16 APPENDICES

16.1 Study Information

16.1.1 Protocol and Protocol Amendments

Protocol Amendment 2 (17 June 2009)

Swedish Match AB
SWEDEN

Covance

3402 Kinsman Boulevard, Madison, Wisconsin 53704

STUDY PROTOCOL No. SM 08-01:

A CONTROLLED STUDY OF THE ABILITY OF A TRADITIONAL SWEDISH SMOKELESS TOBACCO PRODUCT ("SNUS") TO INCREASE THE QUIT RATE AMONG CIGARETTE SMOKERS WHO WISH TO STOP SMOKING

Principal Investigator:

Karl Fagerström, Ph. D.

LIST OF ADDRESSES

SPONSOR:	**SWEDISH MATCH AB** **ROSENLUNDSGATAN 36** **SE-118 85 STOCKHOLM** **SWEDEN**
SPONSOR'S RESPONSIBLE MEDICAL DIRECTOR:	**LARS E. RUTQVIST, M. D., PH. D.**
COVANCE STUDY MANAGER:	**JASMINE ROPERS** **3402 KINSMAN BOULEVARD** **MADISON, WI 53704**
COVANCE COORDINATOR:	**LEANNE MCGANN** **3402 KINSMAN BOULEVARD** **MADISON, WI 53704**
COVANCE DATA MANAGEMENT:	**CHRISTY SEAHOLM** **3402 KINSMAN BOULEVARD** **MADISON, WI 53704**
INSTITUTIONAL REVIEW BOARD (IRB):	**INDEPENDENT INVESTIGATIONAL REVIEW BOARD LLC.** **6738 WEST SUNRISE BLVD, SUITE 102** **PLANTATION, FLORIDA 33313**

SIGNATURE PAGE

SWEDISH MATCH APPROVAL:

Signature: _____ Date: 2013-01-28

Name: Lars E. Rutqvist, M.D., Ph. D
Vice President – Scientific Affairs
Swedish Match AB

COVANCE APPROVAL:

Signature: _____ Date: 1 Feb 2013

Name: [Name] Jasmine Ropers
[Department, Title]
Early Clinical Dev.
Project Manager

INVESTIGATOR PROTOCOL AGREEMENT PAGE

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by the sponsor.
- Not to implement any changes to the protocol without written agreement from the sponsor and prior review and written approval from the Institutional Review Board (IRB) except where necessary to eliminate an immediate hazard to subjects.
- That I am thoroughly familiar with the appropriate use of the study product, as described in this protocol and any other information provided by the sponsor including, but not limited to, the current protocol.
- That I am aware of, and will comply with, "good clinical practices" (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the study product and of their study-related duties and functions as described in the protocol.

Signature: _____ Date: 23 JUN 2009

Name (print): H Frank Farmer JR MD
Investigator

Site Number: 01

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Signature: _____ Date: 18 Jun 2009

Name (print): David C. Carter, MD
Investigator

Site Number: 02

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Signature: _____ Date: 22 JUNE 2009

Name (print): KEITH KLATT, MD
Investigator

Site Number: 03

INVESTIGATOR PROTOCOL AGREEMENT PAGE

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Signature: _____ Date: 10 JUN 2009

Name (print): _____
Investigator

Site Number: 05

INVESTIGATOR PROTOCOL AGREEMENT PAGE

I agree:

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Signature: Georgia Latham Date: 24 JUN 2009

Name (print): Georgia Latham, MD
Investigator

Site Number: _____

SYNOPSIS

Title Of Study	A controlled study of the ability of a traditional Swedish smokeless tobacco product ("snus") to increase the quit rate among cigarette smokers who wish to stop smoking
Investigator/Study Center	Multicenter; an estimated 6 sites in the United States
Phase Of Development	Phase III
Objectives	*Primary:* to examine the ability of a traditional Swedish low nitrosamine smokeless tobacco product ("snus") to increase the quit rate among cigarette smokers aged between 25-65 years who wish to stop smoking. This will be measured as continuous abstention from smoking during Week 6 through Week 28 documented by subjects and biologically confirmed by expired air carbon monoxide (CO) less than or equal to the cut off point of 8 ppm. The study is double-blind and placebo-controlled using a non-tobacco, non-nicotine snus-like product as placebo. *Secondary:* • To examine the extent of continuous complete abstention from smoking during Week 6 through Week 16 as well as point-prevalence rates of smoking cessation at week 16 and 28, biologically confirmed by expired air carbon monoxide (CO) less than or equal to 8 ppm • To examine the withdrawal symptoms and cravings of snus compared to placebo as measured by the Minnesota Nicotine Withdrawal Scale. Tobacco dependence will also be measured by the Fagerström Test for Nicotine Dependence. • To examine the safety of snus compared to placebo as measured by adverse events, change from baseline in body weight, oral cavity health, physical examinations, and vital sign measurements • To examine compliance to the allocated study product during the intervention period as well as use of OTC NRT and/or smokeless tobacco products during the follow-up • To examine smoking cessation measured as point-prevalence rates at week 16 and 28 (biologically confirmed by expired air carbon monoxide (CO) less than or equal to 8 ppm) among compliants defined as participants who used ≥ 1 sachets of their allocated study product per day during week 1 through 6.
Design	This is a multicenter, randomized, double-blind, placebo-controlled trial designed to examine the ability of snus to increase quit rates among cigarette smokers who wish to stop smoking. The study consists of four phases: pre-randomization screening (up to 2 weeks), Study product test period (4 weeks), Intervention Phase (12 weeks), and a Follow-Up Phase (12 weeks). Potential subjects will be invited to attend an Information Session and Screening visit for evaluation of eligibility. At randomization the participants will be randomly assigned in a 1:1 ratio to receive either snus or placebo snus for 16 weeks. During a 4-week test period the participants will be instructed to use the study products when they feel or expect an urge to smoke, initially without requirement of complete abstention from cigarettes. During the following 12-week intervention phase subjects are encouraged to completely stop smoking. If they feel an urge to smoke they are instructed to use their allocated study product instead of smoking. Participants will be continuously supplied with their allocated product. The participants will be instructed to cut down on product use during the last 3 weeks of the intervention to avoid a too abrupt ending of nicotine intake. After the intervention phase the subjects will be followed for an additional 12 weeks. Subjects will come to the clinic for a

	total of 6 visits, with 8 additional telephone visits. The maximum duration for individual subject participation (including pre-randomization screening) is 30 weeks.
Planned Sample Size	The primary endpoint is the quit rate among cigarette smokers who wish to stop smoking. The quit rate is examined between subjects randomized to snus as compared to subjects randomized to placebo. Assuming a rate of 12% in the placebo group and 27% in the active snus group, a two group continuity corrected χ^2 test with a 0.050 two-sided significance level will have 80% power to detect the difference between the active group proportion, p1, of 0.270 and the placebo group proportion, p2, of 0.0120 (odds ratio of 0.369) when the sample size in each group is 122 (total sample size of 244). The study is therefore intended to include a total of 250 participants. Treatment assignments will be balanced between active and placebo groups. The ITT population will be used for all statistical analyses of treatment efficacy.
Diagnosis And Key Subject Selection Criteria	*Key Inclusion Criteria*: • Subjects between 25 and 65 years of age, inclusive, who smoke > 9 cigarettes per day (average daily consumption during past month) • The subject has smoked daily >1 year • Subjects motivated to quit smoking using a smokeless tobacco product • Subjects in good general health *Key Exclusion Criteria:* • Use of smokeless tobacco during past 6 months or subjects unable to refrain from NRT during the study. • Current oral condition that could potentially be made worse by study treatment • Use of any type of pharmaceutical (including some psychotropics, e.g., wellbutrin) or other products for smoking cessation within the past 3 months • History of clinically significant renal, hepatic, neurological, or chronic pulmonary disease that in the judgment of the investigator precludes participation • History of significant cardiovascular disease, including myocardial infarction within the last 3 months, significant cardiac arrhythmias, or poorly controlled hypertension that in the judgment of the investigator precludes participation • History of alcohol or substance abuse other than cigarette smoking within the past year
Treatments	• Traditional, low nitrosamine Swedish snus in 0.5 or 1.0 g sachets *ad libitum* • Matching placebo (without tobacco or nicotine)
Main Outcome Parameters	• Continuous rates of smoking cessation by self-report and confirmed by expired air CO less than or equal to 8 ppm • Point-prevalence smoking cessation rates (during preceding week) confirmed by expired air CO less than or equal to 8 ppm • Minnesota Nicotine Withdrawal Scale • Fagerström Test for Nicotine Dependence
Main Safety Parameters	• Adverse events • Vital sign measurements, including body weight • Oral cavity health • Physical examinations
Statistical Methods	The primary outcome measure will be continuous complete smoking cessation from Week 6 through Week 28 (at all measurement points/visits) as reported by subjects and corroborated by objective verification using the CO value from exhaled air of less than 8 ppm at all relevant visits. Further exploratory analysis will be performed to assess the relationship between various baseline characteristics (age, gender, etc.) and the defined endpoints. For secondary outcome endpoints, point prevalence of smoke-free subjects at

	Week 16 and Week 28 will be summarized as the rate during the preceding week (self-reported and confirmed by CO measurement). Withdrawal symptoms measured by the Minnesota Nicotine Withdrawal Scale scores will be calculated and summarized by treatment group and overall. The analyses will be done both including all randomized subjects as well as restricted to those who actually managed to stop smoking The differences in the average daily symptom score between the two treatment groups will be analyzed. In addition, "Craving" will be analyzed separately. CO in exhaled air levels will be summarized at Baseline and subsequent applicable visits and the change from baseline will be tabulated by overall and by the two treatment groups. The difference in the change from baseline between the two treatment groups will be analyzed. Scores on the Fagerström Nicotine dependence will be calculated at Baseline, Week 16, and Week 28 and will be summarized at each time point. The change from the baseline in the Fagerström score will be tabulated for the two treatment group and for overall population. Incidence of SAE:s, discontinuation from the study because of an AE, and compliance to allocated study product will be analyzed by allocated treatment. Refer to Section 4.8 for analysis of safety variables.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
CFR	Code of Federal Regulations
CO	carbon monoxide
CRF	case report form
CRO	contract research organization
GCP	good clinical practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
IRB	Institutional Review Board
ITT	intention-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
NRT	nicotine replacement therapy
ppm	parts per million
SAE	serious adverse event
ST	smokeless tobacco
TD	target day
US	United States
WHO	World Health Organization

INTRODUCTION

BACKGROUND AND RATIONALE

Tobacco, which is usually smoked, has well documented detrimental effects on health. Before the mass production of cigarettes, it was common to use tobacco in non-smoked forms, such as a dry, fine-grained powder for nasal sniffing or moist grained tobacco for oral use usually held between check and upper gum. Smokeless tobacco (ST) is still a common form of tobacco used in countries such as India, Sudan, Sweden, and the United States (US).

Smokeless tobacco has been classified by the World Health Organization (WHO) as a carcinogen; however ST products vary widely in tobacco used, curing, production (pasteurization or fermentation), additives, and storage. Because ST is not burned and carcinogenic pyrolysis by-products are not formed, ST has been advocated by many health protection institutions and scientists as a possible harm reduction tool.[1-4]. While the Indian and Sudanese products (e.g., Guthka and Tombak) have been found to be carcinogenic, evidence for the much researched Swedish ST product commonly called "snus" has not been definitive.

