups on gender, diagnosis of ADD, self-reported cocaine use for the historical 30-day period before providing informed consent, and severity of depression determined by HAM-D. After completion of the 8 weeks of double-blind treatment, subjects will be assessed 4 weeks later for post treatment observations.

9 SUBJECT SELECTION

A total of 300 subjects with cocaine dependence will be enrolled in the study (approximately 150/group). Entry into this study is open to both men and women and to all racial and ethnic subgroups. Each site will be asked to commit to enroll at least 20 subjects, with a maximum of 40 subjects, with a target of at least thirty-percent female subjects. Enrollment of more than 20 subjects at one site needs the approval of one of the Principal Investigators. Subjects will be recruited from a variety of sources. The primary source will be subjects seeking treatment for cocaine dependence at each hospital/outpatient clinic. Additional subjects will be recruited from the community by means of referrals from local treatment providers, advertising in local media, and word of mouth among subjects themselves. Recruitment advertisements will be approved by each site's Institutional Review Board (IRB).

9.1 INCLUSION CRITERIA:

1. Males and females, at least 18 years-of-age.
2. DSM-IV diagnosis of cocaine dependence as determined by SCID.

3. At least 3 positive urine BE specimens (> 300 ng/mL) during the 14-day baseline assessment period (6 total samples must be collected in 14 days with a maximum of 4 samples in one 7 day period).
4. Ability to understand and provide written informed consent.
5. Use of one of the following acceptable methods of birth control by female subjects:
 - a. oral contraceptives
 - b. barrier (diaphragm or condom) with spermicide
 - c. intrauterine progesterone contraceptive system
 - d. levonorgestrel implant
 - e. medroxyprogesterone acetate contraceptive injection
 - f. surgical sterilization
 - g. complete abstinence from sexual intercourse

9.2 EXCLUSION CRITERIA:

1. Current dependence, defined by DSM-IV criteria, on any psychoactive substance other than cocaine, alcohol, nicotine, or marijuana. Physiological dependence on alcohol requiring medical detoxification.
2. Individuals with neurological or psychiatric disorders, such as psychosis, bipolar illness, major depression (as assessed by the SCID) and/or current suicidal ideation (as assessed by SCID or HAM-D question #3), organic brain disease, or dementia, which require ongoing treatment or which would make medication compliance difficult. Past history of depression or suicidal attempts (as assessed by history/SCID) will not exclude subjects from participating in the study as long as they don't have a current diagnosis of major depression or suicidal ideation.
3. Subjects with serious medical illnesses including, but not limited to, uncontrolled hypertension, significant heart disease (including myocardial infarction within one year of enrollment), angina, cardiovascular abnormality, hepatic or renal disorders, or any serious, potentially life-threatening or progressive medical illness other than addiction that may compromise subject safety or study conduct.
4. Individuals mandated by the court to obtain treatment for cocaine-dependence.
5. Individuals not seeking treatment for cocaine dependence.
6. Individuals anticipating elective surgery within 14 weeks of signing the informed consent form.
7. 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.
8. Individuals with AIDS.

9. Individuals with active syphilis that have not been treated or refuse treatment for syphilis (see following note pp.19-20).
10. History of neuroleptic malignant syndrome.
11. Known or suspected hypersensitivity to selegiline, any monoamine oxidase inhibitor, or PEA.
12. Known allergic or chronic dermatologic illness (e.g., psoriasis), that might interfere with the STS absorption or which may be exacerbated by STS patch application.
13. Individuals with Hymenoptera allergy that requires carrying prophylactic epinephrine.
14. Therapy with a medication that could interact adversely with selegiline, with the time of administration of study agents relative to other medications based on the longest time interval of A, B, or C, below:
 - A) Five half lives of other medication or active metabolite(s), whichever is longer
 - B) Two weeks
 - C) Interval recommended by other medication's product labeling

Medications that fall into this category include:

- a. MAO inhibitors (e.g., selegiline, phenelzine, etc.) or selective serotonin reuptake inhibitor (SSRI; e.g., fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram) within 8 weeks of anticipated study entry.
- b. Psychotropic medications, centrally active anticholinergics, anticonvulsants (case by case), antiparkinsonian agents, antidepressants, antipsychotics (including lithium carbonate), anxiolytics, psychostimulants, nootropics, cerebral enhancers, vasodilators, benzodiazepine receptor agonists, reserpine, hypnotics; including: oral neuroleptics, depot neuroleptics (10 weeks), methyl dopa, ergot preparations, and tricyclic antidepressants.
- c. Sympathomimetic medications: e.g., amphetamines, methylphenidate, dopamine, epinephrine, norepinephrine, levodopa, tyrosine, phenylalanine, mazindole tyrosine, over-the-counter (OTC) and prescription nasal decongestants, and appetite suppressants.
- d. L-tryptophan, metoclopramide.
- e. Meperidine (Demerol®), dextromethorphan, propoxyphene or other opiates.

- f. 5-HT receptor agonists (e.g., sumatriptan succinate [Imitrex®], zolmitriptan [Zomig®], serotonergic agonists or antagonists (e.g. cyproheptadine [Periactin®], methysergide [Sansert®]).
15. Subjects who have participated in any experimental study within 8 weeks, or who have taken oral selegiline within 8 weeks of participation, or who have ever participated on a clinical trial utilizing the STS formulation.
 16. Pregnant or lactating women (Selegiline is listed as an FDA pregnancy category C drug in the product labeling). The pregnancy test must be completed within 2 days prior to study agent administration.
 17. Subjects, who in the judgment of the investigator, have clinically significant abnormal laboratory values (Appendix I).
 18. Electroconvulsive therapy within the past 90 days.
 19. Individuals who have taken St. John's Wort, yohimbine, ginkgo biloba, or any other central nervous system active herbal preparations within 8 weeks of anticipated study entry.
 20. Therapy with any opiate-substitutes (methadone, LAAM, buprenorphine) within 6 months of enrollment.
 21. Subjects with a diagnosis of adult asthma, including those with a history of acute asthma within the past two years, and those with current or recent (past 2 years) treatment with inhaled or oral beta-agonist or steroid therapy (due to potential serious adverse interactions with cocaine).
 22. Subjects 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.) If respiratory disease is excluded and the subject will consent to discontinue agonist use, s/he may be considered for inclusion.
 23. For subjects suspect for asthma but without formal diagnosis, 1) history of coughing and/or wheezing, 2) history of asthma and/or asthma treatment two or more years before, 3) history of other respiratory illness, e.g., complications of pulmonary disease (exclude if on beta agonists), 4) use of over-the-counter agonists or allergy medication for respiratory problems (e.g., Primatene Mist): a detailed history and physical exam, pulmonary consult, and pulmonary function tests should be performed prior to including or excluding from the study. Subjects with FEV₁ <70% will be excluded.

