STUDY #: NIDA/VA CSP-1022

PHASE 2, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF SELEGILINE TRANSDERMAL SYSTEM (STS) AS AN AID FOR SMOKING CESSATION

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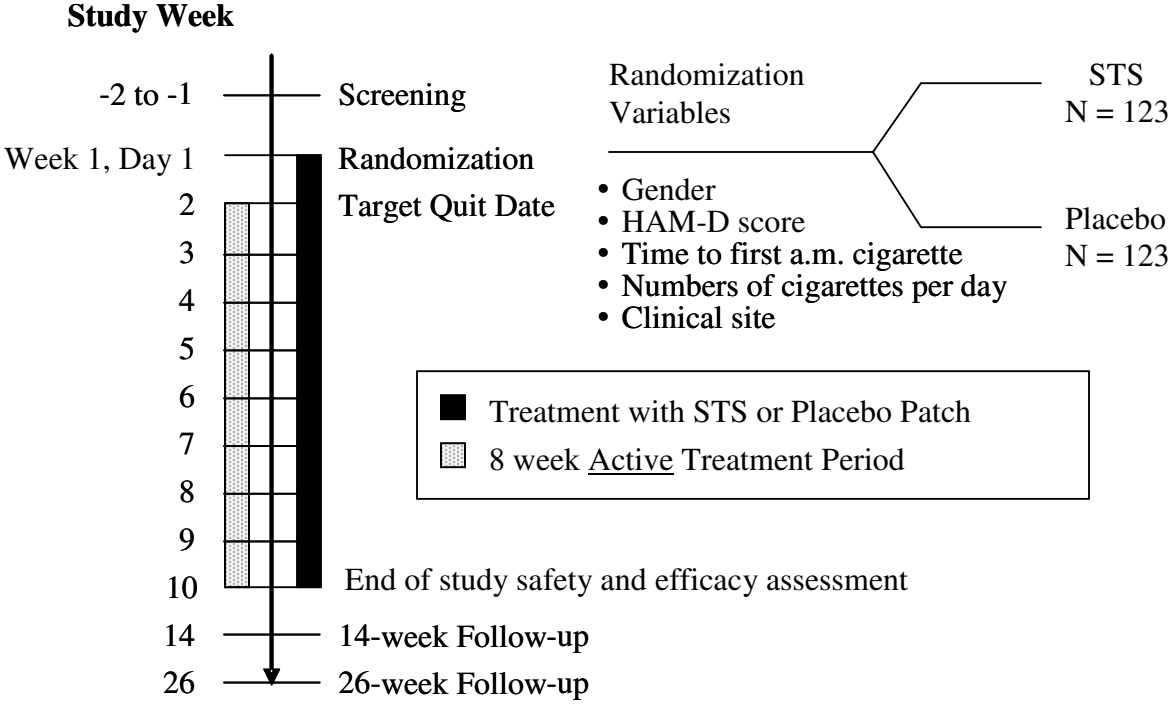
1 LIST OF ABBREVIATIONS

Abbreviation	Definition
ALP	alkaline phosphatase
ALT/SGPT	alanine aminotransferase/serum glutamic pyruvic transaminase
ASR	application site reaction
AST/SGOT	aspartate aminotransferase/serum glutamic oxaloacetic transaminase
bid	twice daily
BUN	blood urea nitrogen
CAP	College of American Pathologists
CLIA	Clinical Laboratory Improvement Amendment of 1988
CRF	Case Report Form
CSPCRPCC	Clinical Research Pharmacy Coordinating Center
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders Fourth Edition
DPMC	Division of Pharmacotherapies and Medical Consequences
ECG	electrocardiogram
FDA	Food and Drug Administration
GERD	gastroesophageal reflux disease
HAM-D	Hamilton – Depression Rating Scale
IRB	Institutional Review Board
ITT	intention-to-treat
5-HT	serotonin
kg	kilogram
LAAM	levomethadyl acetate (L-alpha acetylmethadol)
LDH	Lactic dehydrogenase
MAO	Monoamine Oxidase
mg	milligrams
mL	milliliter
NIDA	National Institute on Drug Abuse
OR	odds ratio
OTC	over-the-counter
PANAS	Positive and Negative Affect Schedule
PCC	Pharmacy Coordinating Center
PEA	phenylethylamine
SAE	serious adverse event
SCID	structured clinical interview for DSM-IV criteria
SNRI	serotonin norepinephrine reuptake inhibitors
SSRI	selective serotonin reuptake inhibitor
STS	selegiline transdermal system
TCA	tricyclic antidepressants
THC	tetrahydrocannabinol
TSF	tyramine sensitivity factor
WSWS	Wisconsin Smoking Withdrawal Scale
VACSP	Veteran's Administration Cooperative Studies Program
VAS	Visual analog scale

2 STUDY SCHEMA



STS Treatment: Daily application of STS (6 mg/24 hours)

Control Treatment: Daily application of placebo patch

Patches are applied daily from Study Day 1 through Study Day 63 (the end of Week 9)

Both treatment groups also receive identical weekly brief behavioral intervention.

3 STUDY SYNOPSIS

STUDY OBJECTIVES: The objectives of this study are to determine the efficacy and safety of selegiline transdermal system (STS) and brief behavioral intervention for smoking cessation in heavy smokers. It is hypothesized that the quit rate of subjects who received STS and behavioral intervention will be significantly greater than the quit rate of a placebo patch control group who will receive the same behavioral intervention. Quit rate is defined as the proportion of individuals who have ceased smoking assessed during study Week 10 as measured by 4 weeks of self-reported abstinence confirmed by exhaled carbon monoxide (CO) measurement during the prior 4 weeks (Study Weeks 6 through 9). Assessing prolonged abstinence rates during Study Weeks 14 and 26, in addition to effects on withdrawal symptoms during treatment, are secondary objectives.

STUDY DESIGN: This is a double-blind, placebo-controlled, parallel-group study, in which 246 subjects will be randomized to one of two treatment groups (123 per group): either a placebo patch or an STS patch (6 mg/24 hours) applied daily for 9 weeks. Both groups will receive brief behavioral intervention for all 9 weeks. Potential study subjects will be screened for eligibility criteria and must have a diagnosis of nicotine dependence according to DSM-IV criteria, self-reported use of ≥ 15 cigarettes/day for the past 30 days, have smoked cigarettes for the past 5 years, and have an expired CO level ≥ 9 ppm. After eligibility is established, subjects will be scheduled for their first treatment visit during which subjects will be randomized approximately equally to one of the two treatment groups using an adaptive randomization method using gender, time to first cigarette after awakening ≥ 30 min or >30 min), average number of cigarettes smoked per day in the 30-days prior to the signing of the informed consent (≥ 25 and < 25), current depression symptomatology as measured by the Hamilton Depression Rating Scale (HAM-D) score > 11, and clinical site as variables to balance groups. Randomization and initiation of STS or matched placebo treatment will be scheduled for 7 days before the target quit date. As treatment with STS or placebo will start before the target quit date to reach steady state levels of selegiline and its effect on monoamine oxidase (MAO) inhibition, the target quit date is considered the start of the 8-week "active treatment" period (Day 8 through Day 63). Subjects will be assessed for smoking status and safety measures weekly during the entire 9 weeks of treatment, during Study Week 10 (at the completion of treatment), and at post treatment follow-up visits during Study Weeks 14 and 26.

STUDY POPULATION: Two hundred forty six (246) males and females, at least 18 years of age, who have a diagnosis of nicotine dependence by DSM-IV criteria and do not have serious medical illnesses, major depressive disorder, or current psychiatric disorders that require medication contraindicated to selegiline, will be enrolled. To be eligible, subjects must have a history of heavy cigarette use (≥ 15 cigarettes/day in the past 30 days), have smoked for the past 5 years, and provide an expired CO level ≥ 9 ppm during the two-week screening period. All women must have a negative pregnancy test during screening (at least within 48 hours prior to initial patch application) and agree to use an acceptable method of birth control throughout the treatment period.

TREATMENTS:

STS or Matched Placebo Patch: STS (6 mg/24 hours) or matched placebo patch will be applied at approximately the same time daily and left in place for 24 hours each day of the 63-day treatment period.

Behavioral Intervention: During screening, the subject's motivation to quit smoking will be assessed using a visual analog scale (VAS) and a target quit date will be selected that is 7 days post the randomization and start of treatment visit (Visit #1, Study Day 1). On the first day of treatment, each subject will be given the National Cancer Institute's Booklet entitled "Clearing the Air." Starting on the day of randomization and continuing once per week at the weekly clinic visits, subjects will be provided individual smoking cessation counseling sessions based on the Public Health Service's *Clinical Practice Guidelines for Treating Tobacco Use and Dependence* (Version 2000) using a manual prepared for this study that incorporates Clearing the Air Concepts with the clinical practice guidelines to provide a uniform behavioral intervention platform.[1] The brief clinical intervention approach consists of an initial 20 minute session focused on setting the target quit date and getting ready to quit with approximately 10 minute weekly individual counseling sessions thereafter focused on quitting or preventing relapse.

SAFETY ASSESSMENTS: Safety will be assessed by monitoring of vital signs, weight, adverse events, blood chemistries, hematology, electrocardiogram (ECG), and physical exam.

EFFICACY ASSESSMENTS: The primary efficacy outcome measure will be the quit rate defined as the proportion of subjects who are abstinent during the last 4 weeks of treatment (Study Weeks 6 though 9) as determined by self-report of smoking cessation and confirmed by expired CO < 9 ppm during the last 4 weeks of measurements. At least two CO measurements must be obtained during this period, with at least one measurement in the last two weeks of treatment. CO measurements will be taken during the weekly visit (i.e., two measurements may be taken during two separate study weeks even though measurements may be less than 7 days apart). Secondary outcome measures include the degree of nicotine craving and the severity of nicotine withdrawal assessed using the University of Wisconsin Center for Tobacco Research and Intervention Smoking Withdrawal Scale (WSWS), prolonged abstinence (self-report of abstinence analyzed separately with and without confirmation by expired CO at follow-up Weeks 14 and 26), weight gain/loss (body weight and waist circumference measurements), and effects on mood [positive and negative affect scale (PANAS)] and severity of depression using the Hamilton Depression Rating Scale (HAM-D).

4 INTRODUCTION AND RATIONALE

4.1 Nicotine Dependence

Tobacco use in the United States is a major cause of death and disability. Over 400,000 deaths in the U.S. each year are attributed to cigarette smoking.[2] The high failure rate reported for smoking cessation (75-90%) challenges health care professionals to explore innovative approaches to treating this highly addictive behavior.[3]

The agent largely responsible for maintaining smoking addiction is nicotine.[4-7] In addition to animal studies that showed the addictive properties of nicotine, studies in humans show that smokers adjust

their smoking habits to maintain a relatively stable concentration of nicotine and that the reinforcing effects of nicotine are blocked by the pretreatment with the nicotine receptor antagonist, mecamylamine.[8] Nicotine addiction perpetuates itself by controlling the release of a cascade of neurotransmitters including serotonin, norepinephrine, dopamine, and gamma amino butyric acid (GABA) to produce stimulation, pleasure, and rewards. Tolerance develops, and the dependence upon nicotine to maintain normal brain function results in withdrawal symptoms after abstinence due to subnormal levels of dopamine, norepinephrine, and serotonin. Withdrawal symptoms are characteristically depressed mood, anxiety, insomnia, irritability, anger, difficulty concentrating, increased appetite, weight gain, and decreased heart rate. These symptoms usually peak at one week and taper off over time.

Besides behavioral interventions, two types of primary pharmacotherapies have been recommended by the Public Health Service Consensus Panel on Clinical Practices Guidelines for Treating Tobacco Use and Dependence. These include nicotine replacement therapy (NRT) with nicotine-gum, patch, inhaler, or nasal spray and bupropion sustained release (SR).[1] NRT works by supplying an alternate source of nicotine. The differences in the pharmacokinetics between NRT and nicotine from cigarette smoke show that NRT has a much slower rate of absorption and, hence, less abuse potential than nicotine from cigarette smoke, which reaches the brain in 10-to-20 seconds. The patch has the slowest rate of absorption of all 4 types of NRT and, therefore has the lowest abuse potential. Quit rates for NRTs have been examined by meta analysis of numerous studies and are in the range of 18 to 40%.[1] Bupropion SR (Zyban) is an inhibitor of norepinephrine and dopamine reuptake and has been approved by the FDA for smoking cessation and treatment of depression (under the trade name Wellbutrin). Bupropion has also been found to interact with nicotine receptors and can possibly act by noncompetitive inhibition at the nicotinic receptor site.[9] Clinical trials suggest that Bupropion SR may be more effective than NRT for smoking cessation. In a study that compared nicotine patch, bupropion, or bupropion plus patch to placebo control, the short-term quit rates were higher for bupropion or the combination, compared to nicotine patch alone or placebo (23, 36, 49, and 58% short term quit rates for placebo, nicotine patch, bupropion, combination patch and bupropion, respectively).

The interest in examining anti-depressants as aids to smoking cessation comes from observations of subjects with a diagnosis of depression or history of depression on smoking cessation trials outcomes.[10] A series of studies have been conducted that show an association between a history of depression with an inability to quit smoking and with an increased likelihood of smoking relapse. The association with history of depression was first observed in studies examining clonidine as a smoking cessation aid even though clonidine is an alpha$_2$ adrenergic agonist commonly used as an antihypertensive. Glassman *et al*.[11] during the conduct of a clinical trial designed to assess the effects of clonidine on smoking cessation observed the following:

a. Sixty percent of subjects had a past episode of major depression (this is much higher than the 10 to 20 % rates reported in the general population).

b. Smokers with a history of major depression were less likely to quit smoking.

c. Smokers with a history of major depression were more likely to report depressed mood during abstinence.