Swedish "snus" is different in many significant respects from American moist snuff. It is manufactured using a heat-treatment technique which renders the finished product virtually sterile. This technique has contributed to the fact that "snus" historically and today have much lower levels of potentially carcinogenic nitrosamines than American moist snuff which is a fermented product. Swedish Match has also introduced an industrial standard for its snus products (GothiaTek) which includes limits for potentially toxic compounds. The guiding principle for these limits has been those set for common food-stuffs.

Traditionally "snus" is used in the upper sulcus (under the upper lip) which reduces salivation so there is no need to spit while using the product.

ORAL CANCER

The use of ST use has been associated with oral cancer for many decades, and there is a strong, widespread belief in this association. However, a recent review concluded that the use of chewing tobacco and moist snuff were associated with only minimally elevated risks, while other types of ST conferred higher risks.[5] Two of seven studies reviewed tested Swedish snus and demonstrated no oral cancer risk.[6,7] These results formed the basis for the European Union's decision in the year 2000 to remove the cancer warning from snus products. In a recent study, 1,115 snus users were followed for 29 years. Snus-induced lesions were common but oral cancer rarely occurred at the site of these lesions ;[8] there are, however, some anecdotal reports of oral cancer in long term snus users. [9]

CARDIOVASCULAR AND OTHER DISEASE

Epidemiological studies have examined the role of snus in cardiovascular disease (five studies), myocardial infarction (four studies), and stroke (one study). In three of the four studies on myocardial infarction, no increased risk was seen in snus users.[10-12] In the fourth study a significant increase in risk was noted but it was lower than that of smoking.[13] There was no association noted with use of snus and the occurrence of stroke.[14]

Two studies have examined the impact of snus as a risk factor for adult-onset diabetes, as some have hypothesised that ST could change glucose tolerance or insulin concentrations. One of

these studies [15] found that snus users had a slightly elevated risk while the other reported that the risk of diabetes was not increased.[16]

OTHER CANCERS

No association with the use of snus and gastrointestinal or urinary tract cancer has been found.[17]

RESPIRATORY DISEASE

As there is no plausible causal mechanism whereby snus could cause respiratory disease, there are no studies available that have examined the effect snus has on respiratory disease.

PREGNANCY

One study has examined the effect of snus on pregnancy, and found snus was associated with increased risk of preterm delivery and preeclampsia.[18] Given that animal studies have implicated nicotine as a cause of some of the widely known adverse effects of tobacco exposure during pregnancy it follows that snus use during pregnancy is likely to incur some of the risks associated with smoking.

EPIDEMIOLOGY OF SNUS USE IN SWEDEN

In 2005, 22% of adult males in Sweden were daily snus users and 13% smoked cigarettes.[19] For women the figures were very different, 4% used snus and 17% smoked. Among young boys (age 15), 14% were daily or almost daily users of snus and 5% smoked. For girls the figures were 3% and 13 %.[19]

It is increasingly evident that snus can replace cigarettes among former smokers. In 2001, 47% of current snus users were found to have been smokers previously, according to a study commissioned by Swedish Match.[20] In another study commissioned by The Swedish Cancer Society and Pharmacia Corporation,[21] 1,000 Swedish ex-smokers were asked about their quitting methods. Fifty percent had not used any help to stop, 33% had replaced their cigarettes with snus, and 17% used nicotine replacement therapy (NRT) during some quit attempt. Twenty-eight percent of men reported having used snus during their last quit attempt. Ramström[22] found that among males using a product on their last quit attempt, 55% used snus. For females the figure was 15%. The rate of complete cigarette replacement with use of snus was 65% for males and 52% for females. For nicotine gum and patch, non-smoking rates were 46% and 32% for males and 37% and 30% for females, respectively. That many Swedish smokers have switched completely to snus is also supported by data from local studies in northern and southern parts of Sweden.[23, 24]

In Sweden, snus is used at least as often as NRT at quit attempts and the rates of total cigarette replacement with snus are at least as high as the smoking cessation rates seen with NRT. Ramström and Foulds recently found that 55% of men attempting to completely replace cigarettes had used snus. A total of 26% used NRT in their latest quit attempt.[25] In a cross-sectional study in southern Sweden, 30% of men and 9% of women had used snus at attempts to replace cigarettes occurring between 2000 and 2004.[26]. In a recent study on Swedish twins it was found that snus use was strongly linked with complete cigarette replacement, particularly among more dependent cigarette smokers.[27]

Interpreting data on the acceptability and safety of snus to replace cigarettes is unclear to most tobacco control advocates, who have voiced fears that promotion of use of ST to replace cigarettes may be harmful because snus could be a “gateway” to later smoking as a more effective tool for nicotine delivery.[28-32] Several studies from Sweden [22, 25, 29] and the US [30, 31]

however show that early ST use does not increase, but rather prevents later cigarette smoking. A few studies have found the opposite effect.[32, 33]

SNUS AND NICOTINE YIELD

Use of NRT to replace cigarettes typically has an under-dosing effect that results in low blood nicotine concentrations due to the low nicotine delivery of several products. NRT is also associated with poor compliance, in part because they are not very consumer friendly. Generally NRT users have 50 to 80% of the blood nicotine concentrations compared to smokers. ST delivers nicotine concentrations much closer to those of the cigarette than NRT.[34] In fact, Swedish snus can deliver blood levels similar to that of cigarettes although the nicotine absorption is slower and there is no "bolus" that results from inhalation of nicotine.[35] In a pharmacokinetic study, administration of nicotine gum (2 mg administered hourly for 12 hours) was compared with snus products in two sachet sizes: 0.5 g and 1.0 g. After 12 hours, the blood nicotine concentrations were 11 ng/ml with a 0.5 g snus sachet, 13 ng/ml for nicotine gum 2 mg, and 21-29 ng/ml with 1.0 g sachets of different snus brands commonly used in Sweden. [36]

SMOKELESS TOBACCO AS A SUBSTITUTE FOR CIGARETTES

Data previously described have spurred an interest in testing ST as a substitute for cigarettes among smokers interested in an alternative, smokeless tobacco product[37] including the Task Force of the European Respiratory Society [38]. The first smoking cessation study with ST, although uncontrolled, obtained a one year smoking cessation rate of 35% in heavily dependent smokers.[39] In a more recent study with 50 head and neck cancer patients, smoking cessation advice was repeatedly given by nurses at radiation therapy visits. Nicotine patches were chosen by 89% and snus was chosen by 50% of these smokers, often in combination. At 1 year, 68% were carbon monoxide (CO)-verified smokefree.[40]. Although both of these studies produced quit rates that are much higher than those typically seen in formal smoking cessation studies,[49] they were uncontrolled studies.

ETHICAL CONSIDERATIONS

Cigarette smoking is a significant public health problem in most countries. The number of smokers in the U. S. has not decreased substantially during the past 10-15 years. The addictive nature of cigarette smoking and the limited success of traditional anti-smoking measures represent a significant challenge to public health. In conclusion, there is a great need for further research on effective strategies for smoking cessation.

The current trial aims to determine the acceptability of Swedish snus among adult U.S. smokers, and to evaluate if use of snus can increase quit rates among cigarette smokers who want to quit smoking. The trial thus has considerable interest both from a scientific and public health point of view.

It might be viewed as problematic from an ethical point of view that the study does not entail treatment with products that have been demonstrated to be effective to achieve smoking cessation in the context of controlled clinical trials, such as, NRT, bupropion or varenicline. However, there are extensive epidemiological data from Sweden suggesting that snus has been used by many smokers to quit smoking and that it might even be more effective than NRT in achieving complete, long-term smoking cessation. All participants will also be informed about all available, evidence-based methods for smoking cessation.

There are extensive data from epidemiological studies demonstrating that smokeless tobacco, particularly low-nitrosamine Swedish snus, is associated with dramatically reduced health risks compared to cigarette smoking. The risk profile with snus thus appears closer to that of no tobacco use, than to cigarette smoking. So, switching from cigarettes to snus, albeit another tobacco product can be expected to be associated with significantly reduced health risks. Moreover, the trial design implies exposure to snus during only 16 weeks.

The addiction to cigarettes may not entirely be a result of the physical addiction to nicotine, but also in part a psychological phenomenon related to the stimuli and attributes of cigarette smoking. It is therefore essential to include a placebo control arm in studies of smoking cessation, and to conduct such trials with a randomized, double-blind technique, even though such study features may be viewed as problematic from an ethical point of view.

The clinical tests in the trial involve invasive methods (blood sampling), but such tests are part of routine medical care and are associated with minimal risks. Individual test results will be treated confidentially and will only be revealed to the study participants to minimize problems related to personal integrity. All participants will provide written informed consent to participate in the trial.

The participants will receive economic compensation for their participation in the study. However, the compensation is moderate and does not exceed what is typical in studies of this complexity so there is no reason to assume that the compensation *per se* will act as a pressure on potential participants to accept participation or on participants to continue in the trial should they wish to terminate their participation prematurely.Conduct of the study will be approved by an appropriately constituted institutional review board (IRB) or independent ethics committee (IEC). No study products will be shipped to a site until written IRB/IEC authorization has been obtained.

STUDY PURPOSE

The current study will be the first randomized, placebo-controlled, double-blind clinical trial to test if use of a low-nitrosamine, Swedish snus product can increase the smoking cessation rate among cigarette smokers who wish to quit smoking.

STUDY OBJECTIVES

PRIMARY OBJECTIVE

The primary objective of this study is to examine if a traditional Swedish low-nitrosamine smokeless tobacco product ("snus") compared to placebo can increase the quit rate among cigarette smokers who wish to stop smoking measured as continuous, complete smoking cessation during Week 6 through Week 28 documented by subjects and biologically confirmed by expired air CO less than or equal to 8 ppm.

SECONDARY OBJECTIVES

The secondary objectives of this study are:

- To examine continuous complete quit rates (biologically confirmed) during Week 6 through Week 16,

- To examine point-prevalence (preceding week) quit rates (biologically confirmed) at the clinical visits during Week 10, 16, and 28

- To examine the withdrawal symptoms and cravings of snus compared to placebo as measured by the Minnesota Nicotine Withdrawal Scale at Weeks 6, 10, 16, and 28. Additionally, tobacco dependence will be measured by the Fagerström Test for Nicotine Dependence at Week 16 and 28.

- To examine the safety of snus compared to placebo as measured by adverse events, change from baseline in body weight, oral cavity health, physical examinations, and vital sign measurements.

- To collect blood samples at baseline and at week 6, 16, and 28 which will be used for exploratory analyses of nicotine metabolites and biomarkers of exposure and/or disease related to tobacco use.

INVESTIGATIONAL PLAN

DESCRIPTION OF OVERALL STUDY DESIGN AND PLAN

This is a multicenter, randomized, double-blind, placebo-controlled trial designed to examine the ability of snus compared to placebo to increase the quit rate among cigarette smokers who wish to stop smoking. A total of 250 subjects who are habitual cigarette smokers aged 25 through 65 years will be randomly assigned to be offered tobacco-based, nicotine-containing snus or matching placebo snus (without tobacco and nicotine).

The study consists of three phases: Screening (up to 2 weeks), Study Product Test Period (4 weeks), Intervention Phase (12 weeks), and a Follow-Up Phase (12 weeks).

Potential subjects will be invited to the clinic to attend an Information Session and Screening visit for further evaluation of eligibility.