Notes on inclusion/exclusion criteria: Although AIDS is an exclusion criteria, a positive antibody titer to HIV is not. Individuals will be offered HIV testing during screening but may not have the test performed until after enrollment. This test is offered as a courtesy to the subjects

along with HIV education. Subjects who agree to HIV testing will be asked to sign a separate consent form for this test.

Individuals that are positive for syphilis by the RPR test, will have a fluorescent treponemal antibody absorbant assay (FTA-abs), a Microhemagglutination Assay-Treponema pallidum (MHA-TP), or a Treponema pallidum-particle agglutination (TP-PA) confirmatory test performed. If the confirmatory test is positive, subjects must be treated for syphilis. If the subject can provide evidence that they have been previously treated for syphilis or undergoes treatment for syphilis, they can be enrolled upon providing proof of completed treatment.

The infectious disease panel for hepatitis and tuberculosis is performed as an aid to determine if the individual has active hepatitis or tuberculosis. Either will exclude the individual from participation according to exclusion criteria number 3 (serious medical illnesses). Positive hepatitis or tuberculin PPD results do not, in and of themselves, exclude an individual from participation.

10 ENROLLMENT PROCEDURES

To qualify for the study, subjects are required to meet all inclusion/exclusion criteria, and to complete a 14-day baseline assessment period during which subject baseline assessment values and cocaine use patterns are established via repeated measures. Prior to conducting any screening assessments, the investigator will obtain signed and witnessed informed consent. Screening and baseline assessments may occur simultaneously, and both must be completed within the 30 days prior to randomization. However, a subject may not be randomized on the last day of the baseline assessment period. A subject will be included in the study after having been examined by the investigator or study physician who verifies that the inclusion criteria are met and no exclusion criteria are present.

10.1 ENROLLMENT

Investigators or study coordinators will telephone the CSPCC interactive touch tone randomization system (ITTRS) to randomize subjects. Eligibility criteria will be reviewed and a non-sequential subject number will be assigned. Subjects will be dosed as soon as possible after receiving the subject number. Non-sequential subject numbers will be assigned to ensure that investigators cannot start a subject on medication without first contacting the CSPCC.

10.2 RANDOMIZATION

Randomization codes for subject treatment assignments during the double-blind phase of the study will be developed and maintained at the data-coordinating center (Department of Veterans Affairs Cooperative Studies Program Coordinating Center (CSPCC), Perry Point, Maryland). Randomization will be accomplished by assigning subjects to precoded medication supplies. The CSPCC will prepare a randomization (non-sequential) list of subject numbers with assigned treatment codes for each participating center. The list will be submitted to the pharmacy-coordinating center (Department of Veterans Affairs Cooperative Studies Program Pharmacy Coordinating Center (PCC), Albuquerque, NM) which will then prepare medication supplies for each subject based on the treatment assignment on the list.

10.3 ADAPTIVE RANDOMIZATION

Adaptive random allocation of subjects to study groups was developed to balance groups with respect to screening prognostic variables. The procedure allocates treatment assignment based on the assignments and prognostic variable levels for all previously enrolled subjects. The treatment groups will be balanced with respect to gender, diagnosis of ADD, historical Self-Report of cocaine use (< 18 or ≥ 18 days of use in the last 30 days), and severity of depression (HAM-D score ≤ 11 or > 11). 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.¹⁰ The randomization process will be performed by computer at CSPCC.

Rationale for ADD as a stratification variable. It has been observed that a relatively high percentage of cocaine abusing or dependent individuals have a current diagnosis of ADD or a past history of ADHD. For example, in one sample of 281 cocaine abusers seeking treatment, 12% of the individuals met DSM-IV criteria for childhood ADHD, and 10% for adult ADD.¹¹ In another report, 35% of 298 treatment-seeking cocaine abusers met DSM-III-R criteria for childhood ADHD.¹² Compared to those who did not have a childhood ADHD diagnosis, those that did, reported more severe substance use, earlier onset of cocaine abuse, and more frequent and intense cocaine use. Other studies assessing the prevalence of ADD in individuals seeking treatment for cocaine abuse or dependence, as well as those assessing the prevalence of cocaine use in subjects seeking treatment for ADD, and evaluating the adult status of children who were treated for ADHD, support the association between ADD and cocaine use. It is possible that cocaine use by some individuals with ADD/ADHD may be an attempt to self-medicate for the disorder. Given the association between ADD/ADHD and cocaine use, as well as preliminary data indicating that selegiline may be effective for the treatment of ADD/ADHD, it is appropriate to balance groups in the present study with respect to a diagnosis of ADD. Individuals who are identified as having ADD as part of the study screening process will be informed of this, and will be encouraged to seek further evaluation and appropriate treatment.

11 INVESTIGATIONAL AGENTS

STS, 20 cm² patch containing 1.0 mg/cm² of selegiline and matched placebo will be supplied by Somerset Pharmaceuticals, Inc. Investigational agents will be distributed through the VA Pharmacy Coordinating Center (PCC) as described.

11.1 DISPENSING INVESTIGATIONAL AGENTS

Study patches will be dispensed weekly. Unused patches will be collected and inventoried each week. Used patches will be discarded. Extra study patches will be maintained by study personnel. The subject will be thoroughly instructed on how to apply the STS or placebo patch (Appendix II). During the study, the patch will be replaced every 24 hours.

11.2 LABELING

Investigational agents (STS patch and matching placebo) will be packaged in patient kits. Each kit will contain 8 boxes of ten transdermal patches with unique patch numbers. Each box in the kit will be labeled with the protocol name, protocol number, site number, subject number, and the words "Keep out of Reach of Children."

11.3 INVESTIGATIONAL AGENT ADMINISTRATION

The subject will be instructed on the procedure for application of study patches. During the study, patches will be applied at the same time each day. If the medication administration schedule does not coincide with the subject's personal schedule (e.g., evening or night work shift), application of the patch can occur at another time. However, the time of study medication administration must remain consistent for that subject over the course of his/her participation.

11.4 APPLICATION OF STS/PLACEBO PATCHES

The patch is to be applied to a clean, hairless area on the subject's upper torso or upper thigh (see Appendix II). The skin at application site should not be oily, irritated, broken, scarred or calloused. The patch application site should be rotated daily to allow for multiple applications. Prior to application, the site should be gently washed, not rubbed, with lukewarm soapsuds avoiding any local irritation. The site should be rinsed with clear water and gently towel dried. The patch is removed after 24 hours and replaced with a new patch within an hour of removal. Showering or bathing should be scheduled just prior to reapplication of the patch.

11.5 STORAGE

Investigational agents will be stored at room temperature in a secure location at each investigator's facility.

11.6 RECORD OF ADMINISTRATION

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

11.7 USED/UNUSED SUPPLIES

During the study, all investigational agents not used by the subject must be returned to the investigator for assessment of subject compliance. At the end of the study, all unused investigational agents must be inventoried. If any investigational agent is lost or damaged, its disposition should be documented. Unused investigational agents will be retained at the clinic site pending instructions for disposition by the Sponsor at the end of the study. Used patches will not be collected.