In addition to bupropion, another anti-depressant, nortriptyline, is recommended by the Public Health Service as a second–line treatment for smoking cessation. Nortriptyline is a tricyclic

antidepressant that is thought to exert its therapeutic effects via inhibition of the re-uptake of norepinephrine and serotonin.[5] Quit rates with nortriptyline are reported to be 24% at six months.[12,13]

Another class of anti-depressants that has a non-nicotine mechanism of action that is being examined for smoking cessation treatments is the class of MAO inhibitors. This approach was based on a study conducted by Fowler *et al*.[14,15] who showed that the brains of smokers have 40% lower levels of MAO-B and 23% lower levels of MAO-A than the brains of non-smokers or former smokers. MAO-B is involved in the breakdown of dopamine, a neurotransmitter implicated in reinforcing and motivating behaviors as well as movement. MAO-B inhibition is, therefore, associated with enhanced activity of dopamine, as well as with decreased production of hydrogen peroxide, a source of reactive oxygen species. Fowler *et al*.[14,15] proposed that reduction of MAO-B activity might synergize with nicotine to produce the diverse behavioral effects of smoking.

This approach has shown positive preliminary results in smoking cessation clinical trials for two MAO inhibitors, moclobemide and selegiline. Berlin *et al*.[16] conducted a randomized, double-blind, placebo-controlled parallel-group study of moclobemide, 400 mg/day for 2 months and 200 mg/day during the third month in 88 smokers [moclobemide (n = 44) or placebo (n = 44)]. The continuous self-reported abstinence rate was higher with moclobemide than with placebo (intention-to-treat analysis until the end point, 6 months: $p < 0.05$; until the end of follow-up, 1 year: $p = 0.09$). No difference occurred for withdrawal symptoms assessed with the Montgomery Asberg Withdrawal Scale or the Hamilton anxiety scale.

George *et al*.[17] conducted a randomized, placebo-controlled trial of 40 subjects with DSM-IV criteria for nicotine dependence, expired CO levels ≥ 10 ppm, and plasma cotinine levels ≥ 150 ng/mL. Subjects were randomized with 20 in each group to: 1) selegiline hydrochloride (5 mg orally twice daily) or 2) placebo in this 8-week trial. Selegiline significantly ($p <0.05$) increased Week 8, 7-day point prevalence smoking cessation rates by 45.0% [9/20] compared to 15.0% for placebo controls [3/20]. Smoking cessation rates during the last 4 weeks of the trial were 30.0% (6/20) for the selegiline group and 5.0% (1/20) for the placebo group ($p =0.07$). Biberman *et al.*[18] also conducted a randomized controlled trial of oral selegiline for smoking cessation, but in this trial, selegiline was combined with nicotine patch and compared to a group that received nicotine patch instead of placebo. In this study, 109 smokers who smoked ≥ 15 cigarettes per day were randomized to receive oral selegiline, 2.5 mg, or placebo twice/day initiated 1 week before the quit day, followed by 5 mg oral selegiline or placebo twice daily for 26 weeks, plus active nicotine skin patch for all subjects for the first 8 weeks only. Short term abstinence (abstinent after 8 weeks of treatment) and long-term abstinence (abstinent at one year) showed an increasing trend towards abstinence in the group treated with selegiline. However, this difference was not statistically significant. Short-term abstinence was 34% for the selegiline plus nicotine patch group and 25% for the nicotine patch group; long-term abstinence was 25% for the selegiline plus nicotine patch group and 11% for nicotine patch group ($p=0.08$). There were no differences in adverse events between the two treatment groups. The most frequently reported adverse events (> 5% of patients) were headache, backache, flu-like symptoms, fatigue, and application site reactions. Craving for cigarettes at Week 4 was significantly reduced in the selegiline plus nicotine group ($p=0.02$). These preliminary small trials suggest that a MAO inhibitor may be efficacious as an aid for smoking cessation either alone or in combination with NRT, thus targeting a novel mechanism as a smoking cessation aid.

4.2 Rationale for Study

This study is designed to examine the effects of STS and behavioral intervention in smoking cessation as compared to behavioral intervention. MAO inhibition in the brains of smokers is associated with increases in neurotransmitters including norepinephrine, dopamine, serotonin, and phenylethylamine (PEA). As MAO inhibition is reversed during smoking cessation, neurotransmitter levels drop and the individual experiences withdrawal symptoms and craving. Likewise, nicotine addiction perpetuates itself by controlling the release of a cascade of neurotransmitters including serotonin, norepinephrine, dopamine, and GABA to produce stimulation, pleasure, and rewards. Tolerance develops, and the dependence upon nicotine to maintain normal brain function results in withdrawal symptoms after abstinence due to subnormal levels of dopamine, norepinephrine, and serotonin. While NRT is a successful smoking cessation aid in a significant number of individuals, the use of STS may offer improved rates of success by targeting additional neurotransmitter pathways.

Selegiline ((R)-(-)N2,2-dimethyl-N-2-propynlphenethylamine HCL) was chosen for evaluation because it is a highly selective irreversible inhibitor of MAO-B at low doses. Both MAO-A and MAO-B inhibition can be achieved in the brains of animals treated with selegiline using the transdermal formulation.[19] Selegiline hydrochloride in tablet form was approved by the FDA in April 1998 for the treatment of Parkinson's disease under the trade name Eldepryl®. The STS (trade name EMSAM®) was approved by the FDA on February 27, 2006 for the treatment of major depressive disorder. Thus, the pharmacology and safety of selegiline has been well established in humans; its efficacy as an anti-depressant is accepted[20-22]; and preliminary data suggest it is efficacious in treating smoking cessation.

The selection of the STS, instead of the oral dosage formulation, is based on selegiline's pharmacokinetic parameters. In oral form, the doses of selegiline resulting in a therapeutic effect in patients with depression were sufficient to inhibit both MAO-A and MAO-B activity. These doses also increased tyramine activity. Tyramine is found in cheese products at sufficiently high levels to induce acute hypertension in combination with high dose selegiline. Thus, dietary restrictions have been placed on the STS for the 9 mg/24 hours and 12 mg/24 hours patches, but not for the 6 mg/24 hours patch planned for investigation in this study. The STS was developed to deliver sustained selegiline blood concentrations without extensive inhibition of intestinal mucosa and liver MAO-A (associated with the tyramine effect). 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-desmethylselegiline, 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. Thus, the dose to be used in the proposed clinical trial, is considered safe without dietary restrictions.[23-25]

In the two clinical studies of oral selegiline for smoking cessation either alone[17] or in combination with the nicotine patch[18], a dosage of oral selegiline of 10 mg per day was evaluated. These preliminary studies showed a trend toward improved abstinence in the groups treated with selegiline or selegiline plus patch compared to controls, but the differences in the rate of abstinence at 8-weeks between the selegiline plus patch to nicotine patch control group was only 9%. Thus, use of the 6 mg/24 hours STS offers a substantially higher exposure to selegiline when supplied as a transdermal

formulation than when given in oral form to determine if an increased exposure can improve upon the modest effect observed with the oral dosage form.

4.3 Selegiline Transdermal System

4.3.1 Previous Human Experience with STS

Tyramine Sensitivity Studies in Humans. Somerset Pharmaceuticals, Inc. has performed numerous studies to evaluate the tyramine sensitivity of subjects administered STS. FDA has approved the 6 mg/24 hours dose without dietary restrictions; however, higher doses do have specific restrictions. Tyramine challenge studies evaluated the potential of tyramine-induced hypertensive episodes secondary to treatment with MAO inhibitors under controlled clinical conditions. An increase in systolic blood pressure > 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.[24] 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 systolic blood pressure increase of 30 mm Hg in subjects administered the 15, 20, and 30 mg of STS, respectively. Tyramine content of most meals is negligible including those with red wine and cheese. A tyramine-enriched meal may contain up to 40 mg of tyramine.

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 systolic blood pressure 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 phenylzine and tranylcypromine sulfate can increase the TSF 13 to 55-fold. Studies with the STS (6 mg/24 hours) yielded a TSF value of 2.9 following chronic administration. Previous studies reported 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. In a crossover study conducted by Somerset, the TSF value was nearly identical following treatment with STS (6 mg/24 hours) or oral selegiline (5 mg, bid). 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. Based upon these Phase 1 tyramine challenge studies and the favorable safety record for oral selegiline, Somerset has conducted nearly the entire development program for major depressive disorder without dietary tyramine restriction and without reports of hypertensive crisis.

Major Depressive Disorder. STS has been examined for the treatment of major depressive disorder in two large, randomized, placebo-controlled clinical trials at a dose of 6 mg/24 hours daily for 6 or 8 weeks, with and without dietary restrictions.[25,26] In both studies, STS was found to significantly improve major depression as assessed by HAM-D. In these studies both STS and placebo treatment

conditions were well tolerated. The only significant safety difference between the STS and placebo groups in the Amsterdam (2003) study which did not include dietary restrictions, was patch application site reactions (31.5 % versus 15.1%, STS:placebo) which included mild to moderate rash, itching, erythema, redness, irritation, swelling, and urticarial lesion.[26] Five of the 144 (3.4%) patients randomized to STS discontinued treatment due to application site reactions. Approximately 20% of the application site reactions required treatment with medication, usually an over-the-counter (OTC) topical hydrocortisone. Similar findings were reported in the Brodkin and Amsterdam study (2002) which included dietary restrictions.[25]

Normal Volunteer Studies. 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 adverse events (SAEs) or significant laboratory changes (Somerset Pharmaceuticals, Investigator's Brochure for STS).

Treatment of Cocaine Dependence. NIDA conducted a double-blind, placebo-controlled trial of STS for the treatment of cocaine dependence in 300 patients through its interagency agreement with the Veterans Administration Cooperative Studies Program (VACSP). Patients were randomized to placebo control patch or STS (6 mg/24 hours) for the 8-week duration of the study. The most commonly reported adverse events in all patients were headache (45% of patients), pain (30% of patients), rash (26% of patients), pruritis (20% of patients) and diarrhea (18% of patients). There were only three types of adverse events for which there was a significant increase in the STS group compared to placebo control, rash (32% of STS patients versus 19.3% placebo patients), diarrhea (23.3% of STS patients versus 12.7% placebo patients), and abdominal pain (11.3% of STS patients versus 4.7% of placebo patients).

Clinical Pharmacology in Smokers. A clinical pharmacology study was conducted by NIDA to examine the safety of the STS as a potential treatment for nicotine dependence. In this study, the 9 subjects received a daily dose of STS 6 mg/24 hours for a period of 5 weeks. The data show that STS was well tolerated when used for a period of 5 weeks by cigarette smokers. Side effects were relatively few and predominantly mild as reported by subjects. Two subjects discontinued treatment early, but only one of these may have been attributed to the medication. Subjects reduced their level of cigarette use significantly over the course of treatment and 30% were abstinent at the final visit. Subjects remarked that the STS had a calming effect and greatly assisted in the efforts of making a quit attempt.

4.3.2 Pharmacokinetics of STS

Selegiline is rapidly metabolized via N-demethylation and oxidative dealkylation to N-desmethylselegiline and l-methamphetamine, respectively. Subsequently, N-desmethylselegiline and l-methamphetamine are further metabolized to l-amphetamine. STS (6 mg/24 hours) offers a delivery system that bypasses first-pass metabolism resulting in relatively constant plasma levels (steady state plasma fluctuations are approximately 50%) with 50 % reduction in metabolite concentrations, when compared to 10 mg/day of orally administered selegiline. In a steady-state

study conducted with the STS (6 mg/24 hours), the mean plasma C_{max} for selegiline was 3,019 pg/mL, T_{max} was 11.73 hours, and apparent dose delivered was approximately 5 mg for selegiline. T_{max} values were relatively similar for all three metabolites.

Single-dose pharmacokinetic values show that dermal absorption occurs continuously over a 24-hour period and achieves the maximal selegiline plasma concentration toward the end of the dosing interval. In a 10-day study with the STS administered to normal volunteers, steady-state selegiline plasma concentrations were achieved within five days of daily dosing. Absorption of selegiline is similar when the STS is applied to the upper torso and upper thigh.

4.3.3 Preclinical Pharmacology of STS

The mitochondrial enzyme, MAO (monoamine-oxygen oxidoreductase deaminating, flavin containing, EC1.4.3.4.) exists as two isozymes referred to as MAO-A and MAO-B. MAO-A and MAO-B are present throughout all mammalian tissues as a constituent of the outer mitochondrial membrane and act as major catabolic enzymes for neurotransmitters and neuromodulators such as norepinephrine, dopamine, serotonin, and phenylethylamine (PEA). Serotonin and norepinephrine serve as preferred substrates for MAO-A while dopamine serves as common substrates for either isoform of MAO. The trace amine, PEA, demonstrates a high degree of specificity for MAO-B. Thus, elevation in the synaptic activity of one or more of these amine neurotransmitters is related to the degree of inhibition of MAO-A and/or MAO-B activity in the brain tissue.