During the Baseline Visit, subjects will be randomly assigned in a 1:1 ratio to receive either snus or placebo. Over the next 4 weeks, subjects will be acclimatized to the allocated product and will be instructed to try to refrain from cigarettes through the use of the product when they feel or expect an urge to smoke. If subjects still feel an urge to smoke after c. 15-20 minutes, they may do so. Subjects will be encouraged to gradually substitute as many cigarettes as possible and to refrain from all cigarettes at the latest by the first day of Week 5 (or sooner if they can manage to do so). Use of study product will continue for a total of 12 weeks. The participants will be instructed to cut down on product use during the last 3 weeks of the intervention to avoid a too abrupt ending of nicotine intake.

Cigarette replacement will be assessed by self-report and exhaled CO. Subjects will be provided with an education booklet on the hazards of cigarettes (the National Cancer Institute's "Cleaning the Air" booklet) and will be provided with brief (< 10 minutes) counseling at each visit following Agency for Healthcare Research and Quality guidelines (Appendix 4).

After the intervention phase all subjects will be followed-up for an additional 12 weeks. Subjects will come to the clinic for a total of 6 visits, with 8 additional telephone visits. The

maximum duration for individual subject participation is 30 weeks, including the 2 week screening phase.

The amount of nicotine needed to prevent withdrawal symptoms among cigarette smokers varies considerably. The amount of study product used by subjects is therefore also expected to vary and is dependent on the extent to which the products actually replace cigarettes. Subjects will therefore be instructed to use the products *ad libitum*, and will be informed that one 1.0 g snus sachet typically can replace one cigarette. Subjects will be instructed to use at least 10 1.0 g sachets per day (or 20 sachets if the subject has elected to use the 0.5 g sachets).

Recommended maximum number of 1.0 g sachets per day is 24. However, among those who are heavy smokers (≥ 15-20 cigarettes per day), or who are strongly nicotine dependent as evidenced by a Fagerström score of 7 or higher at baseline, and who try to replace all cigarettes with study product, total number of sachets needed per day may be higher

BIOMARKER BLOOD TESTS

In addition to the lab tests used to assess eligibility, blood will be drawn for biomarkers on all participants during screening, and at weeks 6, 16, and 28. The total amount of blood drawn on each occasion will be approximately 40 ml with equal amounts of serum and plasma samples. The research samples will be used for exploratory analyses of nicotine metabolites and biomarkers of exposure and/or disease related to use of tobacco.

SCREENING (UP TO 2 WEEKS, WEEK -2 TO BASELINE)

The Screening Phase will consist of an Information Session and Screening Visit (which may be scheduled consecutively at one occasion at the discretion of the Investigator). During the Information Session potential subjects will receive information on the health risks associated with the range of nicotine products including cigarettes, non-snus smokeless, snus and NRT, and their relative harm. Possible alternative treatments will also be outlined. The physiological effects of nicotine will be described, and an account given of experience with Swedish snus, including potential health risks associated with different types of smokeless tobacco products.

The Screening Visit will include an explanation of the purpose and nature of the study and subjects will provide voluntary written informed consent. A complete medical history will be taken (including assessment of smoking status; i.e., age of initiation of daily smoking; average number of cigarettes smoked per day during the past year; history of previous quit attempts; desire to quit cigarettes & smoking; history of previous use of NRT, other pharmaceutical, or other smoking cessation aids, history of previous ST use), along with a physical examination, blood tests, ECG (supine position for at least 5 minutes), oral cavity examination, and vital sign assessment. Subjects will also be provided with an education booklet (the National Cancer Institute's "Cleaning the Air" booklet) and will be provided with brief (<10 minutes) counseling following Agency for Healthcare Research and Quality guidelines.

STUDY PRODUCT TEST PERIOD (BASELINE THROUGH WEEK 4)

Baseline Visit

Qualifying subjects will return to the clinic for a Baseline assessment and random allocation to study product (snus or placebo). Assessments will be completed as outlined in *Schedule of Events).*

Subjects will be given a diary to record their use of study product consumption, including number and size of sachets used, and number of cigarettes smoked, if any.

Usage of study products including how it is placed in the mouth will be demonstrated to the participants.

Week 1 through Week 4

During this phase, subjects will undergo acclimatization to treatment and will be instructed to try to refrain from cigarettes by the use of allocated study product when they feel an urge to smoke. Each subject will be provided with blinded study products of two sachet sizes. Preferred sachet size and the number of sachets consumed per day are determined by the participants themselves and will vary based on individual preferences and smoking habits. One 1.0-gram sachet delivers roughly the same amount of nicotine as one cigarette. If subjects still feel an urge to smoke after c. 15-20 minutes, they can do so provided sachets of study product are removed to avoid nicotine overdosage.

Subjects will be encouraged to gradually substitute as many cigarettes as possible with the study products. The recommended number of 1.0 g sachets to be used per day is 10-24 unless the subject habitually have smoked >15-20 cigarettes per day, or are highly nicotine dependent as evidenced by a score on the Fagerström scale of 7 or more, and attempts to replace all cigarettes with study products. Among such individuals the number of sachets needed per day may be higher than 24. The goal is to replace all cigarettes completely no later than the first day of Week 5 (start of the Intervention Phase).

Subjects will also be instructed that no other source of nicotine (other than cigarettes) or study product should be used during the Test Period, and that NRT or any other pharmaceutical smoking cessation aid is not allowed.

Each week during this period sites will contact each subject by telephone to monitor progress and to assess compliance and adverse events. Brief behavioral counseling will also be included. Subjects will be reminded about the complete switch from cigarettes no later than the first day of Week 5.

INTERVENTION PHASE (WEEK 5 THROUGH WEEK 16)

Clinic visits will occur at Week 6, Week 10, and 16. These visits will include monitoring of each subjects progress (including self-reported smoking status and measurement of CO in exhaled air), brief behavioral counseling, and vital sign assessment. Clinic visits must be performed +/- 3 days from the target date of the visit. Other assessments will be completed as outlined in *Schedule of Events.*

At the Week 6 and 10 visits, subjects will receive continued supply of study product in their preferred size. Subjects will be provided with a sufficient quantity of the study product to last until the next clinic visit, or to the end of the Intervention Phase.

Telephone contacts will be completed at Weeks 8 and 13 to monitor each participant's progress, to assess compliance and any adverse events, and to provide brief behavioral counseling. At the week 13 contact, the participants will be instructed to cut down on product use during the last 3 weeks of the intervention to avoid a too abrupt ending of nicotine intake.

At Week 16, subjects will return to the clinic to assess smoking cessation (based on self-report and measurement of CO in exhaled air), study product use and compliance, vital sign

assessment, and assessment of adverse events. Other assessments will be completed as outlined in the *Schedule of Events.*

FOLLOW-UP PHASE (WEEK 17 THROUGH WEEK 28)

All subjects will be encouraged to continue in the study for follow-up independent of smoking status. Use of study product will be discontinued. Telephone contacts will occur during Weeks 20 and 24, with a final clinic visit at Week 28. Assessments at the Week 28 visit will include review of subjects' self-reported tobacco status relative to the use of cigarettes, verified by CO in exhaled air. Other assessments as described on the *Schedule of Events* will also be completed at the final visit.

If a subject has managed to quit cigarettes during the *Intervention Phase* with the help of their allocated study product and at the 16 wk visit or anytime thereafter there is an imminent danger of smoking relapse during the *Follow-Up Phase*, that subject should be informed that use of NRT or a smokeless tobacco product is a better option in terms of health risks than a smoking relapse.

If a subject discontinues participation during the *Intervention Phase*, the procedures that would be done at Week 16 will be completed at the time of discontinuation. If a subject discontinues participation during the *Follow-Up Phase*, the procedures that would be done at Week 28 will be completed at the time of discontinuation.

SELECTION OF STUDY POPULATION

Subjects will be identified from clinic data bases and/or through advertisements. A total of 250 male and female smokers aged between 25 and 65 years who are otherwise healthy will be eligible for study entry. It is anticipated that approximately 6 sites in the United States with sufficient experience and access to the desired subject population will participate.

INCLUSION CRITERIA

Subjects meeting all of the following inclusion criteria at screening should be considered for admission to the study:

1. The subject is male or female, between 25 and 65 years of age, inclusive. If female, the subject has a negative urine pregnancy test and is not lactating, or has not been of childbearing potential for at least 3 months prior to use of study product. To be considered to be not of childbearing potential, the subject must be postmenopausal for at least 2 years; have had a hysterectomy or bilateral tubal ligation, or be proven to be otherwise incapable of pregnancy. If of childbearing potential, the subject must have been practicing one of the following methods of contraception consistently for at least 1 month prior to study entry and agree to continue practicing it during the study: hormonal contraceptives, intrauterine device, spermicide and barrier, spouse/partner sterility; or is practicing abstinence and agrees to continue abstinence or to start an acceptable method of contraception from the above list if sexual activity commences.
2. The subject smokes > 9 cigarettes per day (average daily consumption during past month)
3. The subject has smoked daily for > 1 year.
4. The subject is motivated to quit smoking with the help of a smokeless tobacco alternative

5. The subject is in good general health as evidenced by medical history, physical examination, routine blood chemistry (Hb, total WBC, transaminases, creatinine, electrolytes) , and an ECG
6. The subject practices, by self-report, oral hygiene (including brushing teeth once per day on average and having dental check-ups).
7. The subject is able and willing to provide written informed consent.
8. The subject agrees to comply with the requirements of the protocol and complete study measures.
9. The subject has stable residence and telephone.

EXCLUSION CRITERIA

Subjects meeting any of the following exclusion criteria at screening will not be enrolled in the study.

1. The subject is a current user of ST (defined as daily usage during more than 1 week within past 6 months) or is unable to refrain from NRT or any other non-protocol treatment during the study. Use of pipes, cigars, cigarillos, snuff, and chewing tobacco is also prohibited during the study.
2. The subject is a female who is pregnant or lactating.
3. The subject has oral conditions that could potentially be made worse by use of study product, for instance, exposed dental cervices in the upper sulcus.
4. The subject has used any type of pharmaceutical (including some psychotropics, e.g., wellbutrin) or other products for smoking cessation within the past 3 months.
5. The subject has a history of clinically significant renal, hepatic, neurological, or chronic pulmonary disease that in the judgment of the investigator precludes participation
6. The subject has a history of cardiovascular disease, including myocardial infarction within the last 3 months, significant cardiac arrhythmias, or poorly controlled hypertension (defined as a diastolic pressure of more than 90 mm Hg or a systolic pressure of more than 140 mm Hg) that in the judgment of the investigator precludes participation
7. The subject has a history of alcohol or substance abuse or dependence other than cigarette smoking within the past year
8. Use of any illicit drug or smoked marijuana in the last 3 months.
9. The subject is unwilling to be randomized into active or placebo conditions, or be available for follow-up assessments.
10. The subject resides in a household where another member is currently participating in the study.

REMOVAL OF SUBJECTS FROM THERAPY OR ASSESSMENT

A subject will be considered to have completed the study when he completes the final assessment visit at Week 28. If a subject discontinues study procedures at any time after entering the study, the Investigator will make every effort to contact the subject and complete the termination case report form (CRF).