12 TREATMENT PLAN

12.1 STS OR PLACEBO

STS, 20 cm² patch containing 1.0 mg/cm² of selegiline or matched placebo will be applied daily for the 8 week duration of the study.

12.2 BEHAVIORAL/PSYCHOSOCIAL TREATMENT

All subjects will receive standardized, manual-guided individual psychotherapy by a certified therapist once per week during the double-blind phase of the study. Psychotherapy will consist of one, 1-hour session of individualized counseling per week, in addition to initial HIV education. This therapy will be administered as a brief, structured program based on a relapse prevention model. No privileges or service contingencies based on urine results, nor extra services such as

family or employment counseling will be offered. Study participants will not be discouraged from seeking any additional therapy.

The goal of this behavioral treatment intervention is to increase protocol compliance and educate the subject about his/her dependence and factors associated with drug use, and assist study participants in achieving abstinence from cocaine without obscuring the impact of the pharmacological treatment. The primary purpose of using a manual-guided procedure for therapists is to achieve a 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 audio-tape therapy sessions. Original tapes are to be maintained at the site. These tapes will be used only by selected study researchers and will be destroyed when the study is over. 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. Additional emergency crisis management sessions will be available up to a maximum of four along with visit documentation.

13 STUDY PROCEDURES

Interested candidates who have been determined by telephone interview to have diagnostic criteria for cocaine dependence, are seeking treatment, and are available to come to the clinic for 14 weeks will meet with the investigator and receive an explanation of the study purpose and requirements. 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. Individuals are then given a screening number and proceed to the screening phase of the study. Screening assessments (including the 14-day baseline assessments) must be completed within 30 days before randomization. At no time during the screening process of the study 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.

13.1 SCREENING

After the subject has consented to participate in the study, the screening process begins. The first part of the screening process includes determining how many days in the last 30 was cocaine used and if the individual is planning any elective surgery in the next 14 weeks. Prior medications are reviewed and a complete medical history and physical are performed. A psychiatric evaluation, ADD assessment, and SCID for evaluation of DSM-IV criteria for cocaine dependence and axis I disorders are performed. A HAM-D questionnaire is completed and laboratory tests including hematologic assessments, blood chemistries, routine urinalysis, urine drug screen for substances of abuse, infectious disease panel, and syphilis test are performed. An ECG and a RAB are completed. A pretreatment blood sample will be collected for determination of selegiline/selegiline metabolite levels. A pregnancy test (if female) will be completed within two days before study agent administration. Prior medications will be recorded for the 60 days preceding the day that the subject receives the first day's study agents.

13.2 BASELINE ASSESSMENTS DURING SCREENING

Baseline assessments will occur over a 14-day period. If a subject fails to provide the required six urine specimens, including three positive for urine BE, and the accompanying other baseline repeated measures within the 14-day period, the baseline period may be shifted until the subject meets the requirements in any consecutive 14-day period but within 30 days before randomization. Potential participants will not be provided with the results of the urine analysis for BE. Screening assessments are considered valid if the subject is randomized onto the study within 30 days of the start of screening. However, the subject may not be randomized on the last day of the baseline assessment period. If the subject does not meet the requirements within the 30 days, then the informed consent process and all of the screening and baseline assessments must be repeated before subject randomization.

Baseline assessments include three-times weekly urine BE plus creatinine measurements, vital signs, urine drug screen, and self report of use (SUR), including cocaine, opiates, nicotine, alcohol, and marijuana for two weeks. BSCS, CGI-S, and CGI-O will be assessed once per week for two weeks. Subjects must have 6 vital signs and weight assessments performed in a consecutive two-week period. Assessments should be performed when urine specimens are collected. Ideally no more than 4 assessments should be obtained in one week of the two-week baseline.

13.3 SUBJECT RANDOMIZATION AND ENROLLMENT

If the individual meets all of the study inclusion and does not meet the exclusion criteria (a checklist will be provided in the CRF package – see form 1) then the subject can be randomized into the study. The investigator or study coordinator will call the CSPCC ITTRS and review the eligibility criteria and provide information such that adaptive randomization procedures can be followed including:

- Subject's gender
- Subject's ADD status
- Amount of cocaine used in the last 30 days
- HAM-D score

The ITTRS will provide the caller with a non-sequential subject number. The investigator or coordinator will arrange for investigational agent to be dispensed and arrange for the first visit of the subject to initiate treatment.

13.4 DOUBLE-BLIND TREATMENT

At the first clinic visit, subjects will be given instructions on how to apply patches and will be given a week's supply of patches (10 total). At study visits, investigative staff will remove old patches and apply new study patches. The site of the removed patch will be inspected for a reaction. Subjects will be scheduled for treatment and assessments three times per week usually on a Monday, Wednesday, and Friday, for 8 weeks. Two consecutive days may be scheduled around holidays or other schedule conflicts. All subjects will be provided an opportunity for HIV testing. All subjects will be provided with HIV/AIDS education (Appendix III). All subjects will

be provided with manual-guided psychosocial therapy once per week during the 8 weeks of treatment.

13.5 PREVENTION OF STUDY DROP-OUTS

Subjects will be encouraged to come for treatment and for the evaluation sessions as described in this protocol. To minimize missed sessions, they will be compensated for their transportation and time spent in completing study assessments. It will be emphasized to subjects during screening that even if they have a relapse they should come to all scheduled appointments. They will be discouraged from using cocaine, but there will be no penalty for relapsing, or for missed sessions.

13.6 PREMATURE STUDY TERMINATION

Since an intent-to-treat paradigm is being used for this study, subjects will be encouraged to continue completing study visits, study assessments and psychosocial treatment sessions, even if they are unable to tolerate investigational agents. If a subject decides to drop out of the study prior to week 8, s/he will be asked to complete all final assessments (termination) at the time of drop out (see section 14.3). If a subject wishes to stop taking drug but to continue to participate in psychosocial treatment, s/he will continue to have all scheduled assessments according to the protocol and will complete the study at week 8. During the period of psychosocial measures safety and efficacy data will be collected with the exception of data strictly related to patch use. Section 14.5 details the procedures to be followed in the event that a subject dies while participating in the study.

13.7 FOLLOW-UP

At the end of study week 8, subjects will be asked to come to the clinic four weeks later for a final follow-up visit and assessments. If it is possible to have the subject return to the clinic, a urine specimen for BE will be collected and the subject will be 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 medication. If it is not possible to arrange for the subject to return to the clinic, then they should be telephoned and asked to provide a current self-reported cocaine and other drug use, current treatment for drug or alcohol abuse, and an impression of the study medication. 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.