Selegiline inhibition is the result of the formation of a reversible bond with the flavin portion of the enzyme. Subsequent oxidation leads to the formation of a covalent bond that inactivates the enzyme. The selectivity of selegiline for MAO-B arises from a greater affinity for the MAO-B flavin site and a greater reactivity of selegiline to form the covalent bond with MAO-B as compared to MAO-A.

Greater than 95% inhibition of MAO-B enzymatic activity is obtained after 3 days of oral dosing of selegiline 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. MAO-B selectivity of selegiline HCl in striatum or whole brain was evident in acute *in vivo* experiments at parenteral doses of 1 mg/kg in rats[27] and at a single oral dose of 10 mg/kg.[28] 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.[29] In mice, specific MAO-B inhibition was demonstrated with a single treatment of 2.5 mg/kg.[28] The chronic doses administered to rodents to maintain MAO-B selectivity 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.

In addition to increasing dopamine levels through MAO inhibition, selegiline may also affect dopamine through a selective increase in endogenous phenylethylamine (PEA).[30] 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 $beta_1$ adrenoreceptors[31], 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 intestinal and hepatic MAO activity.[19,32] 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.

4.3.4 Safety of STS

Expected Adverse Events: The premarketing development program for STS included selegiline exposures in patients and/or normal subjects from two different groups of studies: 702 healthy subjects in clinical pharmacology/pharmacokinetics studies and 2,036 exposures from patients in controlled and uncontrolled major depressive disorder clinical trials. The conditions and duration of treatment with STS varied and included double-blind, open-label, fixed-dose, and dose titration studies of short term and longer-term exposures. Adverse events leading to discontinuation of STS treatment included application site reactions, contact dermatitis, tachycardia, and orthostatic hypotension. In the pool of short-term, placebo-controlled major depressive disorder studies, application site reactions (ASR's) were reported in 24% of EMSAM-treated patients and 12% of placebo-treated patients. Most ASR's were mild or moderate in severity. None were considered serious. ASR's led to dropout in 2% of EMSAM-treated patients and no placebo-treated patients (EMSAM Drug Label). Systemic adverse events that occurred in a higher proportion of patients as compared to controls included headache, diarrhea, dyspepsia, insomnia, dry mouth, pharyngitis, and sinusitis.

As with other MAOI's, postural hypotension, sometimes with orthostatic symptoms, can occur with STS. In short-term, placebo-controlled depression studies, the incidence of orthostatic hypotension (i.e., a decrease of 10 mmHg or greater in mean blood pressure when changing position from supine or sitting to standing) was 9.8% in EMSAM-treated patients and 6.7% in placebo-treated patients.

Patients with major depressive disorder may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications. Subjects will be monitored closely in this trial for signs of worsening of depression via HAM-D assessment at screening and weeks 4, 8 and 10.

The effect of direct heat applied to the STS on the bioavailability of selegiline has not been studied. However, in theory, heat may result in an increase in the amount of selegiline absorbed from the STS and produce elevated serum levels of selegiline. Subjects should be advised to avoid exposing the STS application site to external sources of direct heat, such as heating pads or electric blankets, heat lamps, saunas, hot tubs, heated water beds, and prolonged direct sunlight.

Teratogenic Effects: Selegiline Transdermal System is a Pregnancy Category C drug. There are no adequate and well-controlled studies of selegiline in pregnant women. The effects of selegiline transdermal system on labor and delivery and lactating women are not known. Pregnant and lactating women will be excluded from participation in the study. Women must agree to use an acceptable form of birth control to participate in this study and urine pregnancy tests will be performed every 4 weeks.

Contraindications: STS is contraindicated with selective serotonin re-uptake inhibitors (SSRI's, e.g., fluoxetine, sertraline, and paroxetine), dual serotonin and norepinephrine re-uptake inhibitors

(SNRI's, e.g., venlafaxine and duloxetine), tricyclic antidepressants (TCA's, e.g., imipramine and amitripyline), bupropion hydrochloride; meperidine and analgesic agents such as tramadol, methadone and propoxyphene; the antitussive agent dextromethorphan; St. John's wort; mirtazapine; and cyclobenzaprine. STS should not be used with oral selegiline or other MAO inhibitors (MAOI's e.g., isocarboxazid, phenelzine, and tranylcypromine). Carbamazepine and oxcarbazepine are also contraindicated in patients taking selegiline. As with other MAOI's, STS is contraindicated for use with sympathomimetic amines, including amphetamines as well as cold products and weight-reducing preparations that contain vasoconstrictors (e.g., pseudoephedrine, phenylephrine, phenylpropanolamine, and ephedrine).

If a subject needs to undergo emergency surgery (those planning elective surgeries should not be enrolled), s/he should not be given cocaine or local anesthesia containing sympathomimetic vasoconstrictors. STS should be discontinued at least 10 days prior to elective surgery. If surgery is necessary sooner, benzodiazepines, mivacurium, rapacuronium, fentanyl, morphine, and codeine may be used cautiously.

4.4 Behavioral Intervention

The Public Health Service *Clinical Practice Guidelines for Treating Tobacco Use and Dependence* (2000) is the result of an evidence based consensus panel evaluation of smoking cessation treatments.[1] The following conclusions were drawn by the panel regarding behavioral interventions:

- Minimal interventions lasting no longer than 3 minutes increase overall tobacco abstinence rates.
- There is a strong dose-response relation between the session length of person-to-person contact and successful treatment outcomes.
- Person-to-person treatment delivered for four or more sessions appears especially effective in increasing abstinence rates.

In order to incorporate the behavioral intervention approach into the clinical trial setting, the brief clinical intervention approach consisting of an initial 20 minute session focused on setting the target quit date and getting ready to quit with approximately 10 minute weekly individual counseling sessions thereafter focused on quitting or preventing relapse as described in the Clinical Practice Guidelines will be followed. The National Cancer Institute has created a brochure entitled "Clearing the Air" which is designed as a take-home aid for individuals in smoking cessation programs. This guide is consistent with the principals promoted by the Clinical Practice Guidelines and will be distributed to subjects at the initiation of treatment.

5 STUDY OBJECTIVES

The primary objectives of this study are to:

1. Determine the efficacy of STS with brief behavioral therapy (the investigational intervention) for smoking cessation in heavy smokers. It is hypothesized that the quit rate at the end of treatment for subjects who receive STS with behavioral intervention will be greater than the quit rate for subjects in the placebo patch control group with behavioral intervention.

2. Determine the safety of the investigational intervention for smoking cessation in heavy smokers as assessed by adverse events, weight gain/loss, vital signs, ECG, and clinical laboratory assessments.

Secondary objectives include:

1. Determining if the investigational intervention increases prolonged abstinence at Study Weeks 14 and 26.
2. Determining if the investigational intervention has any effect on depression (decrease in HAM-D scores).
3. Determining if the investigational intervention has any effect on the degree of nicotine craving and the severity of nicotine withdrawal assessed using the WSWS.
4. Determining if the investigational intervention has any effect on mood assessed with the PANAS.
5. Determining if the investigational intervention has any effect on weight gain or loss as measured by body weight and waist circumference.

6 STUDY SPONSOR

NIDA is the study sponsor. In addition, this study will be conducted under a Cooperative Research and Development Agreement (CRADA) between Somerset Pharmaceuticals and NIDA.

7 STUDY SITES

Four clinical sites will participate in this study with each site enrolling approximately the same number of subjects. Enrollment is projected to be completed over a nine-month period.

8 STUDY DESIGN

This is a double-blind, placebo-controlled, parallel-group study, in which 246 subjects will be randomized to one of two treatment groups (123 per group): either a placebo patch or an STS patch (6 mg/24 hours) applied daily for 9-weeks. Both groups will receive brief behavioral intervention for all 9-weeks. Potential study subjects will be screened for eligibility criteria and must have a diagnosis of nicotine dependence according to DSM-IV criteria, self-reported use of ≥ 15 cigarettes/day for the past 30 days, smoked cigarettes for the past 5 years, and have an expired CO level ≥ 9 ppm during screening. After eligibility is established, subjects will be scheduled for their first treatment visit during which subjects will be randomized approximately equally to one of the two treatment groups using an adaptive randomization method using gender, time to first cigarette after awakening (≤ 30 min or >30 min), average number of cigarettes smoked per day in the 30-days prior to the signing of the informed consent (≥ 25 and < 25), current depression symptomatology as measured by the HAM-D score > 11, and clinical site as variables to balance groups. Randomization and initiation of STS or matched placebo treatment will occur the same day 7 days before the target quit date. As treatment with STS or placebo will start before the target quit date to reach steady state levels of selegiline and its effect on MAO inhibition, the target quit date is considered the start of the 8-week "active treatment" period (Day 8 through Day 63). Subjects will be assessed for smoking status and safety measures weekly during the entire 9 weeks of treatment, during Study Week 10 (at the completion of treatment), and at post-treatment follow-up visits during Weeks 14 and 26.

The study will be conducted in three phases: **Screening** (information session/informed consent and eligibility assessments), **Treatment** (Weeks 1-9) with active treatment defined as treatment during Study Weeks 2 – 9, and final treatment assessments being performed at Week 10, and **Follow-Up** at Week 14 (abstinence and safety follow-up), and Week 26 (long-term abstinence follow-up). Treatment Week 1 is not considered part of the active treatment phase of the study. This will allow sufficient time to establish steady state drug concentrations of selegiline before the target quit date.

During screening, subjects will set a target quit date for smoking cessation. The Study Day 1 visit for randomization and initiation of treatment will be scheduled 7 days prior to the target quit date in order that subjects receive a minimum of 7 days of STS or placebo patch prior to the target quit date. For example, if a subject starts treatment on a Monday, their target quit date will be the following Monday. Subjects will be seen weekly during the 9-week Treatment Phase for investigational product dispensing, behavioral intervention and outcome measures assessments and once during Week 10 for a final assessment. If the subject misses a visit, they will be contacted by a clinician and encouraged to continue with the smoking cessation program and provided behavioral intervention over the phone.

9 CONTROL OF BIAS

Numerous studies have evaluated prognostic variables associated with success rates of smoking cessation either unaided or with behavioral or pharmacological interventions.[33-38,39] [40] A common set of prognostic variables emerges from these studies including: male gender [odds ratio (O.R.) = 1.48][35,] , absence of current depressive symptoms or lifetime depression (O.R = 1.26)[35], average number of cigarettes smoked during the day [relative risk (R.R.) = 1.15[38] and O.R. 1.36[35]], increased number of previous quit attempts > 24 hours (O.R.= 1.30 men and women) [35], concerns about weight gain (R.R.=1.7)[34], and delay in time to first cigarette after awakening (O.R. = 4.58 for men and 1.29 for women).[36]

In order to balance groups with respect to prognostic variables, gender (male/female), current depression symptomatology as measured by the HAM-D score > 11, time to first cigarette after awakening (≤ 30 minutes or >30 minutes), and average number of cigarettes smoked per day in the 30-days prior to the signing of the informed consent (≤ 25 and < 25) have been selected as variables for adaptive random allocation of subjects to study groups within each clinical site.

10 SUBJECT SELECTION

10.1 Inclusion Criteria

To be eligible for the study, each subject must:

1. Be ≥ 18 years of age.

2. Have a DSM-IV diagnosis of nicotine dependence.

3. Be currently (past 30 days) smoking ≥ 15 cigarettes/day and have smoked cigarettes for the past 5 years.

4. Be motivated to quit smoking (score ≥ 6 on motivation to quit scale).

5. Have an expired CO level ≥ 9 ppm during screening.

6. Use one of the following acceptable methods of birth control (for female subjects):

   a. oral contraceptives
   b. contraceptive patch
   c. vaginal ring (NuvaRing)
   d. barrier (diaphragm, condom, cervical cap, sponge or Lea's Shield) with spermicide
   e. intrauterine device (IUD) containing progesterone contraceptive system or copper
   f. levonorgestrel implant
   g. medroxyprogesterone acetate contraceptive injection
   h. surgical sterilization (medically documented hysterectomy, tubal ligation, or bilateral oophorectomy)
   i. postmenopausal (one year post last menses)

7. Be able to understand and provide written informed consent.

8. Be available for participation in the study for 28 weeks.

9. Agree not to use any other smoking behavioral intervention (self-help or formal treatment), acupuncture, or other smoking cessation pharmacotherapy during the study.

10.2 Exclusion Criteria

To be eligible for the study, each subject must not:

1. Have current neuropsychiatric disorders diagnosed by SCID that require current contraindicated pharmacological treatment, or that would make medication compliance difficult (see Exclusion Criterion #10). Subjects with a diagnosis of current major depressive disorder, as diagnosed by the DSM-IV criteria as assessed with the SCID, will be excluded.

2. Have current serious medical illnesses including, but not limited to, uncontrolled hypertension, significant heart disease (including myocardial infarction or stroke within one year of enrollment), angina, cardiovascular abnormality, clinically significant irregular heart beat (arrhythmia), pheochromocytoma, vasoplastic diseases (e.g., Buerger's disease, Prinzmetal's angina), diabetes requiring insulin, hepatic or renal disorders, a serious endocrine disorder, or any other unstable medical disorder that may compromise subject safety or study conduct.

3. Have a history of substance use disorders by DSM-IV criteria within the past year as determined by SCID with the exception of alcohol, caffeine, marijuana, and nicotine abuse

(subjects with physiological dependence on alcohol that requires medical detoxification will be excluded).