A termination case report form (CRF) page should be completed for every randomized subject, whether or not the subject completed the study. The reason for any early discontinuation should be indicated on this form. The primary reason for a subject withdrawing prematurely should be selected from the following standard categories of early termination:

- *Protocol Violation*: The subject's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements Every effort should be made to establish contact with participants who fail to show up for scheduled visits to determine the cause of the non-compliance.
- *Lost to Follow-Up*: The subject stopped coming for visits and study personnel were unable to contact the subject.
- *Withdrawal of consent*: The subject desired to withdraw from further participation in the study in the absence of an investigator-determined medical need to withdraw. If the subject gave a reason for withdrawing, it should be recorded in the CRF.
- *Adverse Event (Adverse Reaction)*: Clinical events occurred that in the medical judgment of the Investigator for the best interest of the subject are grounds for discontinuation. This includes serious and nonserious adverse events regardless of relation to study product. Clinical events that are reported by the subject and result in the subject choosing to withdraw from further participation are recorded as a discontinuation due to adverse event (not withdrawal of consent).
- *Death:* The subject died.
- *Other*: The subject was terminated for a reason other than those listed above

INTERVENTIONS

DESCRIPTION OF STUDY PRODUCTS

For comprehensive information about the study products, refer to protocol Appendix 1. Snus and matching placebo sachets will be provided to the study sites by the sponsor or its representative as white sachets weighing 0.5 or 1.0 g. Placebo sachets will include herbal material with flavoring without tobacco and nicotine. Additional details are provided in Table 1 below.

TABLE 1: DETAILS OF STUDY TREATMENTS

	Preparations to be Administered	
	Snus	**Placebo**
Active Substance	Nicotine	None
Manufacturer	Swedish Match	Swedish Match
Dose(s)	Ad libitum	Ad libitum
Route	Oral	Oral
Sachet Weight	0.5 mg and 1.0 mg	0.5 mg and 1.0 mg

DOSAGE, ADMINISTRATION, AND BLINDING

Subjects will be randomly assigned to receive snus or matching placebo in a 1:1 ratio at the Baseline Visit. Each subject will be given products at baseline, and at the clinic visits at Week 6 and 10. The amount of products given at each occasion is estimated to cover the need of a smoker who completely switches from cigarettes to snus during the entire *Intervention Phase*.

The sachets are placed under the upper lip (upper sulcus) which reduces salivation compared to placement in the lower part of the mouth. This means that there no need to spit while using the products. As the products have a relatively high pH, subjects may initially feel a slight

burning sensation at the location of the sachet. This sensation is alleviated if the location of the sachet in the upper sulcus is changed.

The number of sachets consumed per day is determined by the participants themselves and will vary based on smoking habits. The amount of nicotine needed to prevent withdrawal symptoms among smokers varies considerably, therefore the amount of study product used by subjects is expected to vary and is dependent on the extent to which the products actually can replace cigarettes. Subjects will be instructed to use the products *ad libitum* with a recommended maximum number of 24 large sachets per day (recommended maximum number is 30 for those who smoke more than 15-20 cigarettes per day or have a Fagerström score of 7 or higher), and will be informed that one 1.0 g snus sachet typically can replace one cigarette. Recommended maximum number of small sachets is double that of large sachets, that is, 48-60 per day. When subjects feel or expect an urge to smoke, they will be instructed to try their allocated study product for at least 15-20 minutes. Subjects will also be informed that nicotine overdose may occur with excessive use of the product, particularly with concomitant smoking, but those symptoms (typically nausea, tachycardia, etc.) quickly subside upon cessation of smoking or use of the product. The average snus consumption among snus users in Sweden who do not smoke is about 10 to 15 large sachets per day.

During the *Study Product Test Period* subjects will be instructed to replace as many cigarettes as possible with their allocated study product in order to achieve smoking cessation at the latest by the first day of week 5. The participants will be instructed to cut down on product use during week 14-16 to avoid a too abrupt ending of nicotine intake. Use of study product will be discontinued at the Week 16 visit.

If a subject has managed to quit cigarettes with the help of their allocated study product and there is an imminent danger of smoking relapse during the *Follow-Up Phase*, that subject should be informed that use of NRT or a smokeless tobacco product is a better option in terms of health risks than a smoking relapse.

UNBLINDING

Only in case of an emergency, when knowledge of the study product is essential for the clinical management or welfare of the subject, the investigator may unblind a subject's treatment assignment. If the blind is broken for any other reason, the investigator must notify the sponsor's medical representative immediately, and discontinue the subject from study product. If the investigator breaks the blind for a subject, the data and reason must be recorded in the CRF.

METHOD OF RANDOM ASSIGNMENT

Subjects will be randomly assigned chronologically in the order in which they are enrolled into the study stratified by treatment center and will be assigned a unique study number. The random sequence determining the allocation will be generated using a computer-based algorithm based on the permuted block technique with a block size of six.

Each participating center will be provided with four product "bins" that are uniquely numbered. Two bins at each center will include placebo products (large and small sachets), and two bins will include snus products. Each unique study number will be linked to bin numbers from which the participant shall receive study products (placebo or snus).

The trialist will document which products were provided to each participant and study product labeling will ensure that it can be verified that correct products according to the random

allocation were issued to each participant.

PRODUCT PACKAGING AND LABELING

Study products will be supplied in "bins" (=for each study site uniquely numbered card-board boxes). Products are routinely packed in stacks of ten boxes ("logs"). All products will be labeled according to applicable laws and regulations and ICH-GCP Guidelines.

STORAGE AND HANDLING OF STUDY PRODUCTS

Receipt of product supplies

Product supplies will not be provided to the Investigator until Institutional Review Board (IRB) approval has been obtained.

The Investigator or his/her designees will inventory all supply shipments upon receipt, acknowledge possession by signing the certificate of delivery, and return the form to the sponsor or its representative.

Storage

Study products should be kept refrigerated at 2-8 centigrades in a securely locked or in a limited access, secure area. Neither the Investigator nor designees may provide the study product to individuals not participating in this protocol.

Return of study product

Throughout the study, the sponsor or designee will make arrangements for the Investigator to return all unused study product to the sponsor or its representative. This shipment will be documented on the product accountability form. The Investigator must provide an explanation for any missing study product.

Responsibilities

In addition to responsibilities upon receipt previously outlined, the Investigator or his/her designees must maintain an inventory record of administered products to assure regulatory authorities and the sponsor that the investigational study product will not be administered to any person who is not participating in this study under the terms and conditions set forth in this protocol.

The inventory record will include:

- Name of the sponsor
- Protocol name and number
- Product name and description
- Study site and name of the Investigator
- Number of snus boxes dispensed and study participant identifier to whom study product was dispensed
- Product balance
- Name and signature of the qualified individual dispensing study product

Representatives of the sponsor will review these records.

Compliance

Self-reported number of cigarettes smoked daily and snus sachets used per day will be recorded in the subject's diary. The recommended number of 1.0 g and 0.5 g sachets to be used per day is 10-30 and 20-60, respectively.

PRIOR AND CONCOMITANT ILLNESSES AND TREATMENTS

Prior and concomitant illnesses

As this study is to be performed in healthy subjects, there should be no significant concomitant illnesses at the time of entry into the study. Illnesses first occurring or detected during the study, or a significant deterioration of a pre-existing condition will be documented as adverse events in the CRF. All data on medical history etc. collected as part of this trial will be based on the subject's self-reported information.

Prior and concomitant medications

Any concomitant medication is acceptable except NRT or other treatments used for smoking cessation, for instance, bupropion or varenicline. Other psychotropics (e.g., antidepressants other than bupropion) should also not be used. If a subject has used such treatments previously, they must be discontinued at least 3 months prior to randomization.

Use of any other product containing tobacco (e.g., pipes, cigars, cigarillos, snuff, and chewing tobacco) is prohibited throughout the study.

SUBJECT EVENTS

SCHEDULE OF EVENTS

The procedures to be performed throughout the study are outlined in Table 2, Schedule of Events, and the text following.

Table 2. Schedule of Events

	Screening	Baseline	Study Product Test Period (Week 1-4)				Intervention Phase (Week 5-16)					Follow-Up (Week 17-28)		
Study Week	-2, -1	0	1	2	3	4	6	8	10	13	16	20	24	28
Clinical Visit[a]	X	X					X		X		X[e]			X[e]
Telephone Contact[a]			X	X	X	X		X		X[d]		X	X	
Visit/Contact Window			± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 1 wk	± 1 wk	± 1 wk	± 1 wk
Interventions/Evaluations:														
Information Session	X													
Written Informed Consent	X													
Assessment of Eligibility	X	X												
Medical and Smoking History, ECG	X													
Physical & Oral[c] Examination	X[b]										X			X
Biomarkers (blood tests)	X						X				X			X
Screening tests (urine & blood tests)	X													
Vital Signs, including weight	X						X		X		X			X
CO Exhaled Air Test		X					X		X		X			X
Fagerström Test for Nicotine Dependence		X									X			X
Minnesota Nicotine Withdrawal Scale		X					X		X		X			X
Brief behavioral counseling	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X												
Dispense study product		X					X		X					
Review self-reported tobacco status		X	X	X	X	X	X	X	X	X	X	X	X	X
Assess AEs			X	X	X	X	X	X	X	X	X	X	X	X
Assess Compliance, Review & Dispense diary		X	X	X	X	X	X	X	X	X	X	X	X	X

[a] All clinical visits and telephone contacts (except those during screening and at baseline) to be scheduled at the end of the designated week

[b] Includes height

[c] Additional unscheduled exams may be done at any clinic visit, if needed.

[d] At the week 13 contact the participants will be instructed to cut down on product use during week 14-16 to avoid a too abrupt ending of nicotine intake.

[e] If a subject discontinues prior to Week 16, the procedures that would be done at Week 16 should be completed at the time of discontinuation. If a subject discontinues after Week 16, the procedures that would be done at Week 28 should be completed at the time of discontinuation.

ASSESSMENTS BY VISIT

SCREENING (WEEK -2, WEEK -1)

During a preliminary Information Session, potential subjects will receive information on the health risks associated with cigarettes as well as possible alternatives. The physiological effects of nicotine will be outlined, and an account given of experience with Swedish snus, including potential health risks associated with different types of smokeless tobacco products. Potential subjects will be invited to the clinic for a Screening Visit (Visit 1), for an explanation of the purpose and nature of the study. Written informed consent will be obtained and the following evaluations will be completed:

- Evaluation of entry criteria
- Complete medical and smoking history, including assessment of tobacco use and smoking status (i.e., age at initiation of daily smoking, average number of cigarettes smoked per day during the past year, history of previous quit attempts, desire to quit cigarettes and smoking, history of use of smokeless tobacco products), history of psychiatric disorders, and history of previous use of NRT or other pharmaceutical or other smoking cessation aids)
- Oral examination
- Vital signs, including weight
- Urine pregnancy test for females of childbearing potential
- Investigators will verify post-menopausal status with a Follicular Stimulating Hormone (FSH) test for women between the ages of 45 and 55.
- Physical examination, including height and ECG (supine position for at least 5 minutes)
- Blood chemistry (Hb, total WBC, transaminases, creatinine, electrolytes)
- Biomarker blood tests
- Urine test for illicit drugs (amphetamine, opioids, cocaine, cannabis)
- Brief behavioral counseling in the form of educational materials on smoking cessation, the National Cancer Institute's "Cleaning the Air" booklet

The Information Session and Screening Visit may occur on the same day.

STUDY PRODUCT TEST PERIOD (WEEK 1 THROUGH WEEK 4)

Baseline Visit

After Screening procedures have been completed and results reviewed, qualifying subjects will return to the clinic (at any time within 2 weeks from the Screening Visit date) for a Baseline assessment and random allocation to study product (snus or placebo). The following assessments will be completed:

- Confirmation of eligibility criteria
- CO exhaled air test
- Fagerström Nicotine Dependence test
- Minnesota Nicotine Withdrawal Scale
- Brief counseling following Agency for Healthcare Research and Quality guidelines (see Appendix 5)
- Randomization
- Dispense study product with instructions on use

- Dispense subject diary with instructions to record number and size of study product used
- Instruct subjects to gradually decrease the daily number of smoked cigarettes through the use of study products
- Instruct subjects to refrain totally from cigarettes no later than the first day of Week 5

Week 1 through 4

Telephone contacts will occur at Weeks 1, 2, 3, 4, and will include a review of the subject's smoking status, use of study products, and brief behavioral counseling. Adverse events will also be assessed.