13.8 MAO-I SAFETY

No significant changes in blood pressure have been observed in the Somerset sponsored clinical trials in depression or in the NIDA clinical pharmacology studies with cocaine and STS. Based on studies performed by Somerset, tyramine dietary restrictions have been removed from STS protocols. In the unlikely event of a hypertensive crisis and/or STS overdose, the transdermal system should be discontinued and the underlying skin washed with soap and cold water to remove any residual investigational agent.

Vital signs will be measured to detect a pressor response in subjects receiving MAO inhibitors. Full reliance should not be placed on blood pressure readings, and the subject should also be observed for clinical signs of a sympathomimetic reaction. Accordingly, clinical judgment should be exercised regarding discontinuation of investigational agent if symptoms such as

palpitations, tachycardia, sense of constriction in the throat or chest, or frequent headaches occur during the trial.

Subjects will be instructed to report promptly the occurrence of headache or other unusual symptoms, i.e., palpitations and/or tachycardia, a sense of constriction in the throat or chest, sweating, dizziness, neck stiffness, nausea, or vomiting.

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

13.9 MAINTAINING AND BREAKING STUDY BLIND

The decision to break the study blind for an individual subject lies with the site investigator and study principal investigator or with the NIDA medical monitor, but should be resorted to only in cases of life-threatening emergency when knowledge of the treatment arm investigational agent will influence clinical management.

13.10 PARTICIPANT REIMBURSEMENT

Subjects will be compensated for time involved, in providing data, and inconvenience, at a rate of \$10 per clinic visit during which a urine specimen is provided in the screening phase and \$10 per clinic visit during the treatment and follow-up phases upon completion of the specified requisite assessments. The maximum payment is \$370. Subjects will be compensated regardless of whether they continue to receive study medication. It is emphasized that this remuneration is for time and inconvenience (e.g., gasoline, public transportation, etc.), not for protocol compliance. Subject reimbursements may be made by cash or vouchers in accordance with local site policies. Subjects (or potential subjects as is the case during screening) should be paid on a daily or weekly basis, whichever is most convenient/acceptable locally.

13.11 SUBJECT CONFIDENTIALITY

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

13.12 SUBJECT WITHDRAWAL

An investigator may terminate a subject if s/he deems it clinically appropriate or for any of the following reasons: 1) significant side effects from investigational agents, 2) serious or unexpected AEs, 3) inability to comply with the study protocol, 4) protocol violation, or 5) serious intercurrent illness. A subject may withdraw from the study anytime s/he wishes. In the event a subject is discontinued from receiving the investigational agent, s/he will be allowed to continue the psychosocial-behavioral treatment with the approval of the investigator.

Any subject who discontinues prematurely, regardless of the reason, will be requested to return for a final visit to perform the necessary procedures and obtain data for end of study/early termination (see section 14.3).

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

All study participants will be encouraged to carry a wallet card that identifies them as a participant in a clinical research study. The card will provide the name and phone number of the site investigator 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 site investigator with regards to that care.

13.13 CONCOMITANT MEDICATIONS

Any medications to be taken during the study must be approved by the investigator. The following medications should not be used during treatment with STS:

1. MAO inhibitors (e.g., phenelzine (Nardil®), tranylcypromine (Parnate®), selegiline (Eldepryl®), etc.)
2. Selective serotonin reuptake inhibitors (SSRI; e.g., fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram)
3. Psychotropic medications
4. Centrally active anticholinergics
5. Anticonvulsants (case by case)
6. Antiparkinsonian agents
7. Antidepressants
8. Antipsychotics, including lithium carbonate
9. Anxiolytics
10. Psychostimulants
11. Nootropics
12. Cerebral enhancers
13. Vasodilators
14. Benzodiazepine receptor agonists
15. Reserpine
16. Hypnotics
17. Oral neuroleptics, depot neuroleptics, methyldopa, ergot preparations.
18. Sympathomimetic medications: e.g., amphetamines, methylphenidate, dopamine, epinephrine, norepinephrine, levodopa, tyrosine, phenylalanine, mazindole tyrosine; OTC and prescription nasal decongestants, and appetite suppressants.
19. L-tryptophan, metoclopramide
20. Meperidine (Demerol®), dextromethorphan or opiates
21. Propoxyphene
22. 5-HT receptor agonists (e.g., sumatriptan succinate [Imitrex®], zolmitriptan [Zomig®], serotonergic agonists or antagonists (e.g. cyproheptadine [Periactin®], methysergide [Sansert®])

23. CNS active herbal preparations including, but not limited to, St. John's Wort, yohimbine, valerian, kava/kavatrol and ginkgo biloba
24. Any opiate-substitutes (methadone, LAAM, buprenorphine)
25. Inhaled or oral beta-agonist or steroid therapy for asthma (due to potential serious adverse interactions with cocaine, e.g., albuterol)
26. OTC agonists or allergy medication for respiratory problems (e.g., Primatene Mist).

14 CLINICAL EVALUATIONS

Table 1 provides a summary of assessments to be conducted over the entire study.

14.1 ASSESSMENTS AT SCREENING/BASELINE

Prior to enrollment on the study, subjects will be screened to determine if they meet eligibility requirements. In addition, certain baseline assessments will be made that are part of eligibility determinations but also provide physiological, psychological, and disease status information prior to active treatment. Because the initial assessments are intensive, they have been separated into groups designated as screening and baseline assessments. The screening and baseline assessments should be conducted concurrently as scheduling permits.

14.1.1 Screening Assessments:

Screening assessments to be completed within 30 days of randomization (unless otherwise indicated) include:

1. Complete medical history and physical exam.
2. Psychiatric evaluation including assessment of adult ADD and SCID evaluation for DSM-IV diagnosis of cocaine dependence and Axis-I disorders.
3. ASI evaluation
4. HAM-D evaluation
5. Hematology
6. Blood chemistries
7. Routine urinalysis
8. Urine drug screen
9. Infectious disease panel
10. Rapid Plasma Reagin (RPR) test for syphilis
11. RAB
12. ECG
13. Pregnancy test (if female) within 2 days before study agent administration.
14. Blood sample as a control for assessments of selegiline/selegiline metabolite levels.
15. Prior medications. All medications taken by the subject for the 60 days prior to the first day that the subject receives study agents will be documented on a Prior Medication CRF. Data will be reviewed and recorded on the day that the subject first receives study agents but before study agent administration.