4. Have a positive urine drug screen for cocaine, opiates, tetrahydrocannabinol (THC), and methamphetamine, except that the subject may test positive for THC once, but a subsequent negative test result must be obtained during the screening period.

5. Be anticipating elective surgery within 10 weeks of signing the informed consent form that would preclude his/her active study participation.

6. Be anyone who in the opinion of the investigator would not be expected to complete the study protocol.

7. Have a known or suspected hypersensitivity to selegiline or any monoamine oxidase inhibitor.

8. Have a history of allergy to latex or known allergic or active dermatologic illness (e.g., psoriasis) that might interfere with drug absorption or which may be exacerbated by patch application.

9. Have any allergy that requires carrying prophylactic epinephrine.

10. Be taking 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. Selective serotonin re-uptake inhibitors (SSRI's, e.g., fluoxetine, sertraline, and paroxetine),
    b. Dual serotonin and norepinephrine re-uptake inhibitors (SNRI's, e.g., venlafaxine and duloxetine),
    c. Tricyclic antidepressants (TCA's, e.g., imipramine and amitripyline),
    d. Bupropion hydrochloride,
    f. The antitussive agent dextromethorphan,
    g. St. John's wort; mirtazapine; and cyclobenzaprine,
    h. Oral selegiline or other MAO inhibitors (MAOI's e.g., isocarboxazid, phenelzine, and tranylcypromine),
    i. Carbamazepine and oxcarbazepine, and,

j. Sympathomimetic amines, including amphetamines as well as cold products and weight-reducing preparations that contain vasoconstrictors (e.g., pseudoephedrine, phenylephrine, phenylpropanolamine, and ephedrine).

11. Have participated in any experimental study within 4 weeks, or have ever taken oral selegiline or used the STS.

12. Be currently using any other treatment (medication or behavioral) for smoking cessation.

13. Be using tobacco products other than cigarettes (e.g., pipes, cigars, snuff, chewing tobacco).

14. Be a pregnant or lactating woman (a negative pregnancy test must be obtained within 48 hours prior to enrollment).

15. Have clinically significant abnormal laboratory values in the judgment of the investigator (mild anemia in women is acceptable).

NOTE: If any medical conditions requiring treatment are uncovered during screening, the individual will be notified of the results and referred to appropriate treatment.

11 INVESTIGATIONAL PRODUCTS

11.1 Investigational Product Formulations

STS (EMSAM®), 6 mg/24 hours (20 cm^2) patch, and matched placebo (20 cm^2) patch, will be supplied by Somerset Pharmaceuticals, Inc. The 6 mg/24 hours patch delivers, on average, 6 mg of selegiline over 24 hours. Kits containing STS or placebo patches will be distributed by the Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (CSPCRPCC) in Albuquerque, NM. The STS is a rectangular shaped patch with rounded corners. Each patch consists of three parts: the drug delivery adhesive matrix, the backing film, and the protective release liner. The drug delivery adhesive matrix consists of Selegiline Base dispersed in a pressure sensitive acrylic adhesive. The backing film is a polyester/polyurethane/ethylene vinyl acetate/low density polyethylene laminate material (translucent) that provides structural support to the drug delivery adhesive matrix. The release liner is a silicone coated polyester liner that provides protection for the drug delivery system and is discarded prior to application by the subject.

The STS is packaged in a white paper/foil pouch that is notched in the corners for ease of opening. Pouched systems are supplied in cartons appropriately sized and labeled for a given study. Systems should be stored at controlled room temperature (15°C to 30°C or 59°F to 86°F). Systems should remain stored in their cartons and sealed in their pouches until time of use.

11.2 Patch Application

STS (6 mg/24 hours) or matched placebo patch will be applied approximately at the same time daily and left in place for 24 hours each day of the 9-week treatment period (Study Weeks 1-9).

Instructions for Patch Application: The subject will be instructed on the procedure for application of study patches and provided with an instruction sheet for patch application (Appendix I). During

the study, patches will be applied at the same time each day, preferably between the hours of 8:00 a.m. and 12:00 p.m. 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.

11.3 Dispensing/Reconciliation of Study Patches

STS and matching placebo patch will be packaged by the VA CSPCRPCC in Albuquerque in ten-patch kits (an extra 3-day supply in case weekly dispensing is delayed).
Each kit will be labeled with the protocol name, protocol number, randomization number (Subject ID Number) and treatment kit number to maintain the blind. The identification label will include a tear-off portion containing the protocol name, protocol number and the treatment kit number that will be removed and affixed to the subjects' Progress Notes when dispensing.

A supply of extra study patches will be maintained at the clinical site for each subject, in case replacements are needed. Accurate recording of all investigational product dispensing will be made in the medical record and transcribed to the appropriate CRF. Subjects will discard used patches after use. Unused patches will be collected and inventoried each week.

11.4 Unused Investigational Products

During the study, all patches 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 products must be inventoried. If any investigational product is lost or damaged, its disposition should be documented. Unused investigational products 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.

11.5 Storage

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

12 STUDY PROCEDURES

A study time and events schedule is shown in Table 1.

12.1 Subject Recruitment

Subjects will be recruited by NIDA and IRB-approved advertisements and/or news releases through the local media. Efforts will be made by all participating sites to enroll representative samples of both genders and minority subjects. Candidates who contact the site to express interest in participating in the study will be scheduled for an information session at the clinic.

12.2 Informed Consent

During the information session, all potential candidates for the study will be given a current copy of the Informed Consent Form to read. The principal 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. After the subject has read the consent form, a short questionnaire will be given to the subject before signing the form. This questionnaire will review all aspects of the study discussed in the consent form. A research staff member will review the answers provided by the subject to show complete understanding of the information discussed in the consent form before providing consent. Any subject who is unable to demonstrate understanding of the information contained in the informed consent will be excluded from study participation and assisted in finding other sources of treatment.

Table 1. Time and Events Schedule

Study Phase	**Screen**	**Treatment[a]**									**Follow-up**		
Study Week	**-2 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9[b]**	**10**	**14**	**26**
Visit Number	**0[c]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Informed consent	X												
Medical/Psychiatric History	X												
Smoking History	X												
Motivation to Quit VAS	X												
SCID for Axis I Disorders	X												
Demographics	X												
Physical Exam	X[g]										X		
Vital Signs/Weight	X	X	X	X	X	X	X	X	X	X	X	X	X
Waist Circumference	X										X		X
Leisure Time Exercise Questionnaire	X										X		X
Weight Control Smoking Scale	X												
Pregnancy Test (Females)	X	X[h]			X				X		X		
12-lead ECG	X										X		
Fagerström (FTND)	X												
Blood Chemistries[d]	X										X		
Hematology[e]	X										X		
Urine Toxicology Screen[f]	X												
HAM-D	X				X				X		X		
Expired CO	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X											
Brief Counseling Session		X	X	X	X	X	X	X	X	X			
Medication Dispensing/ Reconciliation		X	X	X	X	X	X	X	X	X	X		
Smoking Status	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events			X	X	X	X	X	X	X	X	X	X	X[i]
Prior/Concomitant Medications	X[g]	X	X	X	X	X	X	X	X	X	X		
PANAS	X				X				X		X		
WSWS	X	X	X	X	X	X	X	X	X	X	X		

[a]Treatment visits are scheduled to occur the same day of the week, each week, as much as possible.

[b]The assessments to be conducted during Week 10 should be scheduled as soon as possible after the completion of treatment during week 9. Should a subject be withdrawn early, the final assessments listed for Week 10 should be completed at the time of subject withdrawal, if possible.

[c]Screening may take place over more than one visit; however, this period and all assessments will be considered visit 0 for consistency in numbering.

[d] Blood chemistries include sodium, potassium, chloride, carbon dioxide, glucose, creatinine, calcium, ALT/SGPT, AST/SGOT, GGT, total bilirubin, ALP, and BUN.

[e]Hematology includes CBC with differentials and platelets.
[f]The urine toxicology screen includes THC, opiates, cocaine, and methamphetamine.
[g]These assessments must be completed during screening and updated prior to randomization at Visit #1 as part of the final eligibility exam.
[h]Females must have a negative pregnancy test within 48 hours prior to application of study patches.
[i]Only unresolved AEs being followed after Visit 11 will be assessed.

If the candidate desires to participate in the study, s/he will be asked to sign the Informed Consent. No screening assessments or other study procedure will be performed prior to signing the Informed Consent. Subjects who refuse to participate or who withdraw from the study will be treated without prejudice. After signing the consent form, candidates will be assigned a subject identification number and proceed to the screening phase of the study.

12.3 Screening

The purpose of screening is to establish the candidate's eligibility for study participation. All screening assessments must be completed within a two-week period. Anyone who consents to the study and does not complete the screening assessments in the allowed time or who is a screening failure cannot be screened a second time. It is expected to take between 3 - 4 hours to complete all screening assessments. The screening assessments to be performed to determine eligibility are summarized in **Table 1**.

A medical and psychiatric history will be taken by a clinician. The candidate will be asked to complete a smoking history questionnaire and a smoking status form that assesses his/her recent smoking habits. A physical examination and ECG will be performed and vitals signs, height, weight, and waist circumference will be measured. A Weight Control Smoking Scale and Leisure-Time Exercise Questionnaire will be administered. All women must have a negative pregnancy test during screening. If randomization occurs within 48 hours of obtaining this initial negative pregnancy test, the pregnancy test does not need to be repeated. However, if the initial pregnancy test is longer than 48 hours before the time of initial patch application, the pregnancy test must be repeated and be negative for the subject to be eligible. Blood will be collected for chemistries and hematology assays. No more than 20 mL of blood will be collected during screening, unless repeat samples are needed. Urine will be collected for a urine drug screen. If the urine drug screen is positive for THC, it may be repeated once, and if negative, the subject will not be excluded for this criterion. If still positive for THC or positive for cocaine, opiates, or methamphetamine during any test, the subject will not be eligible for study participation. Baseline assessments for nicotine dependence and withdrawal will be performed including the Fagerström Test and WSWS. Medication use in the past 60 days will be recorded. A SCID for Axis I disorders and HAM-D, and PANAS assessments will be performed. Expired CO will also be measured. Any tests to determine eligibility may be repeated during the two-week screening period at the discretion of the investigator to establish eligibility.

12.4 Enrollment and Randomization

Once it has been determined that a candidate meets preliminary eligibility requirements, s/he will be scheduled to come into the clinic for a final eligibility determination to be enrolled in the study. This visit (Study Day 1) should be scheduled within the two-week window for completion of screening assessments and should be 8 days before the subject's proposed target quit date. All female subjects must have a negative pregnancy test at this visit or within 48 hours of this visit prior to the first application of investigational product to be eligible for enrollment in the study. The candidate's medical history will be reviewed for any changes since his/her initial assessment. Once final eligibility has been established, the candidate will be randomized and enrolled in the trial. The treatment groups will be balanced within each clinical site with respect to gender, time to first cigarette after awakening (≤ 30 min or > 30 min), and average number of cigarettes smoked per day

in the 30-days prior to the signing of the informed consent ($\geq$ 25 and < 25), and current depression symptomatology as measured by the HAM-D score > 11.

Adaptive random allocation of subjects to study groups will be used to balance groups with respect to baseline prognostic variables. This procedure allocates treatment assignment based on the assignments and prognostic variable levels for all previously enrolled subjects. A new subject will be randomized with a "biased coin" procedure that uses randomization probabilities, favoring the treatment with the deficit enrollment, to improve the balance on group assignment.[41]

The VA Cooperative Studies Program Coordinating Center (CSPCC) in Perry Point, MD will act as the Data Management Center for this trial. Information pertinent to the randomization variables for treatment assignment will be obtained from site personnel through the CSPCC's Interactive Touch Tone Randomization System (ITTRS). The ITTRS is an automated phone system which is able to provide random treatment assignments 24 hours/day, 7 days/week. Site personnel who are authorized to randomize subjects and who have completed training for the ITTRS will call the system and provide the site number, unique Subject ID and Alpha Code, the subject's gender, time to first cigarette after awakening (≤ 30 min or > 30 min), average number of cigarettes smoked per day in the 30 days prior to the signing of the Informed Consent ($\geq$ 25 and < 25), and current depression symptomatology as measured by the HAM-D score > 11. The ITTRS will provide a random treatment kit number, which assigns the subject to one of the two treatment groups.

12.5 Treatment

Patches: On the day of randomization (Study Day 1), subjects will be given their initial weekly supply of STS or matched placebo patches and instructions for application. Extra placebo patches will be supplied for use in training the subject on patch application. On Study Day 1, STS or matched placebo patches will be applied in the clinic by the study staff. After Study Day 1, the subject will apply the study patch himself/herself at approximately the same time each day and record the time of application and removal on the subject smoking and patch application diary card.

Behavioral Intervention: During screening, the candidate's motivation to quit smoking will be assessed and a target-quit date will be selected that is 7 days post-randomization. On the first day of treatment (Study Day 1), each subject will be given a modified version of the National Cancer Institute's Booklet entitled "Clearing the Air." Starting on Study Day 1 and weekly at clinic visits, subjects will be provided individual smoking cessation counseling sessions based on the Public Health Service *Clinical Practice Guidelines for Treating Tobacco Use and Dependence* (Version 2000). The brief clinical intervention approach consists of weekly individual counseling sessions, lasting approximately 10 minutes long.