INTERVENTION PHASE (WEEK 5 THROUGH WEEK 16)

Week 5 through Week 16

Throughout the Intervention Phase, clinic visits and telephone contacts will be completed. Telephone contacts will occur at Weeks 8, and 13 and will include a review of the subject's smoking status, and brief behavioral counseling. Adverse events and compliance with study product will also be assessed. At the telephone contact scheduled at week 13 the participants will be instructed to cut down on product use during week 14 through 16 to avoid a too abrupt ending of nicotine intake.

Clinic visits will be scheduled at Week 6, as well as during Weeks 10, and 16. They will include the following assessments:

Week 6 and Week 10

- Vital signs, including weight
- CO exhaled air test
- Biomarker blood tests (Week 6 only)
- Minnesota Nicotine Withdrawal Scale
- Provision of brief counseling following Agency for Healthcare Research and Quality guidelines
- Dispense study product
- Review self-reported smoking status
- Assess adverse events
- Review diary information regarding product use and assess compliance. Dispense new diary.

Week 16

- Vital signs, including weight
- Physical examination
- Oral examination
- CO exhaled air test
- Fagerström Nicotine Dependence test
- Minnesota Nicotine Withdrawal Scale
- Biomarker blood tests
- Brief counseling following Agency for Healthcare Research and Quality guidelines
- Review self-reported smoking status
- Assess adverse events
- Review diary information regarding product use and assess compliance.

If a subject discontinues prematurely, the procedures that would be done at Week 16 should be completed at the time of discontinuation.

FOLLOW-UP PHASE (WEEK 17 THROUGH WEEK 28)

Throughout the Follow-Up Phase, clinic visits and telephone visits will be completed. Telephone visits will occur at Weeks 20 and 24 and will include a review of the subject's smoking status and brief behavioral counseling. Adverse events will also be assessed.

A final clinic visit will occur at Week 28 and will include the following assessments:

- Physical examination
- Oral examination
- Vital signs, including weight
- CO exhaled air test
- Fagerström Nicotine Dependence test
- Minnesota Nicotine Withdrawal Scale
- Biomarker blood tests
- Brief counseling following Agency for Healthcare Research and Quality guidelines
- Review self-reported smoking status
- Assess adverse events
- Use of OTC NRT, smoking cessation services, smokeless tobacco, or smoking products other than cigarettes since week 16.

If a subject discontinues during the Follow-Up Phase, the procedures that would be done at Week 28 should be completed at the time of discontinuation.

DESCRIPTION OF ASSESSMENTS

All assessments to be used in this study are common, standard measurements frequently used in smoking cessation studies. Descriptions of outcome and safety assessments completed during the study are described below.

MEDICAL AND SMOKING HISTORY

Investigators should document all significant acute illnesses that the subject has experienced within 90 days of Screening. Additional acute or chronic illnesses present at the time informed consent is given are to be regarded as concomitant illnesses. Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study are to be documented as AEs on the CRF.

OUTCOME ASSESSMENTS

Smoking Status/Product Use Diary

Self-reported smoking status will be determined by a simple "yes/no" question on smoking cessation (i.e., "Have you smoked a cigarette since the last visit?"). Subjects will also record study product consumption each day (number and size of product) and number of cigarettes smokes, and will return the diary at each clinic visit.

CO Exhaled Air Test
The amount of carbon monoxide in end-expired alveolar air provides a rapid and accurate measure of carboxyhemoglobin.[41] CO in exhaled air will be analyzed using Micro Smokerlyser EC-50® (Bedfont Scientific Ltd, U. K.).

Fagerström Nicotine Dependence Test
The Fagerström Test for Nicotine Dependence is a standard instrument for assessing the intensity of this physical addiction.[42] The higher the Fagerström score, the more intense the physical dependence on nicotine. Higher scores indicate that treatment of withdrawal symptoms, usually with nicotine replacement therapy, will be an important factor in the participant's plan of care. A total score of 7 to 10 points indicates highly dependent, 4 to 6 points indicates moderately dependent, and less than 4 points indicates minimally dependent (refer to Appendix 2).

Minnesota Nicotine Withdrawal Scale (MNWS)
The MNWS [43] features two separate measures for examining the severity of nicotine withdrawal symptoms in a subject: a self-report scale and an observer scale. Only the self-report scale will be used in this trial. Nine items are included that assess urge to smoke (craving); depressed mood; irritability, frustration, or anger; anxiety; difficulty concentrating; restlessness; increased appetite; difficulty going to sleep; and difficulty staying asleep. Each item is rated by a subject on an ordinal scale from 0 (not at all) to 4 (extreme) relative to symptoms experienced over the past week. A total withdrawal discomfort score is obtained by summing the 9 items, with higher scores indicating more withdrawal symptoms. Refer to Appendix 3.

SAFETY ASSESSMENTS

Physical Examinations
Physical examinations will include examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, heart, lungs, abdomen, lymph nodes, extremities, and nervous system. An AE form must be completed for all changes identified as clinically noteworthy. Height without shoes will be recorded in inches at Baseline.

Oral Examinations
Examinations of the oral cavity will be performed to identify tobacco-and snus-related oral conditions. Exams are scheduled at Screening, and at Weeks 16 and 28 (or final) visits. Unscheduled exams may be conducted at the discretion of the Investigator at any time during the study. An AE form must be completed for all changes identified as clinically noteworthy.

Vital Signs
Vital signs (body temperature, heart rate, respiratory rate, and blood pressure) will be assessed according to the Schedule of Events. Blood pressure will be measured after subjects have been in the seated position for at least 5 minutes.

Temperature will be measured by either the oral or tympanic route, also consistent throughout the study for a particular subject. Body weight without shoes will be recorded in pounds whenever vital signs are recorded. An AE form must be completed for all changes identified as clinically noteworthy.

Concomitant Medications

Medications taken by or administered to the subject for 30 days before the Screening Visit will be recorded in the CRF. Any medication or therapy that is taken by or administered to the subject during the course of the study must be recorded in the CRF. The entry must include the dose, regimen, route, indication, and dates of use.

Adverse Events

An adverse event (AE) is any symptom, physical sign, syndrome, or disease that either emerges during the study or, if present at screening, worsens during the study, regardless of the suspected cause of the event. All medical and psychiatric conditions (except those related to the indication under study, that is, nicotine addiction) present at screening will be documented on the Prior Illnesses CRF. Changes in these conditions and new symptoms, physical signs, syndromes, or diseases should be noted on the AE CRF during the rest of the study.

AEs may be volunteered spontaneously by the subject, or discovered as a result of general questioning by the study staff. At each visit the subject will be asked, "Have you experienced any problems since your last visit?" All AEs will be recorded on the CRF. For all AEs, the Investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious AE requiring immediate notification. Follow-up of the AE, even after the date of discontinuation of study products, is required if the AE persists until the event resolves or stabilizes at a level acceptable to the Investigator.

In order to avoid vague, ambiguous, or colloquial expressions, all AEs should be recorded in standard medical terminology rather than the subject's own words. Each AE will also be described in terms of duration, frequency, intensity, association with the study product, assessment of possible causes, actions taken, and outcome, using choices given on the CRF. Specific guidelines for classifying AEs by intensity and relationship to study product are given in the tables below.

CLASSIFICATION OF ADVERSE EVENTS BY INTENSITY	
MILD:	The symptom is barely noticeable to the subject and does not influence performance or functioning. Prescription drug treatment is not ordinarily needed for relief of mild AEs but may be given because of personality of subject.
MODERATE:	The symptom is of sufficient severity to make the subject uncomfortable, and performance of daily activities is influenced. Treatment for the symptom may be needed.
SEVERE:	The symptom causes severe discomfort, sometimes of such severity that the subject cannot continue in the study. Treatment for the symptom may be necessary.

CLASSIFICATION OF ADVERSE EVENTS BY RELATIONSHIP TO STUDY PRODUCT	
UNRELATED:	This category applies to those AEs that are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.).
UNLIKELY:	This category applies to those AEs that are judged to be unrelated to the test product, but for which no extraneous cause may be found. An AE may be considered unlikely to be related to study product if or when it meets 2 of the following criteria: (1) it does not follow a reasonable temporal sequence from administration of the test product; (2) it could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it does not follow a known pattern of response to the test product; or (4) it does not reappear or worsen when the product is re-administered.
POSSIBLY:	This category applies to those AEs for which a connection with the test product administration appears unlikely but cannot be ruled out with certainty. An AE may be considered possibly related if or when it meets 2 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the product; (2) it could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; or (3) it follows a known pattern of response to the test product.
PROBABLY:	This category applies to those AEs that the Investigator feels with a high degree of certainty are related to the test product. An AE may be considered probably related if or when it meets 3 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the product; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it disappears or decreases on cessation or reduction in dose (note that there are exceptions when an AE does not disappear upon discontinuation of the product, yet product-relatedness clearly exists; for example, as in bone marrow depression, fixed drug eruptions, or tardive dyskinesia); or (4) it follows a known pattern of response to the test product.
DEFINITELY:	This category applies to those AEs that the Investigator feels are incontrovertibly related to test product. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence from administration of the product; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it disappears or decreases on cessation or reduction in dose and recurs with re-exposure to product (if rechallenge occurs); and (4) it follows a known pattern of response to the test product.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the experience should be noted. If the intensity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

Serious Adverse Events

A serious adverse event (SAE) is defined as any AE that meets one or more of the following criteria:

- The event is fatal or life-threatening.

- The event is permanently disabling (incapacitating or interfering with the ability to resume usual life patterns).
- The event results in unplanned inpatient hospitalization or prolongation of existing hospitalization.
- The event is a congenital anomaly.
- The event requires medical intervention of any kind in order to prevent any of the aforementioned outcomes.

A death occurring during the study or within 1 week of discontinuing use of study product must be reported to the trial safety coordinator. A serious AE is not necessarily severe; for example, an overnight hospitalization for a diagnostic procedure must be reported as a serious AE even though the occurrence is not medically serious. By the same token, a severe AE is not necessarily serious: nausea of several hours' duration may be rated as severe but may not be considered serious.

Any serious adverse event due to any cause that occurs during the investigation, whether or not related to the study product, must be reported within 24 hours of occurrence or when the Investigator becomes aware of the event. The Investigator must send a preliminary report of any SAE encountered during the study and for 1 month after a subject has discontinued or completed the study to the trial safety coordinator by fax within 24 hours using an SAE Report Form. The event must also be recorded on the standard AE CRF. Preliminary reports of SAEs must be followed by detailed descriptions later on, including clear photocopies of hospital case reports, consultant reports, autopsy reports, and other documents when requested and applicable. SAE reports must be made whether or not the Investigator considers the event to be related to the investigational product.

Appropriate remedial measures should be taken to treat the SAE and the response should be recorded. Subjects must be closely followed until sufficient information is obtained to indicate a return to normal status or until the event stabilizes at a level acceptable to the Investigator. Clinical, laboratory, and diagnostic measures should be employed as needed in order to determine the etiology of the problem. The results will be reported promptly to the sponsor.