Table 1. Overview of Study Assessments During Screening and Double-Blind Treatment

Assessment	Screening	Baseline	R A N D O M I Z A T I O N	Treatment								Termination ^a	Follow-up
Study Week	(completed within 30 days of randomization)			1	2	3	4	5	6	7	8		12
Screening													
Informed Consent	X												
SCID	X												
Psychiatric evaluation	X												
ADD	X												
Medical History	X												
Infectious disease panel/RPR	X												
Safety													
Physical exam	X											X	
Prior Medications	X ^b												
Vital Signs/weight		3 X/week for 2 weeks		3X	3X	X	X	X	X	X	X	X	
Hematology	X						X					X	
Blood Chemistry	X						X					X	
Routine Urinalysis	X						X					X	
12-lead ECG	X											X	
Pregnancy test	(completed within 2 days before agent administration)						X					X	
Adverse Events				X	X	X	X	X	X	X	X	X	X
Con. Meds.				X	X	X	X	X	X	X	X	X	
Efficacy													
HAM-D	X					X		X		X		X	
ASI	X							X				X	
Urine BE/creatinine		3 X/week for 2 weeks		3 X	3 X	3 X	3 X	3 X	3 X	3 X	3 X	X	X
SUR		3 X/week for 2 weeks		3 X	3 X	3 X	3 X	3 X	3 X	3 X	3 X	X	X ^c
Urine drug screen		3 X/week for 2 weeks		X	X	X	X	X	X	X	X	X	
RAB	X											X	
BSCS		Weekly x 2 weeks		X	X	X	X	X	X	X	X	X	
CGI-self		Weekly x 2 weeks		X	X	X	X	X	X	X	X	X	
CGI-observer		Weekly x 2 weeks		X	X	X	X	X	X	X	X	X	
Treatment Compliance-Drugs				3 X	3 X	3 X	3 X	3 X	3 X	3 X	3 X	X	
Treatment Compliance-Therapy			X	X	X	X	X	X	X	X	X		
Blood selegeline/metabolites	X				X			X					

^a At the termination study visit or if the subject discontinues prematurely.

^b Prior medications will be recorded on the date the subject signs the informed consent for the prior 60 days and will be updated on study day 1 before patch application.

^c SUR at follow-up is subject's report of use of cocaine, opiates, alcohol, nicotine, and marijuana in the last 30 days.

14.1.2 Baseline Assessments

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

1. Three-times weekly urine BE plus creatinine measurements for two weeks. Subjects must provide six urine specimens in a consecutive 14-day period, three of which must be positive for urine BE (> 300 ng/mL). Ideally 3 of the specimens will be obtained in one week and 3 in the next week. No more than 4 of the specimens may be obtained in a 7-day period of the 14-day baseline.
2. Three-times weekly urine drug screen.
3. Three-times weekly vital signs and weight collected during visits when urine specimens are provided.
4. The following must be obtained weekly for two weeks:
 - a. BSCS
 - b. CGI-S
 - c. CGI-O
5. SUR including cocaine, alcohol, nicotine, and marijuana must be obtained 3 times per week for two weeks, documenting daily self report of use for the two week period.

14.2 ASSESSMENTS DURING DOUBLE-BLIND TREATMENT

Over the 8-week period of active treatment, subjects will return to the clinic three times per week (ideally on Monday, Wednesday, and Friday). Assessments will be performed as follows:

At each visit:

1. SUR
2. Urine BE and creatinine
3. Vital signs (just the first two weeks then weekly thereafter)
4. Treatment compliance-drugs
5. Treatment compliance-therapy (at each session attended)

Once per week at the first visit each week:

1. Vital signs (after the first two weeks when vital signs are taken at each visit)
2. Urine drug screen
3. AEs
4. Concomitant medications
5. BSCS
6. CGI-S
7. CGI-O

At the first visit of weeks 3 and 6:

1. Blood for selegiline/selegiline metabolites

At the first visit of study week 4:

1. Hematology
2. Blood chemistries
3. Routine urinalysis
4. Pregnancy test (if female)

At the first visit of study weeks 3, 5, and 7

1. HAM-D

At the first visit of study week 5

1. ASI

14.3 ASSESSMENTS AT DOUBLE-BLIND STUDY TERMINATION

At the final scheduled study visit during the treatment phase of the study or if the subject discontinues prematurely, regardless of the reason (request that the subject return for final assessments), the following assessments will be performed:

1. If the subject discontinues prematurely, determine the reason for termination.
2. Physical exam
3. Vital signs
4. SUR
5. Urine BE and creatinine
6. AEs
7. Urine drug screen
8. BSCS
9. CGI-S
10. CGI-O
11. Hematology
12. Blood chemistries
13. Routine urinalysis
14. Pregnancy test (if female)
15. ASI
16. RAB
17. HAM-D
18. ECG
19. Treatment compliance
20. Concomitant medications

NOTE: Subjects that start the study on a Monday will finish the last day of the last week on a Sunday. The final assessments in these subjects will be on the next possible day after Sunday, preferably Monday. Any urine BE data collected after treatment day 56 will be used to score a day as a use or non-use day up to study day 54.

14.4 ASSESSMENTS AT FINAL FOLLOW-UP

Final off-treatment assessments will be performed four weeks after the 8 week period of double-blind treatment and include:

1. Questions regarding amount of cocaine/other substance used over the last 4 weeks, current treatment for drug or alcohol abuse, and an impression of the study medication.
2. Urine BE and creatinine
3. AEs

14.5 ASSESSMENTS IN THE EVENT OF DEATH ON STUDY

In the event a subject dies while on study, the site investigator is responsible for informing the local medical examiner's office of this protocol, and of the procedures to be followed for collecting specimens and information required for study-related toxicological analyses. The site investigator may also refer the medical examiner directly to the Center for Human Toxicology (801-581-5117) for additional information. The following specimens will be collected:

- 10 ml of whole blood in non-fluoride tube (red top).
- 10 ml of whole blood in a fluoride tube (grey top).
- 10 ml of urine.
- 20 gm of liver tissue.

NOTE: If whole blood cannot be obtained then blood is to be collected from body fluids in the thoracic cavity.

Subjects will be asked to consent to allow the site investigator to request the following in the event of their death while participating in the study: 1) samples of certain bodily fluids and tissues taken for the purposes of this study only, and 2) an autopsy. The consent for these is not mandatory for subject's participation in the study.

14.6 ASSESSMENT METHODS

14.6.1 Vital Signs

Vital signs to be assessed include oral temperature, sitting blood pressure, pulse rate, respiratory rate, and standing blood pressure and pulse rate (standing 1 minute), and standing blood pressure and pulse rate (standing 3 minutes). More frequent monitoring of vital signs may be obtained at the investigator's discretion.

14.6.2 Hematology

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

14.6.3 Blood Chemistries

Blood will be collected in non-anticoagulant containing vacutainer tubes and serum separated according to standard procedures. Quantitative analysis will be performed for the following analytes: sodium, potassium, chloride, carbon dioxide, glucose, creatinine, albumin, total protein, calcium, cholesterol, triglycerides, alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), gamma glutamyltranspeptidase (GGT), total bilirubin, lactic dehydrogenase (LDH), alkaline phosphatase (ALP), blood urea nitrogen (BUN), and uric acid. Laboratories performing these assessments should be either directly regulated by CAP or CLIA or indirectly according to CLIA guidelines.