The first session will last approximately 20 minutes, as a more extensive review of the Clearing the Air booklet and planning the target-quit date will be conducted. Subjects will be instructed not to attempt to quit or reduce smoking prior to their target-quit date. In the event that the subject cannot come to the clinic for their weekly session, a telephone intervention session will be substituted for the in-clinic session, if possible. During the initial counseling session, the five major steps (the "5 A's") to intervention will be followed. These include: *asking* the subject about their tobacco use; *advising* him or her to quit (i.e., review medical consequences of not quitting); *assessing* his/her willingness to make a quit attempt; *assisting* him or her in making a quit attempt (setting the quit date and changing smoking behavior patterns); and *arranging* for follow-up contacts to prevent

relapse. A manual will be provided as a standardized guide for clinical staff to follow who will conduct the behavioral intervention sessions. Should the subject be unable to attend his/her weekly session, a telephone intervention session will be substituted.

Subjects will be discouraged from engaging in additional treatment to quit smoking outside of what is being offered in the study (e.g., motivational books, audiotapes or CDs, hypnosis, acupuncture, or any other type of pharmacotherapy). Additional methods employed by subjects to quit smoking will be assessed weekly and will be recorded on a treatment compliance CRF. Pharmacotherapies used will also be collected during the weekly assessment of concomitant medications.

12.6 Precautions During Treatment

12.6.1 Orthostatic Hypotension

Because MAOIs are known to have a hypotensive effect, subjects should be appropriately informed of the symptoms of orthostatic hypotension and cautioned to rise slowly from supine and seated positions.

12.6.2 Hypertensive crisis

STS (transdermal selegiline) should not be used without dietary tyramine restrictions at daily doses exceeding those outlined in the study protocol because of the potential risk of hypertensive crisis associated with non-selective inhibition of MAO at peripheral tissue sites. The selectivity of MAO-B inhibition is diminished with increasing concentration of selegiline. Nonselective MAO inhibition has the potential to produce an acute hypertensive reaction following the ingestion of tyramine-rich foods (the so-called "cheese effect") or sympathomimetic amines such as dopamine, epinephrine, phenylpropanolamine, pseudoephedrine, etc. (excluded medications, see "Exclusion Criteria #9"). A hypertensive reaction can be fatal due to cardiovascular complication or intracranial bleeding.

Hypertensive reactions are characterized by some or all of the following symptoms: sudden severe headache, occipital headache which may radiate frontally, palpitations, neck stiffness or soreness, nausea, vomiting, sweating (sometimes with fever and sometimes with cold, clammy skin), blurred vision, dilated pupils, or photophobia. Cardiac arrhythmia, including tachycardia or bradycardia, may be present and can be associated with constricting chest pain.

Vital signs should be measured to detect a pressor response in subjects receiving MAO inhibitors. It is, however, emphasized that full reliance should not be placed on blood pressure readings, and that the subject should also be observed for clinical signs of the hypertensive syndrome (see above). Accordingly, sound clinical judgment should be exercised regarding discontinuation of study medication following the occurrence of one or more of the above mentioned symptoms (e.g., palpitations, tachycardia, a sense of constriction in the throat or chest or severe or frequent headaches) during subject participation in this clinical trial.

Subjects should 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.

If a hypertensive reaction occurs, the transdermal system should be discontinued and the underlying skin washed with soap and cold water to remove any residual drug substance. **Therapy to lower**

blood pressure should be instituted immediately according to the current standards of medical practice, but parenteral reserpine should not be administered.

12.7 Assessments During Treatment

Subjects will make weekly visits to the clinic for investigational product (STS or matched placebo) dispensing and reconciliation, behavioral intervention, and assessments of cigarette use. Subjects will be given a diary and instructed to complete it daily before going to bed. The daily diary records the number of cigarettes smoked each calendar day and has a place to record the timing of daily patch application and removal. The daily diary will be returned to site personnel each week. If a subject fails to return the diary at his/her weekly visit, a member of the study staff will help the subject complete the weekly diary for cigarette use with the Time Line Follow Back method.

Weekly assessments in the clinic (as shown in **Table 1**) include:

- Expired CO
- Medication Dispensing/Reconciliation
- Smoking Status
- Review of Subject's Smoking and Patch Application Diary
- Adverse Events
- Concomitant Medications
- WSWS
- Vital Signs and Weight

Assessments that occur periodically during the study include:

- HAM-D (Weeks 4, 8, and 10)
- PANAS (Weeks 4, 8, and 10)
- Pregnancy test (Weeks 4, 8, and 10)

See section 12.11 Study Termination for a discussion of subject disposition in the event of pregnancy or worsening of depression as indicated by increase in HAM-D scores.

At the end of the treatment phase (end of Study Week 9), subjects will be scheduled to come to the clinic as soon as possible during Week 10 to perform final assessments. If a subject withdraws from the study before Week 10, final assessments will be performed at the time of withdrawal, if possible. Final assessments include:

- Expired CO
- Medication Reconciliation
- Smoking Status
- Review of Subject's Smoking and Patch Application Diary
- Adverse Events
- Concomitant Medications
- PANAS
- WSWS
- Hematology and Blood Chemistry
- Physical Exam

- 12-lead ECG
- Vital Signs/Weight
- Waist Circumference
- Leisure-Time Exercise Questionnaire
- Pregnancy Test (Females)
- HAM-D

12.8 Follow-Up

Subjects will be scheduled for follow-up clinic visits during Weeks 14 and 26 weeks. Assessments to be conducted at these visits include:

- Expired CO
- Vital Signs/Weight
- Waist Circumference (only during Week 26)
- Leisure-Time Exercise Questionnaire (only during Week 26)
- Smoking Status
- Follow-Up Questionnaire
- Adverse Events (only at Week 14 unless there were unresolved and clinically significant adverse events at Week 14 that will be followed to Week 26).

If a subject cannot return to the clinic, s/he will be contacted by phone to determine his/her current smoking status and adverse events.

12.9 Preventing Study Dropouts

Subjects will be encouraged to come for treatment and for the evaluation sessions as described in this protocol. It will be emphasized to subjects during screening and throughout the study that even if they continue to smoke or have quit and have had a relapse they should come to all scheduled appointments. Subjects will be discouraged from smoking, but there will be no penalty for smoking, or for missed sessions.

12.10 Maintaining and Breaking the Study Blind

The decision to break the study blind for an individual subject lies with the site principal investigator and study principal investigator, or with the NIDA medical monitor. Breaking the blind should be resorted to only in life-threatening cases when knowledge of the treatment arm investigational product will influence clinical management. The Operations Manual contains a detailed list of contact numbers and the procedures for unblinding.

12.11 Subject Reimbursement

Subjects will be compensated at a rate of $20 per clinic visit; except compensation for only one screening visit will made even if multiple visits are needed. The maximum payment any subject may receive is $260. Subjects will be compensated regardless of whether they continue to receive investigational products, or whether or not they quit smoking as long as they continue their clinic

visits. It will be emphasized to subjects that this remuneration is for their time and inconvenience (e.g., gasoline, public transportation, etc.) not for their compliance with study procedures. Subject reimbursement, type (i.e., cash or vouchers) and schedule will be made in accordance with local IRB policies and practices.

12.12 Study Termination

Since an intention-to-treat (ITT) paradigm is being used for this study, subjects will be encouraged to continue completing study visits, study assessments and behavioral interventions, even if they are unable to tolerate investigational products, or are unsuccessful in quitting smoking. If a subject decides to drop out of the study prior to Week 10, s/he will be asked to complete all final assessments (termination) at the time of drop out. If a subject wishes to stop applying study patches but to continue to participate in behavioral interventions, s/he will continue to receive all scheduled assessments.

An investigator may suspend a subject from further study participation if s/he deems it clinically appropriate or for any of the following reasons: 1) significant side effects from investigational products, 2) serious or unexpected adverse events, 3) inability to comply with the study protocol, 4) protocol violation, 5) increases in HAM-D scores suggesting worsening of the severity of depression, in the clinician's judgment, or 6) serious intercurrent illness.

If a female decides to stop using acceptable birth control or becomes pregnant during the study, treatment with all investigational patches will be stopped, and if she chooses to continue in the study, she can continue behavioral treatment and follow-up.

Failure to stop smoking is not a criterion for removing a subject from the study. These individuals will continue to receive pharmacotherapy and behavioral therapy as long as they are willing to continue in the study. A subject may withdraw from the study anytime s/he wishes. In the event a subject is discontinued from receiving the investigational product, s/he will be allowed to continue the psychosocial-behavioral treatment with the approval of the investigator.

Subjects who discontinue 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.

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

All study subjects will be encouraged to carry a pocket card that identifies them as a subject in a clinical research study. The card will provide the name and phone number of the principal investigator (physician) at the site who can be contacted in the event of an emergency. The card will also instruct the non-study physician rendering emergency care to provide information to the study physician with regards to that care. In addition, a pocket card will be provided that contains a list of contraindicated medications.

13 CLINICAL EVALUATIONS

13.1 Medical/Psychiatric History

During screening, a medical and psychiatric history will be obtained by clinical staff member. Subjects will answer whether they currently have or have ever been treated for (and if they are currently being treated for) the following categories of neuropsychiatric disorders: psychosis, bipolar illness, major depression, organic brain disease, Parkinson's disease, dementia, history or current diagnosis of anorexia nervosa or bulimia, history of neuroleptic malignant syndrome, or a past history of suicide attempts (by history/SCID) and/or current suicidal ideation. Each subject will answer whether they have now, or a history of, the following medical problems: uncontrolled hypertension, significant heart disease (including myocardial infarction or stroke within one year of enrollment), angina, cardiovascular abnormality, severely irregular heat beat (arrhythmia), pheochromocytoma, vasoplastic diseases (e.g., Buerger's disease, Prinzmetal's angina), diabetes requiring insulin, hepatic or renal disorders, a serious endocrine disorder, or any other unstable medical disorder. Any other medical or psychiatric conditions not mentioned will also be questioned. All Medical and Psychiatric History CRFs will be reviewed by a study clinician or physician assistant, to determine subject eligibility before randomization.

13.2 Smoking History

The Smoking History Survey is a modified version of the Mayo Nicotine Dependence Center Patient Questionnaire (1991) and will be administered by a research assistant. The Smoking History Survey asks subjects the following: how many cigarettes per day they smoke; at what age they started smoking; number of years smoking, how many times they have attempted to quit (including methods); when the last quit attempt occurred; their longest period of cigarette abstinence; and if there are other smokers in their household. Information on other non-cigarette tobacco products is also noted.

13.3 Motivation to Quit Scale

A 10 point Likert Scale will be used to assess motivation to quit smoking. Subjects will be asked to indicate their level of motivation to quit smoking on a scale of 0 to 10, where 0 is 'Not at All' and 10 is 'Highly Motivated'. A score $\geq$ 6 is considered highly motivated to quit for subject eligibility.

13.4 Axis I Disorders

The DSM-IV criteria for Nicotine Dependence will be used to determine subjects' eligibility for the study. A SCID to assess diagnosis of current depression, and Axis I disorders will be conducted during screening by appropriately trained clinical staff.

13.5 Demographics

Age, gender, ethnicity, years of education, usual employment pattern in the past 30 days, and marital status data will be collected. Demographics information will be completed for all subjects who sign a consent form, whether or not they are randomized.

13.6 Subject Locator Form

A Subject Locator Form will be completed and kept confidential in the subject's records. Data collected on the Subject Locator Form will be used to facilitate contact with the subject during the research and follow-up. Subjects will be asked to provide locator information including their residential street address and a working telephone number, and the address of a relative or friend who can reach the subject in emergencies.

13.7 Physical Exam

A physical exam of the oral cavity, head, eyes, ears nose and throat, cardiovascular system, lungs, abdomen (liver/spleen), extremities, skin, neuropsychiatric mental status and sensory/motor status, musculoskeletal system and general appearance will be performed.

13.8 Vital Signs/Weight/Height

Vital signs to be assessed include blood pressure, pulse rate and respiratory rate. Weight will be measured whenever vital signs are taken. Weight should be taken at the same time of day, as much as possible, with the similar types of garments at each measurement. Height will be measured once, during screening.

13.9 Waist Circumference

The subject's waist circumference will be measured by locating the upper hip bone and the top of the right iliac crest (portion of the pelvic bone at the belt line of the body) and placing a measuring tape in a horizontal plane around the abdomen at the level of the iliac crest. Before reading the tape measure, one should make sure the tape is secure, but not too tight and is parallel to the floor. The reading should be taken at the end of an expiration. The measurement will be reported in inches.

13.10 Weight Control Smoking Scale

The Weight Control Smoking Scale is a three item Likert Scale developed by Pomerleau et al.[42], containing the following items: 1) I smoke to keep from gaining weight; 2) Smoking helps me control my appetite; and 3) I don't get so hungry when I smoke. Responses include: 0= not at all; 1= a little; 2= quite a bit; and 3= very much so. The total score is the sum of the individual items.

13.11 Leisure-Time Exercise Questionnaire

The Leisure-Time Exercise Questionnaire is a three item questionnaire developed by Godin et al.[43] that the subject completes regarding their leisure time exercise activities during the past 7-day period (number of times during the past week spent doing strenuous, moderate, or mild exercise for at least 15 minutes at a time). A composite score is computed by multiplying the number of times of exercise by a factor for each category of exercise (weekly activity = (9 x strenuous) + (5 x moderate) + (3 x mild).