Other Significant Adverse Events

To ensure subject safety, the Investigator should also notify the safety coordinator should any AE occur that is considered significant but does not meet criteria for an SAE, or that is considered unexpected. In addition, any field monitor who notes a significant AE or medical condition while reviewing the CRFs or source documents at the site must immediately convey this information to the trial safety coordinator.

OTHER PROCEDURES OR ASSESSMENTS

Behavioral Counseling

At each clinic and telephone visit, subjects will be provided with brief counseling following Agency for Healthcare Research and Quality guidelines (refer to Appendix 5). Counseling should last no more than 10 minutes per visit. In addition, subjects will be provided with an

education booklet (the National Cancer Institute's "Cleaning the Air" booklet) at the Screening Visit.

Biomarker blood tests

Blood tests will be taken on all participants at screening, and periodically during the study for exploratory purposes. A total of 30-50 ml of blood will be sampled at each occasion.

DATA MANAGEMENT AND STATISTICAL ANALYSIS

Completed CRFs for this study will be forwarded to Covance where editing and construction of a quality-assured database will occur. All data will be listed and summary tables will be provided. Summary statistics will be presented by treatment group.

This section describes the statistical analysis as it is foreseen at the time of planning the study. Any major deviations from this plan, the reasons for such deviations, and all alternative or additional statistical analyses that may be performed will be described in the Statistical Analysis Plan (SAP), which gives a detailed technical description of all statistical analyses prior to the unblinding of the randomization codes. Because of the unpredictability of some problems, it may be necessary to decide the manner with which irregularities will be dealt in a blind data review meeting before breaking the blind.

INTERIM ANALYSIS

No interim analyses are planned.

DETERMINATION OF SAMPLE SIZE

The primary endpoint is the quit rate among cigarette smokers who wish to stop smoking. The quit rate is examined between subjects randomized to snus as compared to subjects randomized to placebo. Assuming a rate of 12% in the placebo group and 27% in the active snus group, a two group continuity corrected χ^2 test with a 0.050 two-sided significance level will have 80% power to detect the difference between the active group proportion, p1, of 0.270 and the placebo group proportion, p2, of 0.120 (odds ration of 0.369) when the sample size in each group is 122 (total sample size of 244). The study is therefore intended to include a total of 250 participants. Treatment assignments will be balanced between active and placebo groups. The ITT population will be used for all statistical analyses of treatment efficacy.

RANDOMIZATION

A listing of subjects and treatment group assignments will be provided. All analyses of efficacy in terms of smoking cessation will be by allocated product (snus or placebo). Analyses of safety will both be done both by allocated product and by product actually received.

SUBJECT POPULATIONS FOR ANALYSIS

Three populations are defined for outcome analyses: the intention-to-treat (ITT) population, compliant subjects, and the fully evaluable population.

INTENTION-TO-TREAT POPULATION (ITT)

ITT is defined as all eligible subjects who had a baseline evaluation, were randomized to receive one of the study products, and used at least one dose of assigned product, irrespective of compliance and protocol violations. The ITT population will be used for analyses of smoking cessation, as well as compliance and safety.

COMPLIANT SUBJECTS

These are defined as those within the intention-to-treat population who used $\geq$ 1 sachets of their allocated study product per day during week 1 through 6. This population will be used, in addition to the ITT population, to evaluate the secondary end-points of point-prevalence of smoking cessation at week 16 and week 28

FULLY EVALUABLE POPULATION

These are defined as all subjects who completed the full 16 weeks of double-blind intervention. This population will be used, in addition to the ITT population, to assess compliance and safety.

DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Subject characteristics, demographics, and other baseline measurements will be described in terms of age, previous smoking history and quit attempts, previous use of NRT or other pharmaceutical smoking cessation aids, Fagerström score, medical history, and other relevant data collected at Baseline. Descriptive statistics (mean, median, standard deviation, minimum, maximum) will be summarized by treatment group and overall, for continuous variables, and numbers and percentages of subjects for categorical variables. The differences in the baseline characteristics of the two groups will be assessed.

COMPLIANCE

Number of cigarette smoked daily and snus or placebo sachets used per day during the past week will be tabulated from self-reported data.

OUTCOME ANALYSES

PRIMARY OUTCOME ENDPOINT

The primary outcome measure will be continuous smoking cessation during Week 6 through Week 28 (at all measurement points/visits) as reported by subjects and corroborated by objective verification using the CO value from exhaled air of less than 8 ppm at all visits during the specified time period.

SECONDARY OUTCOME ENDPOINTS

Secondary outcome measures are:

- Continuous smoking cessation during Week 6 through Week 16 (at all measurement points/visits) as reported by subjects and corroborated by objective verification using

the CO value from exhaled air of less than 8 ppm at all visits during the specified time period.

- Point prevalence of smoke-free subjects at Week 6, 16, and 28 will be summarized as the rate during the preceding week (self-reported and confirmed by CO measurement).
- Withdrawal symptoms during the study will be measured by the Minnesota Nicotine Withdrawal Scale. The differences in the average daily overall symptom score and the score for craving between the two treatment groups will be analyzed.
- CO in exhaled air levels will be summarized at Baseline and subsequent applicable visits and the change from baseline will be tabulated by overall and by the two treatment groups.
- Scores on the Fagerström Nicotine Dependence Test will be calculated at Baseline, Week 15, and Week 27 and will be summarized at each time point. The change from the baseline will be tabulated for the two treatment group and for overall population.
- Point-prevalence of smoking cessation at week 16 and week 28 (self-reported and confirmed by CO measurement) will be analyzed among compliant subjects (defined as those within the intention-to-treat population who used $\geq$ 1 sachets of their allocated study product per day during week 1 through 6)

In general, missing responses to any questions will be imputed by using the last observation carried forward method (LOCF). If participant did not respond to a question at any of the previous visits, a worst score will be assigned for that question and this score will be carried forward until the time participant responded or completed the study. Missing responses or missing data relating to smoking status will be interpreted as though the participant had smoked on that occasion.

SAFETY ANALYSES

Safety analyses will be performed on the ITT population as well as the fully evaluable population on the basis of treatment actually received.

ADVERSE EVENTS

The subject incidence (%) and number of reports of AEs will be calculated and presented for each treatment by MedDRA term and body system. Individual subject listings of all AEs will be provided. AEs will also be presented by severity and relationship to treatment. The number of subjects who withdrew because of an AE or who died will also be summarized. SAEs will be summarized.

VITAL SIGNS, PHYSICAL AND ORAL EXAMINATIONS

Vital signs will be listed by subject and will be summarized at each time point by treatment. Changes from baseline will also be reported at each time point by treatment. Clinically notable

abnormalities will be summarized at each time point by treatment (as percentage of subjects). Summary statistics will be provided.

Status of oral cavity will be summarized at baseline and at the end of study (Week 27) and change from baseline will be tabulated.

PRIOR AND CONCOMITANT MEDICATIONS

Data on medications other than test products used by subjects prior to or during the course of study will be summarized for the overall population and for the two treatment groups.

PRIOR OR CONCOMITANT ILLNESSES

Subjects experiencing any prior or concomitant illness will be reported in subject listings.

WITHDRAWAL OF SUBJECTS FROM THE STUDY AND ANALYSIS

All subjects who discontinued from the allocated intervention will be listed and their reasons for discontinuation will be tabulated for the two treatment groups and for the overall population. Eligible subjects who discontinue after randomization will not be replaced.

STUDY MANAGEMENT

APPROVAL AND CONSENT

REGULATORY GUIDELINES

The study will be performed in accordance with the most recent guidelines of the World Medical Association Declaration of Helsinki, the guidelines of the International Conference on Harmonization (ICH), the Health Insurance Portability and Accountability Act of 1996 (HIPAA), and all other applicable laws and regulations.

INSTITUTIONAL REVIEW BOARD

Conduct of the study must be approved by an appropriately constituted IRB. IRB approval is required for the study protocol, protocol amendments, informed consent forms, subject information sheets, and advertising materials. No study product will be released for the site until written IRB authorization has been received by the Sponsor or its representative and communicated to the Investigator.

INFORMED CONSENT

For each study subject, signed written informed consent will be obtained prior to any protocol-related activities. As part of this procedure, the Investigator must explain orally and in writing the nature, duration, and purpose of the study, and the action of the product in such a manner that the subject is aware of the benefits, potential risks, inconveniences, or adverse effects that may occur as a result of their participation. Subjects should be informed that they may withdraw from the study at any time. Subjects will receive all information that is required by

ICH guidelines. The Investigator will provide the Sponsor or its representative with a copy of the IRB-approved informed consent form (ICF) prior to the start of the study.

DISCONTINUATION OF THE STUDY BY THE SPONSOR

The sponsor reserves the right to discontinue the study at this site or at multiple sites for safety or administrative reasons at any time. In particular, a site that does not recruit at a reasonable rate may be discontinued. Should the study be terminated and/or the site closed for whatever reason, all documentation and equipment pertaining to the study must be returned to the sponsor or its representative.

STUDY DOCUMENTATION

By signing page 2 of this protocol, the Investigator acknowledges that he/she has received appropriate information about the products being tested in the trial and assures the sponsor that he/she will comply with the protocol. No changes in this protocol can be made without the sponsor's written approval.

The Investigator will supply the sponsor with:

- Curricula vitae for all Investigators involved in the trial
- Signed protocol signature page

The sponsor or its representative will supply the Investigator with:

- Clinical study protocol
- Other relevant information about the study products
- Sample informed consent form
- Case report forms (CRFs)/instruction manual
- Equipment for clinical measurements of CO in exhaled air

STUDY MONITORING AND AUDITING

This study will be monitored at all stages of its development by the clinical research personnel employed by the sponsor or its representative. Monitoring will include personal visits and telephone communication to assure that the investigation is conducted according to protocol and in order to comply with guidelines of Good Clinical Practice. On-site review of CRFs will include a review of forms for completeness and clarity, and consistency with source documents available for each subject.

Source documents in this trial will be a variety of documents including clinical records, laboratory reports, participant diaries, and printouts from medical equipment. For machine readings of CO in exhaled air (for which there are no printouts) directly noted on the CRF, the CRF will serve as source document.

Medical advisors and clinical research associates or assistants may request to witness subject evaluations occurring as part of this protocol. The Investigator and appropriate personnel will be periodically requested to attend meetings/workshops organized by the sponsor to assure acceptable protocol execution. The study may be subject to audit by the sponsor or by regulatory authorities. If such an audit occurs, the Investigator must agree to allow access to required subject records. By signing this protocol, the Investigator grants permission to personnel from the sponsor, its representatives, and appropriate regulatory authorities for on-site monitoring of all appropriate study documentation, as well as on-site review of the procedures employed in CRF generation, where clinically appropriate.

DATA VALIDATION

Any data to be recorded directly on the CRFs (to be considered as source data) will be identified at the start of the trial.

All CRF entries must be made in black ink. The Investigator must ensure the accuracy, completeness, legibility, and timeliness of data reported in the CRF and all required reports. Any change or correction to a CRF must be dated, initialed, and explained (if necessary), and must not obscure the original entry. This process applies to both written and electronic changes.

Data reported on the CRF that are derived from source documents should be consistent with the source documents, or the discrepancies must be explained.

Within one week (or other agreed time frame) of completion of each subject, the Investigator should agree to have completed and signed CRFs available for inspection by the clinical monitor.