14.6.4 Routine Urinalysis

Urine will be collected by clean catch and analyzed for specific gravity, pH, glucose, protein, ketones, occult blood, white blood cells, red blood cells, and epithelial cells. Laboratories performing these assessments should be either directly regulated by CAP or CLIA or indirectly according to CLIA guidelines.

14.6.5 Infectious Disease Panel/RPR

Blood will be collected in a non-anticoagulant containing vacutainer tube and serum separated according to standard procedures. Qualitative analysis reporting positive/negative results will be performed for the following analytes: Hepatitis B surface antigen, Hepatitis B surface antibody, Hepatitis B core antibody, and Hepatitis C virus antibody. A purified protein derivative (PPD) skin test for tuberculosis will be performed and if positive a chest x-ray is required to assess active tuberculosis. A rapid plasma reagin test (RPR) for syphilis will be performed. If the RPR test is positive, a FTA-abs, MHA-TP, or TP-PA confirmatory test for active syphilis will be performed. If either confirmatory test is positive, the subject will be referred for treatment and will be considered eligible only after proof of completion of treatment is provided.

14.6.6 Pregnancy Test

Pregnancy tests designed to measure human chorionic gonadotropin will be used. All female subjects will be tested regardless of their child-bearing capacity.

14.6.7 HAM-D

The HAM-D¹³ is a 24-item interviewer administered assessment of the subject's level of depression. The HAM-D will be administered by an experienced staff member with clinical experience in diagnosing psychiatric patients as well as experience with administering the HAM-D.

14.6.8 ADD Assessment

An assessment from the DSM-IV criteria for childhood ADHD has been adapted to diagnose adult ADD. This interview assesses the subject's inattention, hyperactivity, and impulsivity both as the childhood history and as current adult behaviors. The ADD assessment will be administered by a staff member with clinical experience in assessing subjects with ADD.

14.6.9 SCID

A SCID to assess the subject's cocaine-dependence according to DSM-IV criteria, severity of depression, and axis I disorders will be conducted during screening. The SCID will be

administered by a staff member with clinical experience in assessing subjects with psychiatric disorders.

14.6.10 ASI

The ASI Fifth Edition, 1997 version, will be administered by a research staff member having at least a bachelor's degree in the social sciences or equivalent training and experience as determined by the site's investigator. The ASI is used to evaluate treatment outcomes 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.*,¹⁴ Carroll *et al.*¹⁵ A copy of the ASI manual and question-by-question guide may be found in the study operations manual.

14.6.11 Urine BE and Creatinine

Urine samples will be collected ideally at 48-hour intervals 3 times a week (generally Monday, Wednesday, and Friday, barring holidays and schedule conflicts). Two different types of collectors will be used, one at screening, Ontrak Testcups®, and one during treatment, Franklin Collectors. Ontrak Testcups ® provide for the rapid, simultaneous testing of multiple drugs with no urine or reagent handling, and obviate the need for direct observation of the individual. After testing, screening samples will be split at the sites: one-half of each sample will be stored frozen at the site for backup; the other half will be sent to a central laboratory for analysis. If the samples will not be shipped within 10 days of collection, they should be frozen until shipment. Otherwise the samples should be refrigerated until shipping.

The Franklin Collector, a device that documents specimen authenticity through the precise measurement of urine temperature will be used for all urine collections after screening and baseline. Direct observation, however, may be employed in lieu of the Franklin Collectors when urine temperature assessments may not be reliable or appropriate (e.g. pyretic individuals) or the collectors are unavailable.

If a subject fails to give a sample on the day it is due, it will be obtained as close to the missed visit as possible. Urine samples will be sent to a central laboratory to be analyzed for BE and creatinine. Approximately one-half of each urine sample will be frozen at the sites until the samples have been received and analyzed and the results recorded at the central laboratory. Results will not be provided to the individual sites during the study, and sites are prohibited from analyzing samples locally.

14.6.12 Urine Drug 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, barbiturates, benzodiazepines, and opiates and each time during screening.

14.6.13 Self Report of Use (SUR)

The SUR includes the subject's daily report of use of cocaine, alcohol, marijuana, opioids, and nicotine since the last clinic visit.

14.6.14 BSCS

The BSCS is a self-administered assessment that asks the participant 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.¹⁶ If the participant is unable to self-administer this assessment (e.g., physical handicap, poor reading skills), study personnel can assist by reading the questions out loud to the participant and/or marking the participant's response on the CRF. However, study personnel are not to offer interpretations of the questions.

14.6.15 Clinical Global Impression-Observer (CGI-O)

The CGI-O requires the 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 CGI-O will be administered by an experienced staff member with clinical experience in assessing subjects with cocaine dependence.

14.6.16 Clinical Global Impression-Self (CGI-S)

The CGI-Self is a self-administered assessment that asks the participant 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.

14.6.17 Adverse Events (AEs)

AEs will be assessed at each study visit by an investigative staff nurse or physician. If an AE is reported to a nurse that requires medical attention, it should be reported to a study physician immediately. A study physician will meet with the participant once a week to review the AEs recorded by the nurse and to assess for any additional AEs. The investigator or study physician will assess subjects for any medical or psychiatric side effects. Both the research assistant and physician will assess AEs by asking the participant "How have you been feeling since I saw you last". The type of AE, severity of the AE, and the relationship to the study treatments will be recorded on an AE CRF according to the procedures described in section 15.6.

14.6.18 Risk Assessment Battery (RAB)

The RAB is a self-administered assessment of the participant's engagement in activities that increase the likelihood of contracting HIV. If the participant is unable to self-administer this assessment (e.g. physical handicap, poor reading skills), study personnel can assist by reading the questions out loud to the participant and/or marking the participant's response on the CRF. However, study personnel are not to offer interpretations of the questions.

14.6.19 ECG

Twelve-lead electrocardiograms will be performed according to standard procedures. The results will be reviewed by the site physician for interpretation. The site physician may consult with a cardiologist on the results of the ECG if he/she feels that a consultation is necessary. ECG results will be used to assess cardiovascular anomalies during screening to assure that subjects do not meet exclusion criteria and at study completion to assess AEs.

14.6.20 Treatment Compliance-Drugs

Compliance with study agents will be determined by recording patch use at each visit.

14.6.21 Treatment Compliance-Therapy

Compliance with scheduled psychosocial therapy sessions will be monitored by recording the subject's attendance at sessions and the length of each session on the appropriate CRF.

14.6.22 Blood Selegiline/Selegiline Metabolite Levels

Analysis of selegiline, N-desmethylselegiline, L-amphetamine, and L-methamphetamine plasma concentration will be determined during screening and after 2 and 5 weeks of treatment. Blood should be collected prior to the first dose and within 15 minutes prior to the application of new patches during weeks 3 and 6. The analysis will be performed by the University of Utah, Center for Human Toxicology using a validated liquid chromatography atmospheric pressure chemical ionization tandem mass spectrometry measurement. The procedure for blood collection, storage, and shipping is provided in Appendix IV.