13.12 Pregnancy Test (Females)

An FDA approved urine pregnancy test designed to measure β-human chorionic gonodotropin will be used. All female subjects will be tested regardless of their child-bearing capacity.

13.13 12-lead ECG

A twelve-lead ECG will be performed on all subjects at screening and during Week 10 according to standard procedures. A licensed physician (or non-physician certified/accredited by the participating institution to read ECGs) must read all ECGs. A board-certified cardiologist can be consulted, if needed.

13.14 Fagerström (FTND)

The Fagerström Test for Nicotine Dependence[44] is a brief self-report assessment of subject's smoking habits. How many cigarettes are smoked per day, when cigarettes are smoked, and the relationship of smoking behavior to physical health and social function are determined. Time to first cigarette after awakening is also included in this questionnaire and will be used as the randomization variable (> 30 minutes versus ≤ 30 minutes).

13.15 Blood Chemistries

Blood will be collected in serum separation evacuated venous blood collection tubes (e.g., Vacutainer™) and serum separated according to standard procedures. Quantitative analysis will be performed for the following analytes: sodium, potassium, chloride, carbon dioxide, glucose, creatinine, calcium, alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), gamma glutamyltranspeptidase (GGT), total bilirubin, alkaline phosphatase (ALP), and blood urea nitrogen (BUN),. The laboratory performing these assessments should be either directly regulated by the College of American Pathologist (CAP) or Clinical Laboratory Improvement Act of 1988 (CLIA) or indirectly according to CLIA guidelines. The laboratory will need to provide a copy of current certification.

13.16 Hematology

Blood will be collected in evacuated venous blood collection tubes anticoagulant containing (e.g., Vacutainer™) for hematologic assessments. Complete blood counts (CBC) with differentials and platelet count will be performed. Quantitative analyses for hemoglobin, hematocrit, red blood cells, platelets, total white blood cells, neutrophils, lymphocytes, monocytes, eosinophils, and basophils will be performed. The laboratory performing these assessments should be either directly regulated by the CAP or the CLIA or indirectly according to CLIA guidelines. The laboratory will need to provide a copy of current certification.

13.17 Urine Drug Screen

The FDA-approved Instant View 4 panel drug screen for cocaine, opiates, THC, and methamphetamine will be used during screening to identify individuals potentially using illicit drugs.

13.18 Hamilton Depression Scale (HAM-D)

A 24-item HAM-D questionnaire developed by Hamilton (1990) will be used to assess the severity of depression at screening, and during Study Weeks, 4, 8, and 10.[45] Subject's HAM-D scores (>11) will be used to balance randomization.

13.19 Expired CO

Expired CO will be measured at each study visit using a standard calibrated CO gas-monitoring device connected to a disposable mouthpiece. When measuring individual CO levels, subjects are instructed to blow into the mouthpiece for approximately 5 seconds. This procedure is performed at each weekly clinic visit and is documented separately on the CRF including the time of day that CO was measured. Study staff should attempt to collect the sample at a uniform time (in morning, right after subject arrives and before other assessments or counseling sessions begin).

Expired CO has been shown to be an excellent discriminator of smoking status with even higher levels of sensitivity and specificity than other measures including serum thiocyanate and cotinine levels (exhaled CO: 98% and 100%; Serum Thiocyanate: 93% and 82%; Serum Cotinine: 97% and 83%, sensitivity and specificity, respectively).[46] The cut-off level selected as an indicator of smoking is ≥ 9 ppm. This value was selected based on large population studies of heavy smokers including men and women that showed that this cut-off value was highly correlated with self-report and other biochemical methods for determining smoking.[47-49] It takes about 5 to 6 hours to reduce CO levels to half of the original concentration after smoking a cigarette and about 48 hours before levels reach that of non-smokers. The cut-off level for a positive test is higher than that expected for someone exposed to second hand smoke. Some medical conditions may result in a false positive test (i.e., lactose intolerance).

13.20 Compliance with Behavioral Intervention

Weekly attendance at the clinic for assessments and the brief behavioral counseling session will be recorded on a CRF including the length of the session (targeted at 10 minutes), the type of the session (i.e., initial session, getting ready to quit, motivational session for those who have not yet quit, or relapse prevention session for those who have quit), and how the session was conducted (in the clinic versus over the phone). The Behavioral Intervention Compliance CRF will also record any additional behavioral methods the subject may have used on his/her own to quit smoking, e.g., motivational books, audiotapes or CDs; hypnosis; acupuncture; etc., even though the use of these is discouraged during the study.

13.21 Patch Compliance

Treatment compliance with investigational products will be measured by subject's diary of patch application and reconciliation of returned unused patches. The daily smoking diary will be used to record the time of patch application each day. The diary will also contain a place to record, if the patch came off during the day. If the patch is reported as not applied or not left on for the duration of the daily exposure period, this will be noted in the compliance CRF. Reconciliation between the

number of patches dispensed and used as determined by diary of daily application and return of unused patches will be recorded at each visit.

13.22 Smoking Status

Each subject will be given a diary to take home to record daily smoking activities (i.e., number of cigarettes). Subjects will be instructed to return the completed diary during clinic visits. If a subject does not return the completed diary, the research staff will assist him/her in completing the diary using the Time Line Follow-Back method to report daily cigarette use. Subjects will be asked about their smoking behavior since the last visit (i.e., continuously cigarette abstinent or still smoking). Subjects will also be asked whether they have used any tobacco or nicotine products other than cigarettes.

13.23 Adverse Events

Adverse events will be assessed by the study staff throughout the treatment and follow-up phases of the protocol, starting on Day 1 of Study Week 2 and at each subsequent study visit through Week 14 (ongoing adverse events at Week 14 will be checked at Week 26 for resolution). If an adverse event requires medical attention, it will be reported to a study physician immediately. Adverse events will be assessed by asking the subject, "How have you been feeling since I saw you last?" After current adverse events are assessed, the study physician must review with the subject and assess any adverse events unresolved from the previous week. After each weekly adverse event assessment, the type of adverse event, severity of each adverse event, and the relationship to the investigational products will be recorded on the Adverse Event CRF, according to the procedures described in Appendix II. These categories are asking for the clinician's best judgment of the severity and relatedness of each adverse event.

13.24 Prior and Concomitant Medications

All medications taken by the subject within the 60 days prior to screening and during the screening period up to and including the day of randomization will be recorded. The reported medications will be reviewed and approved by the site principal investigator/study physician for possible interactions with investigational products or indication of a serious chronic or acute medical condition that would exclude the candidate from participation.

All medications taken by the subject during the treatment phase of the study through the Week 10 follow-up period will be recorded. Any medications taken during this time must be pre-approved by the study physician whenever possible to avoid interactions with investigational products. The following medications should NOT be used during treatment with STS due to possible interactions.

The following information is taken from the EMSAM® rug Label. STS is contraindicated in patients with known hypersensitivity to selegiline or to any component of the transdermal system. STS is contraindicated with SSRI's (e.g., fluoxetine, sertraline, and paroxetine), dual serotonin and norepinephrine re-uptake inhibitors (SNRI's, e.g., venlafaxine and duloxetine), tricyclic antidepressants (TCA's, e.g., imipramine and amitripyline), bupropion hydrochloride; meperidine and analgesic agents such as tramadol, methadone and propoxyphene; the antitussive agent dextromethorphan; St. John's wort; mirtazapine; and cyclobenzaprine. STS should not be used with

oral selegiline or other MAO inhibitors (MAOI's e.g., isocarboxazid, phenelzine, and tranylcypromine). Carbamazepine and oxcarbazepine are contraindicated in subjects taking selegiline. As with other MAOI's, STS is contraindicated for use with sympathomimetic amines, including amphetamines as well as cold products and weight-reducing preparations that contain vasoconstrictors (e.g., pseudoephedrine, phenylephrine, phenylpropanolamine, and ephedrine).

Subjects will be provided with a pocket card containing a list of contraindicated medications.

As with other MAOI's, subjects taking STS should not undergo elective surgery requiring general anesthesia. Also, they should not be given cocaine or local anesthesia containing sympathomimetic vasoconstrictors. STS should be discontinued at least 10 days prior to elective surgery. If surgery is necessary sooner, benzodiazepines, mivacurium, rapacuronium, fentanyl, morphine, and codeine may be used cautiously. STS is contraindicated for use in subjects with pheochromocytoma. STS is an irreversible MAO inhibitor. As a class, these compounds have been associated with hypertensive crises caused by the ingestion of foods containing high amounts of tyramine. In its entirety, the data for STS 6 mg/24 hours support the recommendation that a modified diet is not required at this dose.

13.25 Positive & Negative Affect Scale (PANAS)

The PANAS developed by Watson *et al.* (1988)[50] consists of two mood scales: positive affect and negative affect. The ten items within the negative affect scale include: afraid, ashamed, distressed, guilty, hostile, irritable, jittery, nervous, scared, and upset. The ten items included within the positive affect scale are: active, alert, attentive, determined, enthusiastic, excited, inspired, interested, proud, and strong. Items in both mood scales can be rated on a scale of 1 to 5, with 1 being "very slightly or not at all," and 5 being "extremely." Positive and negative affects are scored separately.

13.26 Wisconsin Smoking Withdrawal Scale (WSWS)

The WSWS is a 28-item scale that examines the major symptom elements of the nicotine withdrawal symptoms.[51] The WSWS contains 7 subscales: anger, anxiety, concentration, sadness, hunger, sleep, and craving. This self-report questionnaire is scored on a 5-point scale, with several items reverse keyed.

14 REGULATORY AND REPORTING REQUIREMENTS

14.1 Good Clinical Practices

This study will be conducted in accordance with the most current version of the International Conference on Harmonization Guide for Good Clinical Practices (GCP). An Operations Manual will be provided to all investigational sites as a study quality assurance tool. In addition, the standardized behavioral intervention sessions will be conducted by clinicians who have received training.

14.2 FDA Form 1572

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

14.3 IRB Approval

Prior to initiating the study, the principal 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 principal investigator for IRB approval prior to implementation. In addition, IRBs will approve all advertising materials used for subject recruitment and any educational materials given to the subject.

14.4 Informed Consent

All potential subjects for the study will be given a current copy of the Informed Consent Form to read. The principal investigator or designee at each site will explain all aspects of the study in lay language and answer all of the subject's questions regarding the study. After the subject has read the consent form, a short questionnaire will be given to the subject before signing the form. Any subject who does not show understanding of the consent form will be excluded from study participation and assisted in finding other sources of treatment. If the candidate desires to participate in the study, s/he will be asked to sign the Informed Consent. No screening or study procedures will be performed before the candidate signs the Informed Consent. Candidates who refuse to participate or subjects who withdraw from the study will be treated without prejudice.

14.5 Use of Protected Health Information

At the time of informed consent, all potential candidates will be asked to sign a waiver authorizing the release and use of protected health information in this study. Clinical sites will employ a Protected Health Information Disclosure that details the health information that will be collected as part of this research and the agencies that may access that information during the study and after the study has been completed.

Health information gathered during this research study may be reviewed by representatives of NIDA, the Food & Drug Administration (FDA) & Somerset Pharmaceuticals, Inc. for monitoring purposes. All data collected for this study will be sent to the VA CSPCC in Perry Point, MD for processing and analyses. Research data will be transmitted to the VA CSPCC electronically via a secure fax server. From this data, a database will be constructed and maintained and all data contained within will be stored according to the HIPAA Privacy Rule. Access to the database will be limited to data management personnel only.

At the conclusion of the study, the VA CSPCC will provide a limited dataset to Information Management Consultants (IMC), a data management firm that is contracted by NIDA to store and retrieve study data. Data transfer between the VA CSPCC and IMC will take place electronically through secure internet connections. IMC has entered into a Data Use Agreement with NIDA that mandates their compliance with all aspects of the HIPAA Privacy Rule and their employment of all necessary precautions to prevent unauthorized use of, or access to the data. In accordance with this agreement, IMC may not release data to any agency other than the FDA without the express written approval of NIDA and the Director, VA CSPCC. IMC will store the data indefinitely until instructed, in writing, by NIDA to destroy the data.

14.6 Drug Accountability

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

14.7 Outside Monitoring

Data and Safety Monitoring Board: Safety data will be reviewed by the NIDA Data and Safety Monitoring Board that will meet annually during the conduct of this study, or earlier if deemed necessary. The board will be blind to subjects' actual treatment assignments.

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

Clinical Monitors: All investigators will allow representatives of the Sponsor to periodically review, 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: ensure that submitted data are accurate and are in agreement with source documentation; verify that investigational products are properly stored and accounted for, verify that subjects' consent for study participation has been properly obtained and documented, confirm that subjects entered into the study meet inclusion and exclusion criteria, and assure that all essential documentation required by GCP guidelines are appropriately filed.

Clinical 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 GCP 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 investigational products. All sites should anticipate visits by NIDA, the Sponsor, and the FDA.

14.8 Study or Site Closure

If data suggest that subjects are being compromised medically, the study may be discontinued at the discretion of the principal investigator and/or NIDA. The Sponsor reserves the right to discontinue this study at any time.

14.9 Retention of Records

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

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

Government agency regulations and directives require that the investigator must retain all study documentation pertaining to the conduct of a clinical trial. These documents must be kept for a minimum of two years after discontinuation of the IND or 2 years after the approval of a new drug application (NDA) and finalization of all marketing strategies. In all instances you must get permission from NIDA prior to disposition of any study documentation and materials.