STUDY PROTOCOL, DOCUMENTATION, AND RETENTION OF RECORDS

Conduct of the study will strictly follow the protocol. However, if any changes become necessary, both the Investigator and the Sponsor must agree to any amendments made to the protocol. All amendments to the protocol must be signed by the Sponsor's Medical Director and the Investigator, except for those referring to organizational changes. Any amendment to the protocol cannot be implemented by the Investigator until an IRB has reviewed and approved the amendment. The Investigator must treat all of the information related to the study and the compiled data as strictly confidential. The Sponsor must approve any transfer of information not directly involved in the study. The Investigator will be provided with a CRF for each subject to be filled in with all relevant data pertaining to the subject during the study. For each subject, a termination/discontinuation record must be completed. All screened subjects who either entered the study, or were considered ineligible, or were eligible but not enrolled into the study must be documented on a screening log along with the reason for screen failure if applicable.

CRF entries and corrections must be made in a way that does not obscure the original entry. The correct data must be inserted, dated, and initialed by the Investigator. All data entered into the CRF must also be available in the individual subject file either as printouts or as notes taken by either the Investigator or another responsible person assigned by the Investigator. The

Investigator agrees to provide the Sponsor with the subject data and to discuss them with representatives of the Sponsor. The Investigator should take measures to prevent accidental or premature destruction of study documents. Subject identification codes have to be retained according to ICH GCP guidelines or for at least 15 years after the completion or discontinuation of the study, whichever is the longest period of time.

The Investigator must arrange for retention of study records at the site for 15 years. The Investigator should take measures to prevent accidental or premature destruction of these documents.

USE OF STUDY FINDINGS

By signing the study protocol, the Investigator agrees to the use of results of the study for the purposes of national and international regulatory authorities. If necessary, those authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement. Reports covering clinical and biometric aspects of the study will be prepared by the Sponsor or its representative.

It is the intention of the Sponsor that the results of the study based on subjects from all participating centers be published in a peer-reviewed international scientific journal irrespective of the study results. After such a joint publication, each investigator is free to present or publish any data based on this study provided the Sponsor is informed at least four weeks in advance.

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APPENDICES

1. Description of study products
2. Fagerström test of nicotine dependence
3. Minnesota Nicotine Withdrawal Scale (Self-Report)
4. Counseling guidelines (modified from Agency for Healthcare Research and Quality Guidelines, Treating Tobacco Use and Dependence: PHS Clinical Practice Guideline Counseling Participants to Quit)

APPENDIX 1. DETAILED DESCRIPTION OF STUDY PRODUCTS

TRADITIONAL SNUS

Active substance: Nicotine

Product name: Snus

Appearance: Paper sachets

Content : Snus is made from ground tobacco leaves, water, and food-allowed additives (salt, humidifier, acidity regulator, and flavor substances). The finished product adheres to an industrial standard which includes limits for undesired substances, see below. No nicotine is added or removed from the product which implies that the nicotine in the product solely comes from the tobacco.

Content (large sachets):	Tobacco	0.5 g
	Water	0.5 g
	Salt (NaCl)	6%
	Nicotine	8 mg
	Propylene glycol (E 1520)	
	Sodium carbonate (E 500)	
	Flavor substances	
Content (small sachets):	Tobacco	0.25 g
	Water	0.25 g
	Salt (NaCl)	6%
	Nicotine	4mg
	Propylene glycol (E 1520)	
	Sodium carbonate (E 500)	
	Flavor substances	
pH:	8.1 to 8.9 (accepted range)	

Administration: The sachets are placed in the mouth between the upper gingiva and cheek (upper sulcus). Usage is *ad libitum*. Typically, the sachets are retained for 20 to 30 minutes up to 60 minutes. There is large individual variation in total number of sachets used per day, and

the time the sachets are retained in the mouth, which reflects the wide variation in nicotine dose required by habitual users of nicotine products.

Nicotine absorption: 10 to 20% of the nicotine in the sachets is absorbed to the blood through the mucous membranes. The potential nicotine uptake is thus1-2 mg from the large sachets and 0.5 to 1.0 mg from the small sachets.

Side effects: The side effects of the nicotine in snus are the same as those from other sources of nicotine such as cigarettes, and are dose dependent. As is known by every habitual smoker, the side effects are reversible when the dose is reduced or when usage is interrupted.

Common side effects of nicotine include: *Cardiology*: Increased heart rate, slight elevation of blood pressure (typically 5-10 mm Hg), *Neurology*: Vertigo, head ache. *GI*: Nausea, stomach ache, heart burn

The content of sodium carbonate in the product makes it slightly alkaline. This may cause a burning sensation in the mouth at the location of the sachet, particularly among those unaccustomed to the product. Should this problem occur, it can be alleviated by changing the location of the sachet in the upper sulcus, e g by switching to the contralateral side.

Short term use of snus (months) is not associated with any known mucosal side effects. Long term use (several years) may be associated with a mucosal "snus lesion," that is, a whitish thickening of the mucosa. Such lesions are reversible if the placement of the snus sachet is changed, or usage stopped. Snus lesions are not associated with cellular atypia and do not have malignant potential. They are thus quite distinct from oral leukoplakias. Long term use (typically several years), particularly of loose snus products, has in some individuals been associated with exposed dental cervices.

Weight variation of study product: Sachet weight may vary between -10% and +20% of the labelled weight.

Undesired substances: Snus contains traces of undesired substances occurring naturally in tobacco and other agricultural products. The levels are well below the limits of the industrial standard GothiaTek®, and are listed in the table.

Component[1]	Limit[2]	Content[3]	Component[1]	Limit[2]	Content[3]
Nitrite (mg/kg)	3.5	1.1 (<0.5 - 1.9)	Cadmium (mg/kg)	0.5	0.2 (0.1 - 0.3)
TSNA (mg/kg)	5	0.8 (0.4 - 1.1)	Lead (mg/kg)	1.0	0.2 (0.1 - 0.2)
NDMA (µg/kg)	5	0.6 (<0.5 - 1.1)	Arsenic (mg/kg)	0.25	0.08 (<0.03 - 0.13)

BaP (µg/kg)	10	0.9 (<0.5 - 1.8)	Nickel (mg/kg)	2.25	0.8 (0.3 - 1.2)
Pesticides	According to the Swedish Match pesticide policy		Chromium (mg/kg)	1.5	0.5 (0.3 - 0.7)

1: Main undesired components defined by **GothiaTek®**, 2: According to **GothiaTek®**, 3: Results for batches produced by Swedish Match AB 2005, based on a water content of 50%

Packaging & storage: The snus sachets are distributed in round plastic containers. The packaging material is food allowed according to the Swedish Food Act. As the unique production method entails a heat treatment similar to pasteurization, the product is virtually sterile. However, snus should preferably be stored in a refrigerator (2 to 8 °C) to preserve the water content and freshness of the product.

The product is marked with a best-before date which is typically c. 20 weeks after production date. It should be noted that the levels of undesired, potentially toxic substances, such as, nitrosamines, do not increase during storage, even in room temperature. It is mainly the water content that decreases which affects the subjective freshness of the product. There is also a slight decline in the pH level during storage which decreases the amount of bio-available nicotine.

If the product is stored in a freezer (< -18 °C) the best before date is postponed almost indefinitely.

PLACEBO SNUS

Active ingredient/content: No active substance. The product only contains food-allowed constituents, ingredients and additives.

Appearance: Paper sachets. The physical appearance and flavoring is the same as that of the traditional snus.

Content (large sachets):	Cocoa bean fibers, oat fibers	0.5 g
	Water	0.5 g
	Salt (NaCl)	5.5%
	Sodium carbonate (E500)	
	Propylene glycol (E 1520)	
	Flavor substances	

Content (small sachets):	Cocoa bean fibers, oat fibers	0.25 g
	Water	0.25 g
	Salt (NaCl)	5.5%
	Sodium carbonate (E500)	
	Propylene glycol (E 1520)	
	Flavor substances	

pH: 8.1 to 8.9 (accepted range)

Weight variation of study products: Sachet weight may vary between -10% and +20% of the labelled weight, the mean weight is: 1.0 g (large sachets) and 0.5 g (small sachets)

Administration and usage: Same as with traditional snus

Side effects: None reported during short-term usage (a few weeks to months). However, because the product is slightly alkaline just as traditional snus, users may initially experience a burning sensation in the oral mucosa at the location of the sachet, particularly among those unaccustomed to the product. As a result of the pH, long term use (several years) may theoretically be associated with mucosal "snus lesions," just as traditional snus. Such lesions, should they occur, are of minor clinical significance and are expected to be infrequent among participants in the current study.

Packaging & storage: The sachets come in round plastic containers identical to those used for traditional snus. The packaging material is food allowed according to the Swedish Food Act. The product is marked with a best-before date which is typically c. 20 weeks after production date. Water content and freshness is best preserved if the product is stored in a refrigerator (2 to 8^{o}C).

If the product is stored in a freezer (< -18^{o}C) the best before date is postponed almost indefinitely.

APPENDIX 2. FAGERSTRÖM TEST FOR NICOTINE DEPENDENCE

1. How soon after waking do you smoke your first cigarette?

a) Less than five minutes (3p)
b) 5-30 minutes (2p)
c) 31-60 minutes (1p)
d) More than an hour (0p)

2. Do you find it difficult to refrain from smoking in places where it is forbidden?

a) Yes (1p)
b) No (0p)

3. Which cigarette would you most hate to give up?

a) First one in the morning (1p)
b) Any other (0p)

4. How many cigarettes do you smoke per day?

a) More than 30 per day (3p)
b) 21-30 per day (2p)
c) 11-20 per day (1p)
d) 10 or less per day (0p)

5. Do you smoke more frequently during the first hours after waking than during the rest of the day?

a) Yes (1p)
b) No (0p)

6. Do you smoke if you are so ill that you are in bed most of the day?

a) Yes (1p)
b) No (0p)

APPENDIX 3. MINNESOTA NICOTINE WITHDRAWAL SCALE (SELF-REPORT)

Behavior Rating Scale Self-Report

Please rate yourself for the period for the last 24 hours:

0 = none, 1 = slight, 2 = mild, 3 = moderate, 4 = severe

1. Angry, irritable, frustrated	0 1 2 3 4
2. Anxious, nervous	0 1 2 3 4
3. Depressed mood, sad	0 1 2 3 4
4. Desire or craving to smoke	0 1 2 3 4
5. Difficulty concentrating	0 1 2 3 4
6. Increased appetite, hungry, weight gain	0 1 2 3 4
7. Insomnia, sleep problems, awakening at night	0 1 2 3 4
8. Restless	0 1 2 3 4
9. Impatient	0 1 2 3 4

Hughes JR, Hatsukami DK. Signs and symptoms of tobacco withdrawal. Arch Gen Psychiatr 1986; 43:289-294.

Scale available at http://www.uvm.edu/~hbpl/minnesota/2005/Behavior%20Rating%20Scale%20-%20Self%20Report.pdf

APPENDIX 4: COUNSELING GUIDELINES

Modified from Agency for Healthcare Research and Quality Guidelines, Treating Tobacco Use and Dependence: PHS Clinical Practice Guideline Counseling Participants to Quit

The counseling can be divided into practical and supportive counseling advice.