15 REGULATORY AND REPORTING REQUIREMENTS

15.1 FDA FORM 1572

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

15.2 IRB APPROVAL

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

15.3 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. Subjects who refuse to participate or who withdraw from the study will be treated without prejudice. Two additional consent forms will be used: one for consent to allow therapy sessions to be audiotaped and one for those subjects who request HIV testing to provide informed consent for this test.

15.4 DRUG ACCOUNTABILITY

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

15.5 OUTSIDE MONITORING

Data and Safety Monitoring Board: Safety data will be reviewed by a data and safety monitoring board, which will meet after the first 150 subjects have completed/terminated from the study or earlier if deemed necessary. Additional meetings after that will be held on an as needed basis as determined by the medical monitor. The board will be blind to subjects' actual treatment assignments.

Medical Monitor: Dr. Ann Anderson will act as an independent medical monitor for the study. The medical monitor will be responsible for reviewing all AEs to determine whether the AE is serious and should be reported to the FDA as well as to confirm concurrence with the investigator on the severity of the AE and the relatedness to the study treatments. The medical monitor will also be responsible for tracking and assessing trends in the AEs reported.

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

Monitors will conduct a site initiation visit prior to the start of the study. At this visit, they will assure that proper study-related documentation exists, assist in training investigators and other site personnel in study procedures and 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 sponsor's representatives will be scheduled at appropriate intervals. At these visits, the monitors will verify that study procedures are being conducted according to the protocol guidelines. At the end of the study they will advise on storage of study records and return of unused study medication. All sites should anticipate visits by NIDA, the sponsor, and the FDA.

15.6 RECORDS RETENTION

Clinical records for all subjects studied, including history and physical findings, laboratory data, and results of consultations, are to be maintained by the investigator in a secure storage facility. These records are to be retained until notified in writing by the sponsor.

15.7 ADVERSE EVENTS REPORTING.

In accordance with FDA reporting requirements, all AEs occurring after randomization, and up to 4 weeks after completion of treatment, 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 V. The occurrence of AEs will be assessed weekly and an AE CRF completed.

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

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

15.8 SERIOUS ADVERSE EVENTS

Each AE will be classified by a study investigator as serious or non-serious and appropriate reporting procedures followed. Serious adverse events (SAEs) are defined as any fatal event, any immediately life-threatening event, any permanent or substantially disabling event, any event that requires or prolongs inpatient hospitalization, or any congenital anomaly. This category also includes any event that a study investigator or the medical monitor judges to be serious or which would suggest a significant hazard, contraindication, side effect, or precaution. An unexpected event is one that is not described with respect to nature, severity, or frequency in the current Investigator's Brochure.

Any SAE (including death) due to any cause, which occurs during the course of this investigation, whether or not related to the investigational medication, must be reported within 24-hours by telephone to: the NIDA, Clinical Trials Manager, or the Study Medical Monitor, Dr. Ann Anderson, or Dr. Ahmed Elkashef, NIDA Principal Investigator. The telephone report is to be followed by submission of a completed SAE Form with demographic information and a narrative explanation of the event. Attached to the SAE Form should be photocopies of the AE/Concomitant Medications, Physical Exam, and the Medical History Forms from the subject's CRFs. Unexpected serious medical events are also to be reported immediately to the responsible institutional review board according to local regulatory requirements. All participating investigators will be notified of any serious and unexpected AE requiring submission to the FDA in an IND safety report from the sponsor.

NIDA will inform Somerset Pharmaceuticals, Inc. of all SAEs which occur during the study. Somerset, as IND holder, is required by FDA regulations to report these to the FDA in a timely fashion. All AEs that are both serious and unexpected must be reported to the FDA, in writing, within ten working days of notification of the sponsor of the SAE. If the SAE is fatal or life threatening, there is an additional obligation of Somerset to notify FDA by telephone within 3 working days, with a follow-up written report in 10 working days.

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 site investigators in this study have the responsibility of promptly reporting all SAEs to NIDA so that Somerset can comply with these regulations.

In the event that a study subject either withdraws from the study or an investigator decides to discontinue the subject from the study due to a SAE, the subject must have appropriate follow-up medical monitoring. If the subject is hospitalized, medical monitoring will consist of not less than daily evaluation by physical examination, vital signs, laboratory evaluations, and if applicable, ECG monitoring for significant treatment-emergent abnormalities. Monitoring will continue until the problem prompting hospitalization has resolved or stabilized with no further change expected, is discovered to be clearly unrelated to study medication, or progresses to death.

16 ANALYTICAL PLAN

16.1 STATISTICAL HYPOTHESES

The primary objective of this randomized controlled trial is the assessment of the efficacy of STS in reducing cocaine use in subjects with cocaine dependence (DSM-IV criteria). It is hypothesized that STS will reduce the weekly mean proportion of days of cocaine use relative to placebo as determined by SUR confirmed with urine assays for BE.

Secondary objectives include determining the proportion of subjects that achieve measured reductions in cocaine and other drugs use (non-use days on treatment compared to non-use days at baseline), the reduction in the severity of cocaine dependence and craving (ASI, BSCS, CGI-self, and CGI-observer), severity of depression (HAM-D), and the safety of STS (AEs, laboratory data, physical exams, and vital signs) in the study population.

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. A primary response has been chosen for its ability to indicate activity of the test product. Some of the secondary outcome variables add a measure of clinical relevance to the reduction of use by requiring either sustained abstinence or a predetermined, substantial overall reduction in use days. Other secondary outcome variables explore the need for laboratory confirmation of the SUR. Still others explore the effect of therapy on psychosocial aspects of cocaine dependency.

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

“The consensus of the group was that the best overall outcome measure was a composite index of abstinence derived from a combination of confidential patients self-report and objective biological testing (typically urinalysis testing). The recommendation was that this composite index of abstinence be used to classify each day as abstinent or non-abstinent and that the primary outcome analysis be based on these classifications.”

Some data will be collected in this study for scientific use and not as primary or secondary outcome measures. Analyses of data from the RAB are included in this category. These data are being collected in order to build a database of risk behaviors associated with cocaine use.

16.2 OUTCOME MEASURES

16.2.1 Primary Outcome Measure

The basic outcome variable is the weekly proportion of cocaine non-use days. Cocaine use and non-use days will be defined by subject self-report of use, confirmed or disproved by quantification of urine BE. For the primary efficacy response, each day of the 8-week study will be coded as either a use or a non-use day based on the self-reports and on the urine BE data. Three urine collection days are scheduled per calendar week. The first day that the subject receives the investigational agent will not be scored as a use or non-use day.

Because of the pharmacokinetics of cocaine and BE, carryover from previous cocaine use may be difficult to distinguish in the laboratory from new use. The rules enunciated by Preston *et al.*¹⁷, modified to meet the conditions of this study, (Rules 1-5 below) will facilitate classification of each assessment day as use or no-use.