14.10 Adverse Events Reporting

In accordance with FDA reporting requirements, all adverse events occurring during the course of the clinical trial will be collected, documented, and reported by the investigator or sub-investigators according to the specific instructions detailed in this section of the protocol and Appendix II. The occurrence of adverse events will be assessed at the beginning of the treatment phase of the protocol (Day 1 of Study Week 2) and at each subsequent study visit until Week 14. Any ongoing adverse events at Week 14 will be checked during the visit at Week 26 for resolution.

An adverse event 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, adverse events 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 adverse event. Stable chronic conditions, such as arthritis, which are present prior to clinical trial entry and do not worsen are not considered adverse events. All adverse events will be recorded on the Adverse Events CRF. The Adverse Events CRF is also used to record follow-up information for unresolved events reported on previous visits.

Pregnancy at any time starting after the first dose of investigational product administration through the final study visit must be reported on the appropriate CRF. The progress and outcome of the pregnancy must be followed until after the birth of the baby of discontinuation of the pregnancy,

whether through voluntary (i.e., abortion, etc.) of involuntary (i.e., medical complications, etc.) means, whichever occurs first. Every effort should be made to have the mother allow access to the medical records and hospital discharge summaries.

Each week, a study investigator must review the Adverse Events CRF completed for the previous week for any events that were reported as continuing. All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed by study investigators until satisfactory resolution.

14.11 Serious Adverse Events

Each adverse event or reaction will be classified by a study investigator as serious or non-serious. The seriousness of the adverse event or reaction will determine the reporting procedures to be followed. The Code of Federal Regulations Title 21 part 312.32 and International Conference on Harmonization (ICH) Guideline for Industry: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH-E2A March 1995, as implemented by the U.S. Food and Drug Administration, defines a serous adverse event (SAE) or serious adverse drug experience as any untoward medical occurrence at any dose that:

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

In addition, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug reaction, when based on appropriate medical judgment, that may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition.

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

Reporting of adverse events and SAEs is described in Appendix II. There can be serious consequences including ultimately, criminal and/or civil penalties for Sponsors who fail to comply with FDA regulations governing the reporting of SAEs to FDA. The study investigators in this study have the responsibility of promptly reporting all SAEs to NIDA within 24 hours so that it can comply with these regulations.

If a study subject withdraws from the study or if an investigator decides to discontinue the subject from the study because of a SAE, the subject must have appropriate follow-up medical monitoring including, if necessary, hospitalization.

14.12 Confidentiality

To maintain subject confidentiality, all laboratory specimens, CRFs, and reports will be identified by a coded number. Clinical records will be stored separately from research records in a secure location. Subject information will not be released without the subject's written permission, except as necessary for monitoring by the FDA and Sponsor authorized monitors. Release of personal health information will be in accordance with current Standards for Privacy of Individually Identifiable Health Information (45 CFR parts 160 and 164) of the Health Insurance Portability and Accountability Act (HIPAA).

14.12.1 Confidentiality of Data

Particular attention is drawn to the regulations promulgated by the FDA under the Freedom of Information Act providing, in part, that proprietary information furnished to clinical investigators and IRBs will be kept confidential by the FDA only if maintained in confidence by the clinical investigator and IRB.

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

14.12.2 Confidentiality of Subject Records

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

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

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

15 ANALYTICAL PLAN

15.1 Statistical Hypothesis

The objectives of this study are to determine the efficacy and safety of STS with brief behavioral intervention for smoking cessation in heavy smokers as compared to brief behavioral intervention alone. It is hypothesized that the quit rate of subjects who received STS with behavioral intervention will be significantly greater than the quit rate of a placebo patch control group who received behavioral intervention alone. It is further hypothesized that the STS group will also have continued abstinence assessed during Study Weeks 14 and 26.

15.2 Outcome Measures

Efficacy outcome measures were selected based on recommendations made by the Society for Research on Nicotine and Tobacco as described by Hughes, *et al.* (2003).[52] The primary outcome measure is the quit rate that was defined by the FDA for registration trials of smoking cessation phamacotherapies.[53] Secondary outcome measures include those described by Hughes *et al.* (2003) with respect to measures of longer-term abstinence.[52] **Quit Rate** is defined as the proportion of subjects who have ceased smoking as measured by 4-weeks of self-reported abstinence confirmed by at least two exhaled CO measurements during the last 4 weeks of treatment (Weeks 6 through 9).

15.2.1 Primary Efficacy Outcome Measure

The primary efficacy outcome measure is the quit rate as defined above. For determining the quit rate, at least two CO measurements must be obtained during the last 4 weeks of treatment (Weeks 6 through 9) with at least one of these two measurements taken during Weeks 8 or 9). Two measurements may not be taken during any one study week; however, measurements may be less than 7 days apart. In addition, CO levels must be < 9 ppm to confirm abstinence. Evaluating cessation at the end of treatment allows for a period for the treatment to take effect and a grace period for those subjects who may have resorted to occasional smoking during the first weeks of treatment. Previous smoking cessation trials have supported the concept of a grace period as some subjects may smoke occasionally during the first week of treatment yet become a treatment success. A subject who is lost to follow-up, or who does not provide the required CO measurements or self-reports of use during Study Weeks 6 – 9 of the active treatment period, is considered a treatment failure.

15.2.2 Secondary Efficacy Outcome Measures

Secondary efficacy outcome measures include:

1. The proportion of subjects who were abstinent at the end of treatment, as defined for the primary outcome measure, and continue to remain abstinent at Study Week 14, as determined by self-report with abstinence confirmed by exhaled CO (<9 ppm is abstinent). The proportion is determined by dividing the number who achieved abstinence at the end of treatment as defined for the primary outcome measure and are still abstinent by self report with confirmation by exhaled CO by the total number randomized to the treatment group. Only subjects who were considered as initial quitters at the end of treatment will be included as having prolonged abstinence. All ITT subjects who are not evaluable for this measurement will be considered to be not abstinent.

2. The same as secondary measure #1 except that time frame is Week 26.

3. The proportion of subjects who were abstinent at the end of treatment and continue to remain abstinent at study Week 14 as determined by self-report alone. The proportion is determined by dividing the number who achieved abstinence at the end of treatment as defined for the primary outcome measure and are still abstinent by self report by the total number randomized to the treatment group.

4. The same as secondary measure #3 except that time frame is Week 26.

5. Change in severity of depression (change in HAM-D scores at treatment end compared to baseline).

6. The severity of nicotine craving, withdrawal, and dependence and effects on mood using: a) WSWS and b) PANAS.

7. The effects on weight gain/loss as assessed by body weight and waist circumference.

15.2.3 Safety Measures

Safety measures to be assessed include:

1. Frequency and severity of adverse events;
2. weight gain/loss,
3. vital signs,
4. ECG, and
5. clinical laboratory assessments.

15.3 Definition of Study Populations

The intention-to-treat (ITT) and safety populations are defined as the subjects who are randomized to treatment and who receive the first day's investigational product.

15.4 Analysis Plan

Primary Efficacy Outcome. The quit rate will be compared between treatment groups using Pearson Chi square analysis. It is hypothesized that STS with behavioral therapy will result in significantly higher quit rates for the last 4 weeks of active treatment compared to behavioral therapy alone. As a secondary analysis, bivariate logistic regression will be used to determine if any baseline characteristics such as gender, current depression symptomatology as measured by the HAM-D score > 11, previous smoking quit attempts, and time to first cigarette after awakening are predictive of treatment success or failure. As the primary outcome measure assumes that a subject who is lost to follow-up or who does not provide the required CO measurement or self-report of use in Study Weeks 6 through 9 is a treatment failure (in essence, still smoking), bias may be introduced into the analysis if a substantial proportion of the data is missing. This concept was discussed by Hall *et al.* (2001).[54] Thus, several missing data strategies will be used to examine the primary outcome measure. If the proportion of missing data is more than 10% of the total sample and there exists a differential dropout rate between groups, then these methods will be employed:

1. Performing the primary outcome analysis ignoring the missing values.
2. Worst-case analysis- Failure to quit is used to replace all missing values in the STS treatment group and abstinent is used to replace all missing values in the placebo treatment group.
3. Best case analysis-Abstinent is used to replace all missing values in the STS treatment group and failure to quit is used to replace all missing values in the placebo treatment group.
4. Performing the analysis using a multiple missing value imputation methodology.[55] Multiple imputation replaces each missing value with a set of "m" plausible values that represent the uncertainty about the right value to impute. The "m" multiple imputed data sets are then

analyzed by using standard procedures for complete data and then the results from these analysis are combined as follows:

a. A logistic model will be used to model the frequency of missing values, and is used to impute the missing primary outcomes, modeled as a function of baseline characteristics (e.g. gender, current depression symptomatology as measured by the Ham-D score > 11, time to first cigarette in the morning, etc), treatment group assignment, and prior information available before the subject drops out (e.g. weekly CO measurement, etc). This will be done using the SAS multiple imputation (MI) procedure.
b. Each of the "m" complete data sets is analyzed using a Chi-square test.
c. The results from the "m" complete data sets are combined for inference using the SAS MIANALYZE procedure.

Secondary Efficacy Outcomes.

1. The proportion of subjects abstinent (by self report confirmed by exhaled CO) at Study Week 14 will be compared between treatment groups using Pearson Chi square analysis. It is hypothesized that abstinence will continue to be significantly higher in the group receiving STS.

2. The proportion of subjects abstinent (by self report confirmed by exhaled CO) at Study Week 26 will be compared between treatment groups using Pearson Chi square analysis. It is hypothesized that abstinence will continue to be significantly higher in the group receiving STS.

3. The proportion of subjects abstinent (by self report alone) at Study Week 14 will be compared between treatment groups using Pearson Chi square analysis. It is hypothesized that abstinence will continue to be significantly higher in the group receiving STS.

4. The proportion of subjects abstinent (by self report alone) at Study Week 26 will be compared between treatment groups using Pearson Chi square analysis. It is hypothesized that abstinence will continue to be significantly higher in the group receiving STS.

5. As STS is approved for the treatment of depression and depression is frequently a comorbidity in nicotine dependence, it is of interest to examine the reduction in the severity of HAM-D scores, as an indicator of the possible antidepressant effects of STS in this population. The proportion of subjects with a 50% reduction in the HAM-D score at the end of the study as compared to baseline (subtraction of baseline total score from the score at study end for each subject) will be compared between treatment groups using the Fisher's Exact Test. It is hypothesized that there will be a significant increase in the proportion of subjects whose scores are reduced by 50% or more in the STS group compared to the placebo control group.

6a. The WSWS measures nicotine craving and withdrawal (the higher the score the more severe the symptoms). It is expected that subjects who quit smoking will experience increased craving and withdrawal symptoms and that these symptoms may be alleviated by STS with behavioral intervention compared to behavioral intervention alone. As the severity of craving and withdrawal symptoms have a temporal relationship to the time after quitting with the most severe signs of withdrawal occurring in the first two weeks after quitting, simple regression methods will be used to examine and characterize the effects of STS in comparison to placebo patch in the subset of subjects

who quit smoking (met the quit rate criteria) in each treatment group. Bivariate regression plots of WSWS scores (y axis) versus time (x axis) will be constructed to examine treatment effects for these two independent variables.

6b. The PANAS is considered a reliable measure of the dominant dimensions of emotional experience. Anxiety is related to high negative affect. Depression is related to both high negative affect and low positive affect. As mood changes are typical symptoms of nicotine withdrawal, the changes in PANAS scores for both positive affect and negative affect (scored separately) will be examined over time during the treatment period in both treatment groups. This analysis will be performed in a similar manner as that planned for the analysis of WSWS scores described above.

7. The change in body weights and waist circumference of subjects who quit smoking in accordance with the definition of a quitter per the primary outcome measure will be presented for both treatment groups at each assessment to determine if the treatment lessens the typical weight gain experienced by smokers who have quit smoking.

All statistical tests will be two-sided and a probability of $p < 0.05$ will be considered statistically significant.

Safety Outcomes. The severity and frequency of adverse events, laboratory data, physical exams, vital signs, ECG findings, and weight gain/loss reported as an adverse event will be reported in tabular form. Adverse events will be coded using Medical Dictionary of Regulatory Affairs (MedDRA) preferred terms and grouped by system, organ, and class (SOC). The frequencies of adverse events by type will be compared between study arms using Chi-square analyses.

Descriptive Statistics. Summaries of the demographic and smoking history characteristics of the subject population in both treatment groups at baseline will be prepared for the ITT subjects. A summary will be prepared to show dropouts/retention over time in each treatment group and for major subgroups (males/females). The number of missing observations will be compared between treatments and for major subgroups. Weekly treatment compliance of each group will be summarized.

Ad Hoc **Analyses.** Concerns about weight gain during smoking cessation as well as time spent on leisure time exercise will be examined with respect to smoking outcomes.

15.5 Sample Size Analysis

Sample size estimates were performed using 4-week abstinence rates from two smoking cessation studies.[17] **Table 2** shows the results of a randomized, placebo controlled trial comparing bupropion SR, Habitrol (nicotine patch), and the combination of the two to a placebo control group. All study subjects received behavioral intervention. Bupropion SR and Habitrol are approved for smoking cessation treatment, so the effect sizes are representative of two other drugs approved for this indication. **Table 3** shows the results of the study comparing oral selegiline to placebo control. This was a small pilot study that provides a preliminary effect size for selegiline compared to a placebo control in heavy smokers.