The following will indicate “new use”:

RULE 0: Subject reports new use.

The subject self report claims no new use or SUR is missing but any of the following applies:

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

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

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

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

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

Assessment days may be less or more than 48 hours apart in this study. For this reason, the Preston rules were modified to delete reference to previous urine specimen collected at least 48 hours earlier.

Self-report gives preliminary determination of each day as a use or non-use day. Non-use days are confirmed or disproved by the urine BE data as follows:

1. Subject reports no new use since last urine BE or within the preceding 72 hours (whichever is the shorter time frame) but urine BE shows new use, then score the preceding day as a use day.
2. Self report days of non-use will be considered as missing if not followed by a urine BE assessment within 7 days. In the case of obtaining urine within 7 days, data will also be considered as missing if the concordance rate between self report and urine BE for the individual is < 70 %.
3. Self reports of use are accepted in all cases.

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

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

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

The concordance rate of < 70% was established based on a survey of data sets from recently completed NIDA studies that showed that mean concordance rates ranged from 70-90%.

Appendix VI provides examples for scoring use days and non-use days according to the above rules with several combinations of SUR and urine BE data.

16.2.2 Secondary Outcome Measures

Measured reductions in cocaine and other drug use

- 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 proportion of 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.

Severity of depression

- M.** HAM-D scores.

Safety of STS

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

16.3 INTENT-TO-TREAT AND EVALUABLE POPULATIONS

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 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.

16.4 ANALYSIS PLAN

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

All statistical tests will be two-sided at a 5% level of alpha. 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 provide a model-based regression methodology applicable for the analysis of the correlated data that will result from this repeated measures longitudinal study.

The GEE procedure proposed by Liang and Zeger¹⁸ and Zeger and Liang¹⁹ (Biometrics, 1986) model the population average and has several useful features:

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

Secondary Efficacy Outcomes

As a secondary analysis, the baseline proportion of cocaine non-use days, site, gender, diagnosis of ADD, 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, other drug non-use days, BE levels measures D, E, and F, 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. Weekly CGI-self, CGI-observer, and BSCS, monthly ASI, and biweekly HAM-D score, measures I, J, K, L, and M, will be assessed by GEE.
5. Adverse events, laboratory data, physical exams, and vital signs will be reported in tabular form. AEs will be listed indicating the frequency of each type of event by various demographic characteristics such as gender, ethnicity, age, duration of addiction, other

medical problems both related to and independent of the addiction, and combinations of these characteristics. The frequencies of adverse events by type will be compared between study arms using Chi-square analyses.

16.5 OTHER STATISTICAL CONSIDERATIONS AND DATA ANALYSIS

Effects of gender, age and race

The individual effects, if any, of gender, age, and race on the primary treatment effects will be determined where numbers permit. No attempt will be made to determine the effect of two or more of these variables acting together.

Additional summaries and analyses

A summary will be prepared to show dropouts/retention over time in each treatment group and for major subgroups. The number of missing observations will be compared between treatments and for major subgroups. The compliance of each group at each assessment day will be summarized. Unusual blood level determinations (e.g., indicating lack of compliance) will be presented.

16.6 SAMPLE SIZE ESTIMATE

The proposed primary outcome measure is the weekly proportion of cocaine non-use days. Power analyses were made based on assumptions of normal distribution, equal correlation between observations at any two times (exchangeable) working correlation and a common standard deviation of 33.5%. These assumptions are based on preliminary results of an eight-week selegiline study (Protocol Number: CS-1017), in which an oral dose of selegiline was compared to placebo in cocaine dependent subjects. We further make the assumption that a 10% increase in the proportion of cocaine non-use days of the STS treatment group over the placebo group would be considered clinically significant. Based on the sample size calculation for GEE procedures proposed by Liu and Liang²⁰, then 110 subjects will be required in each arm to detect this clinically meaningful difference with a power of 80% at the 0.05 level of significance. The retention rates in studies of cocaine addicts currently being conducted by NIDA are approximately 70%, therefore at least 150 subjects should be randomized into each treatment to ensure an adequate sample size at the end of the trial.

16.7 ADAPTIVE RANDOMIZATION PROCEDURE

Adaptive random allocation of subjects to study groups was developed to balance groups with respect to screening prognostic variables. The procedure allocates treatment assignment based on the assignments and prognostic variable levels for all previously enrolled subjects. The treatment groups will be balanced with respect to gender, diagnosis of ADD, historical self-report of cocaine use for the last 30 days at the time that informed consent is given (balanced for ≥ 18 days of use and < 18 days of use), and severity of depression determined by HAM-D score (balanced for scores ≥ 11 and < 11). 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 (Efron¹⁰). The randomization process will be performed by computer at CSPCC.

16.8 INTERIM ANALYSIS

A single interim analysis will be performed after one half of the subjects have completed the study. The Pampallona-Tsiatis²¹ group sequential design for two-sided hypothesis will be used. The Pampallona-Tsiatis design will allow the possibility of early stopping a trial whenever a large treatment difference is observed or small treatment difference is observed. Using the Pampallona-Tsiatis Design and O'Brien-Fleming²² boundary method, the interim analysis will be performed at a nominal level of $\alpha=0.006$ and $\beta=0.07$ while the final analysis will be performed at $\alpha=0.044$ and $\beta=0.13$. This ensures an overall significance level of 0.05 and power of 0.8.

17 DATA MANAGEMENT AND CASE REPORT FORMS (CRF)

Data management activities and statistical analytical support will be coordinated through the Department of Veterans Affairs Cooperative Studies Program Coordinating Center in Perry Point, MD (CSPCC). Data will be collected at the study sites on CRFs, which will be supplied by CSPCC. Completed forms will be submitted on a regular basis to CSPCC.

When data are received at the CSPCC, they will be verified and edited prior to being entered into the main study database. Incomplete or inaccurate data will be returned to the sites for correction using a series of edit reports that are specifically tailored for the study. 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 VACSP monitoring unit, as well as by NIDA or Somerset Pharmaceuticals. 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 study medications 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 Good Clinical Practice regulations are on file, and sites are conducting the study according to the research protocol. Any inconsistencies will be resolved, and any changes to the data forms will be made using established CSPCC procedures.

The 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, Somerset Pharmaceuticals and the Data Safety and Monitoring Board, and others, as appropriate. These reports, as well as the final analyses, will be prepared in cooperation with the coordinating center in Perry Point.

18 SIGNATURES

SPONSORS REPRESENTATIVE

Typed Name	Signature	Date
_____	_____	_____
Jim Free		

INVESTIGATOR

I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol; deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment with the IRB approval. I also agree to report all information or data in accordance with the protocol, and in particular I agree to report any serious adverse experiences as defined in section 15.8 of this protocol.

Typed Name	Signature	Date
_____	_____	_____
Ahmed Elkashef, MD.		
_____	_____	_____
Paul Fudala, Ph.D.		

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