The quit-rate for the Buproprion SR or nicotine patch (Habitrol) alone in the study shown in Table 2 was 49.2% and 36.1%, respectively compared to placebo control. This is an effect size of 26.1% for Bupropion SR and 13% for Habitrol as compared to placebo. In the oral selegiline study (data shown in Table 3), the quit rate for oral selegiline was 30% compared to 5% for the placebo control; an effect size of 25%. It should be noted that this is an atypically low quit rate for placebo controls in an 8-week study. Thus, if one estimates that the proportion of placebo treated subjects will be 23.1% abstinent at the end of the 8-week treatment period, and assumes a normal approximation to the binomial distribution with a two-sided alpha of 0.05 and an 80% power to detect significant differences and a difference in the proportions of quitters between the groups of 20%, then the number of subjects needed in each group is estimated to be 98. Escalating this number by 20% due to drop-outs, increases the number to 123 per group or a total of 246 total subjects.

Table 2. Four-Week Abstinence at End of 8-Weeks of Treatment – Self Report Confirmed by Expired CO in Bupropion SR/Habitrol Combination Trial in 893 Male and Female Heavy Smokers

Outcome	Placebo	Habitrol	Bupropion SR	Habitrol + Bupropion SR
% abstinent	23.1%	36.1%	49.2%	57.6%
p-value vs placebo	-	<0.01	<0.001	<0.001
p-value vs Habitrol		-	<0.01	<0.001
p-value vs bupropion			-	0.06

Table 3. Four-Week Abstinence at End of 8-Weeks of Treatment – Self Report Confirmed by Expired CO in Oral Selegiline (10 mg/day – 5 mg bid) (N=20) Trial Compared to Placebo Control (N=20)[17]

Outcome	Placebo	Selegiline 10 mg/day p.o.
% abstinent	5%	30%
p-value vs placebo	-	p< 0.05

16 DATA MANAGEMENT AND CASE REPORT FORMS (CRFs)

Data management activities and statistical analytical support will be coordinated through the CSPCC at the VA in Perry Point, MD.

16.1 Data Collection

Data will be collected at the study sites on source documents, which will be entered at the site into CRFs. The CRFs will be supplied by CSPCC. CRFs are to be completed on an ongoing basis during the study. The medical chart and the source documents are the source of verification of data. CRFs should be completed according to the instructions in the study operations manual. Completed CRFs will be submitted on a regular basis to CSPCC. The site principal investigator is responsible for maintaining accurate, complete and up-to-date records for each subject. The site principal

investigator is also responsible for maintaining any source documentation related to the study, including any films, ECG tracings, computer discs or tapes.

16.2 Data Editing and Control

Data received at the CSPCC will be reviewed, verified and edited prior to being entered into the main study database. If incomplete or inaccurate data are found, a data clarification request will be forwarded to the clinical site for a response. Sites will resolve data inconsistencies and errors prior to returning data to the CSPCC. All corrections and changes to the data will be reviewed prior to being entered into the main study database. NIDA DPMC 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 Department of Veterans Affairs Cooperative Studies Program (VACSP) monitoring unit, as well as by NIDA. VACSP monitors will routinely visit each site to assure that data submitted on the appropriate forms are in agreement with source documents at the sites. They will also verify that investigational products have been properly stored and accounted for, subject informed consent for study participation has been obtained and documented in the subject's progress notes, all essential documents required by GCP regulations are on file, and sites are conducting the study according to the research protocol. Any inconsistencies will be resolved, and any changes to the data forms will be made using established CSPCC procedures.

16.3 Data Entry, Processing and Analyses

Data from CRFs will be entered into a database at the CSPCC. When the study is completed and all data have been entered into the clinical database and the database has been checked by Quality Assurance and is locked, statistical analysis of the data will be performed by the CSPCC statisticians in accordance with the Analytical Plan section of this protocol. Periodically, during the investigation, CSPCC will also prepare summary reports of the data so that progress of the study can be monitored by NIDA and the DSMB. Data will also be submitted to the NIDA DPMC central data repository according to procedures specified in the study operations manual.

17 PUBLICATIONS OF THE STUDY RESULTS

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

18 SIGNATURES

NIDA REPRESENTATIVES

Typed Name	**Signature**	**Date**
Ahmed Elkashef, M.D. Co-Chairman	_____	_____
Elmer Yu, M.D., FASAM Co-Chairman	_____	_____
Ivan Montoya, M.D. Medical Monitor	_____	_____
Ann Anderson, M.D. NIDA Principal Investigator	_____	_____
Liza Gorgon, M.A. Project Director	_____	_____

INVESTIGATORS

I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol; deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment with the IRB approval. I also agree to report all information or data in accordance with the protocol, and in particular I agree to report any serious adverse events as defined in section 14.10 of this protocol.

Typed Name	**Signature**	**Date**
Elbert D. Glover, PhD	_____	_____
Robert M. Anthenelli, M.D.	_____	_____
Thomas Jackson, M.D.	_____	_____
Jill Williams, M.D.	_____	_____

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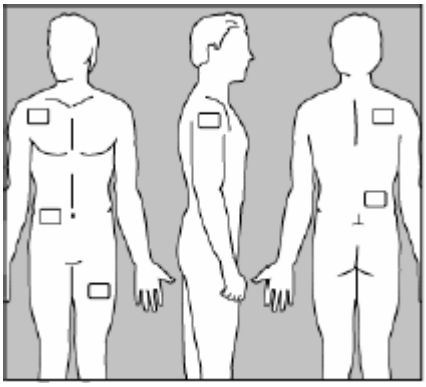
APPENDIX I: Instructions for Study Subjects Regarding Patch Application

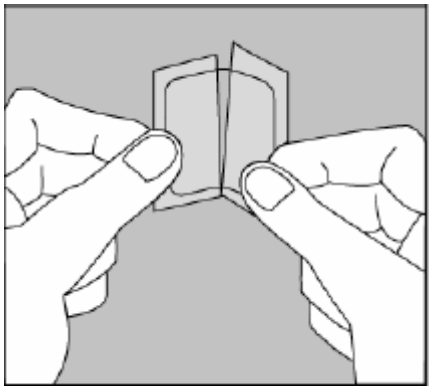
HOW TO APPLY THE STS/PLACEBO PATCH

1. Apply a new **STS/Placebo** patch every day (24hours).
2. **Wear only one STS/Placebo patch at a time.** Wear one **STS/Placebo** patch all the time until it is time to apply a new one.
3. Remove a used patch before applying a new one.
4. Change the patch at the same time each day.
5. Apply an **STS/Placebo** patch to dry, smooth skin on your upper chest or back (below the neck and above the waist), upper thigh or to the outer surface of the upper arm. Choose a new site each time you change your patch. Do not use the same site two days in a row. (See picture 1 for skin sites that may be used.)

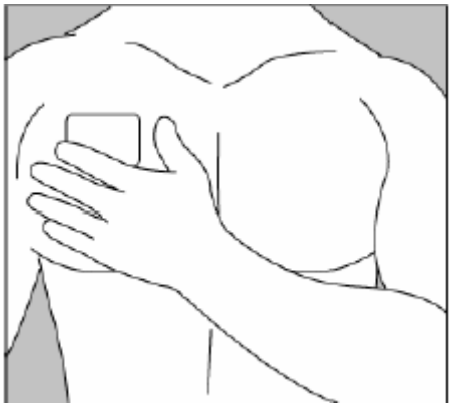


Picture 1. Skin sites for STS/Placebo patch (Do not use more than one patch at a time)

6. Apply an **STS/Placebo** patch to an area of skin that is not hairy, oily, irritated, broken, scarred or calloused. Do not place the patch where your clothing is tight, which could cause the patch to rub off.
7. After you have selected the site for your patch, wash the area gently and well with soap and warm water. Rinse until all soap is removed. Dry the area with a clean dry towel.
8. Just before you apply the patch, remove it from its sealed pouch. Do not keep or store the patch outside of the sealed pouch. **Never cut an STS/Placebo patch into smaller pieces to use.**
9. Remove half of the protective backing and throw it away. (See picture 2) Try not to touch the exposed side (sticky side) of the patch, because the medicine could come off on your fingers. With your fingertips, press the sticky side of the patch firmly against the skin site that was just washed and dried. Remove the second half of the protective liner and press the remaining sticky side firmly against your skin. Make sure that the patch is flat against the skin (there should be no bumps or folds in the patch) and is sticking securely. Be sure the edges are stuck to the skin surface. (See picture 3.)



Picture 2. Removing the protective backing from an STS/Placebo patch.



Picture 3. Applying an STS/Placebo patch

10. After you have applied the patch, wash your hands well with soap and water to remove any medicine that may have gotten on them. **Do not touch your eyes until after you have washed your hands.**
11. After 24 hours, remove the patch slowly and carefully to avoid damaging the skin. Do not touch the sticky side. As soon as you have removed the patch, fold it so that the sticky side sticks to itself.
12. Throw away the folded patch so that children and pets cannot reach it. This patch still contains some medicine and could harm a child or pet.
13. Gently wash the old application site with warm water and a mild soap to remove any sticky material (adhesive) that stays on your skin after removing the patch. A small amount of baby oil may also be used to remove any adhesive. You may need to use a medical adhesive removal pad that you can get from your pharmacist. Alcohol or other dissolving liquids such as nail polish remover may cause skin irritation and should not be used.
14. Wash your hands with soap and water.
15. If the patch becomes loose, press it back in place. If your **STS/Placebo** patch falls off, apply a new **STS/Placebo** patch to a new site and resume your normal schedule for changing patches.
16. If you forget to change your patch after 24 hours, remove the old patch, put on a new patch in a different area and continue to follow your original schedule.

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

A. GENERAL INSTRUCTIONS

1. Adverse events must be assessed at each visit starting when the subject has been enrolled in the study, recorded on Adverse Events CRF weekly, and reviewed weekly by a study physician.

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

3. Report the relatedness of the adverse event to investigational product administration according to the guidance in section C.

B. DEFINITIONS – SEVERITY OF EVENTS

Mild: Awareness of symptom, but easily tolerated.

Moderate: Discomfort enough to cause interference with usual activity.

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

C. DEFINITIONS – RELATEDNESS OF EVENTS

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

- ***Exposure:*** Is there evidence that the subject was actually exposed to the investigational product?

- ***Timing of the study investigational product:*** Did the AE/SAE follow in a reasonable temporal sequence from administration of the investigational product?

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

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

- ***Response to discontinuation*** of the investigational product.

Terms and definitions to be used in assessing the investigational product relationship to the AE/SAE are:

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

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

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

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

D. SPECIFIC INSTRUCTIONS – LABORATORY/ECG ADVERSE EVENT

Any clinically significant abnormal laboratory value or ECG reading that occurs during the course of the study is considered an adverse event. The adverse event may be the first manifestation or the worsening of a previous condition, whether or not considered to be investigational product related. For each adverse event, provide the information requested on date of test, severity, likelihood of a relationship to investigational product, and treatment required.

Laboratory values that can be abnormal should be specified as an increased or decreased test result (e.g., "increased blood glucose," "decreased blood potassium," "increased heart rate") or as a term that implies an abnormality (e.g., hyperglycemia, hypokalemia, or bradycardia). Any abnormal laboratory value that is considered not clinically significant will be recorded as such on the clinical laboratory report CRF along with a comment providing justification for that determination.

E. SERIOUS ADVERSE EVENT AND UNEXPECTED ADVERSE EVENT REPORTING

24-hour Reporting Requirements

Any serious adverse event, including death due to any cause, which occurs to any subject from the time of admission through discharge whether or not related to the investigational product, must be reported ***within 24 hours*** to the NIDA Project Director.

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

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

3-day Supporting Documentation Requirements

Written documentation for all SAEs must be received by the NIDA Project Director within 3 days of reporting the event. Required documents that must be submitted include the following:

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

Follow-Up of All Adverse Events/Serious Adverse Events

All adverse medical events must be followed until they are resolved, or until all attempts to determine the resolution of the adverse event/SAE are exhausted. This may require an extended inpatient period or a change in status from outpatient to inpatient. All treatments, outcomes and information regarding whether or not the subject was referred to their Primary Care Provider for additional follow-up must be recorded in the source document. All serious and unexpected adverse events occurring 30 days after administration of the last dose of investigational product must be reported. All ongoing adverse events at follow-up will be recorded and followed to resolution only if they are serious, or if the study physician assesses them to be clinically significant.

The investigator is required to provide the NIDA Project Director with all relevant follow-up information necessary to facilitate a thorough understanding of the event and judgment regarding the relationship to the investigational product.

Reporting to the FDA

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

- verbally within 7 calendar days if the SAE is unexpected (or, if expected, unusually serious or rarely seen), life-threatening or lethal, and at least possibly related to the investigational product, with a follow-up written report within an additional 8 calendar days;

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

- in an annual report in all other cases.

APPENDIX III: Procedure for Applying for a Certificate of Confidentiality

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

- if necessary to protect subjects' rights or welfare

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

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

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

This certificate is necessary for investigators to avoid being required to involuntarily disclose personally identifiable research information about individual study subjects. Under this statute:

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

Accordingly, this special privacy protection can be granted only to research (i.e., a systematic investigation, designed to develop or contribute to generalizable knowledge). It is granted only when the research is of a sensitive nature where the protection is judged necessary to achieve the research objectives.

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

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

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

or

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

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

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

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

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

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