Practical counseling advice (problem-solving/skills training)	Examples
Recognize danger situations. Identify events, internal states, or activities that increase the risk of cigarette use	• Negative affect. • Being around other smokers. • Drinking alcohol. • Experiencing urges. • Being under time pressure.
Develop coping skills. Identify and practice coping or problem-solving skills. Typically, these skills are intended to cope with danger situations.	• Learning to anticipate and avoid temptation. • Learning cognitive strategies that will reduce negative moods. • Accomplishing lifestyle changes that reduce stress, improve quality of life, or produce pleasure. • Learning cognitive and behavioral activities to cope with smoking urges (e.g., distracting attention).
Provide basic information. Provide basic information about smoking and successful methods to switch to a non-smoking behavior	• Any smoking (even a single puff) increases the likelihood of failure. • Withdrawal typically peaks within 1-3 weeks after switching from cigarettes • Withdrawal symptoms include negative mood, urges to smoke, and difficulty concentrating.

Supportive counseling advice	Examples
Encourage the smoker	• Communicate belief in the participant's ability to replace cigarettes • Note that effective alternatives are now available. • Note that half of all people who have ever smoked have stopped using cigarettes
Communicate caring and concern.	• Ask how the participant feels about replacing cigarettes • Directly express concern and willingness to help. • Be open to the participant's expression of fears of not using cigarettes, difficulties experienced, and ambivalent feelings.
Encourage the participant to talk about the process.	Ask about: • Reasons the participant wants to switch from cigarettes • Concerns or worries about the switch from cigarettes • Success the participant has achieved. • Difficulties encountered with the switch

Internet Citation:

Counseling Patients To Quit. U.S. Public Health Service. Agency for Healthcare Research and Quality. Rockville, MD. http://www.ahrq.gov/clinic/tobacco/counsel.htm

Protocol Amendment 1 (13 January 2009)

Swedish Match AB
SWEDEN

Covance

3402 Kinsman Boulevard, Madison, Wisconsin 53704

STUDY PROTOCOL No. SM 08-01:

A CONTROLLED STUDY OF THE ABILITY OF A TRADITIONAL SWEDISH SMOKELESS TOBACCO PRODUCT ("SNUS") TO INCREASE THE QUIT RATE AMONG CIGARETTE SMOKERS WHO WISH TO STOP SMOKING

Principal Investigator:

Karl Fagerström, Ph. D.

LIST OF ADDRESSES

SPONSOR:	**SWEDISH MATCH AB** **ROSENLUNDSGATAN 36** **SE-118 85 STOCKHOLM** **SWEDEN**
SPONSOR'S RESPONSIBLE MEDICAL DIRECTOR:	**LARS E. RUTQVIST, M. D., PH. D.**
COVANCE STUDY MANAGER:	**JASMINE ROPERS** **3402 KINSMAN BOULEVARD** **MADISON, WI 53704**
COVANCE COORDINATOR:	**LEANNE MCGANN** **3402 KINSMAN BOULEVARD** **MADISON, WI 53704**
COVANCE DATA MANAGEMENT:	**CHRISTY SEAHOLM** **3402 KINSMAN BOULEVARD** **MADISON, WI 53704**
INSTITUTIONAL REVIEW BOARD (IRB):	**INDEPENDENT INVESTIGATIONAL REVIEW BOARD LLC.** **6738 WEST SUNRISE BLVD, SUITE 102** **PLANTATION, FLORIDA 33313**

SIGNATURE PAGE

SWEDISH MATCH APPROVAL:

Signature: _____ Date: 2013-01-28

Name: Lars E. Rutqvist, M.D., Ph. D
Vice President – Scientific Affairs
Swedish Match AB

COVANCE APPROVAL:

Signature: Jasmine Ropers Date: 1 Feb 2013

Name: [Name] Jasmine Ropers
[Department, Title]
Early Clinical Dev.
Project Manager

INVESTIGATOR PROTOCOL AGREEMENT PAGE

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by the sponsor.
- Not to implement any changes to the protocol without written agreement from the sponsor and prior review and written approval from the Institutional Review Board (IRB) except where necessary to eliminate an immediate hazard to subjects.
- That I am thoroughly familiar with the appropriate use of the study product, as described in this protocol and any other information provided by the sponsor including, but not limited to, the current protocol.
- That I am aware of, and will comply with, "good clinical practices" (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the study product and of their study-related duties and functions as described in the protocol.

Signature: _____ Date: 09 Feb 2009

Name (print): H Frank Farmer JR MD
Investigator

Site Number: 01

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Signature: _____ Date: 09Feb2009

Name (print): David C. Carter, MD
Investigator

Site Number: 02

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Signature: _____ Date: 05 FEB 2009

Name (print): Keith Klatt, MD
Investigator

Site Number: _____

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Signature: _____ Date: 16 JAN 2009

Name (print): RANDALL STOLTZ, M.D.

Investigator

Site Number: _____

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- To ensure that all persons assisting me with the study are adequately informed about the study product and of their study-related duties and functions as described in the protocol.

Signature: _____ Date: 04 JUN 2009

Name (print): Georgia Latham, MD
Investigator

Site Number: _____

SYNOPSIS

Title Of Study	A controlled study of the ability of a traditional Swedish smokeless tobacco product ("snus") to increase the quit rate among cigarette smokers who wish to stop smoking
Investigator/Study Center	Multicenter; an estimated 6 sites in the United States
Phase Of Development	Phase III
Objectives	*Primary:* to examine the ability of a traditional Swedish low nitrosamine smokeless tobacco product ("snus") to increase the quit rate among cigarette smokers aged between 25-65 years who wish to stop smoking. This will be measured as continuous abstention from smoking during Week 6 through Week 28 documented by subjects and biologically confirmed by expired air carbon monoxide (CO) less than or equal to the cut off point of 8 ppm. The study is double-blind and placebo-controlled using a non-tobacco, non-nicotine snus-like product as placebo. *Secondary:* • To examine the extent of continuous complete abstention from smoking during Week 6 through Week 16 as well as point-prevalence rates of smoking cessation at week 16 and 28, biologically confirmed by expired air carbon monoxide (CO) less than or equal to 8 ppm • To examine the withdrawal symptoms and cravings of snus compared to placebo as measured by the Minnesota Nicotine Withdrawal Scale. Tobacco dependence will also be measured by the Fagerström Test for Nicotine Dependence. • To examine the safety of snus compared to placebo as measured by adverse events, change from baseline in body weight, oral cavity health, physical examinations, and vital sign measurements • To examine compliance to the allocated study product during the intervention period as well as use of OTC NRT and/or smokeless tobacco products during the follow-up • To examine smoking cessation measured as point-prevalence rates at week 16 and 28 (biologically confirmed by expired air carbon monoxide (CO) less than or equal to 8 ppm) among compliants defined as participants who used $\geq$ 1 sachets of their allocated study product per day during week 1 through 6.
Design	This is a multicenter, randomized, double-blind, placebo-controlled trial designed to examine the ability of snus to increase quit rates among cigarette smokers who wish to stop smoking. The study consists of four phases: pre-randomization screening (up to 2 weeks), Study product test period (4 weeks), Intervention Phase (12 weeks), and a Follow-Up Phase (12 weeks). Potential subjects will be invited to attend an Information Session and Screening visit for evaluation of eligibility. At randomization the participants will be randomly assigned in a 1:1 ratio to receive either snus or placebo snus for 16 weeks. During a 4-week test period the participants will be instructed to use the study products when they feel or expect an urge to

	smoke, initially without requirement of complete abstention from cigarettes. During the following 12-week intervention phase subjects are encouraged to completely stop smoking. If they feel an urge to smoke they are instructed to use their allocated study product instead of smoking. Participants will be continuously supplied with their allocated product. The participants will be instructed to cut down on product use during the last 3 weeks of the intervention to avoid a too abrupt ending of nicotine intake. After the intervention phase the subjects will be followed for an additional 12 weeks. Subjects will come to the clinic for a total of 6 visits, with 8 additional telephone visits. The maximum duration for individual subject participation (including pre-randomization screening) is 30 weeks.
Planned Sample Size	The primary endpoint is the quit rate among cigarette smokers who wish to stop smoking. The quit rate is examined between subjects randomized to snus as compared to subjects randomized to placebo. Assuming a rate of 12% in the placebo group and 27% in the active snus group, a two group continuity corrected χ^2 test with a 0.050 two-sided significance level will have 80% power to detect the difference between the active group proportion, p1, of 0.270 and the placebo group proportion, p2, of 0.0120 (odds ratio of 0.369) when the sample size in each group is 122 (total sample size of 244). The study is therefore intended to include a total of 250 participants. Treatment assignments will be balanced between active and placebo groups. The ITT population will be used for all statistical analyses of treatment efficacy.
Diagnosis And Key Subject Selection Criteria	*Key Inclusion Criteria*: • Subjects between 25 and 65 years of age, inclusive, who smoke > 9 cigarettes per day (average daily consumption during past month) • The subject has smoked daily >1 year • Subjects motivated to quit smoking using a smokeless tobacco product • Subjects in good general health *Key Exclusion Criteria:* • Use of smokeless tobacco during past 6 months or subjects unable to refrain from NRT during the study. • Current oral condition that could potentially be made worse by study treatment • Use of any type of pharmaceutical (including some psychotropics, e.g., wellbutrin) or other products for smoking cessation within the past 3 months • History of clinically significant renal, hepatic, neurological, or chronic pulmonary disease that in the judgment of the investigator precludes participation • History of significant cardiovascular disease, including myocardial infarction within the last 3 months, significant cardiac arrhythmias, or poorly controlled hypertension that in the judgment of the investigator precludes participation • History of alcohol or substance abuse other than cigarette smoking within the past year
Treatments	• Traditional, low nitrosamine Swedish snus in 0.5 or 1.0 g sachets *ad libitum* • Matching placebo (without tobacco or nicotine)
Main Outcome Parameters	• Continuous rates of smoking cessation by self-report and confirmed by expired air CO less than or equal to 8 ppm

	• Point-prevalence smoking cessation rates (during preceding week) confirmed by expired air CO less than or equal to 8 ppm • Minnesota Nicotine Withdrawal Scale • Fagerström Test for Nicotine Dependence
Main Safety Parameters	• Adverse events • Vital sign measurements, including body weight • Oral cavity health • Physical examinations
Statistical Methods	The primary outcome measure will be continuous complete smoking cessation from Week 6 through Week 28 (at all measurement points/visits) as reported by subjects and corroborated by objective verification using the CO value from exhaled air of less than 8 ppm at all relevant visits. Further exploratory analysis will be performed to assess the relationship between various baseline characteristics (age, gender, etc.) and the defined endpoints. For secondary outcome endpoints, point prevalence of smoke-free subjects at Week 16 and Week 28 will be summarized as the rate during the preceding week (self-reported and confirmed by CO measurement). Withdrawal symptoms measured by the Minnesota Nicotine Withdrawal Scale scores will be calculated and summarized by treatment group and overall. The analyses will be done both including all randomized subjects as well as restricted to those who actually managed to stop smoking The differences in the average daily symptom score between the two treatment groups will be analyzed. In addition, "Craving" will be analyzed separately. CO in exhaled air levels will be summarized at Baseline and subsequent applicable visits and the change from baseline will be tabulated by overall and by the two treatment groups. The difference in the change from baseline between the two treatment groups will be analyzed. Scores on the Fagerström Nicotine dependence will be calculated at Baseline, Week 16, and Week 28 and will be summarized at each time point. The change from the baseline in the Fagerström score will be tabulated for the two treatment group and for overall population. Incidence of SAE:s, discontinuation from the study because of an AE, and compliance to allocated study product will be analyzed by allocated treatment. Refer to Section 4.8 for analysis of safety variables.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
CFR	Code of Federal Regulations
CO	carbon monoxide
CRF	case report form
CRO	contract research organization
GCP	good clinical practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
IRB	Institutional Review Board
ITT	intention-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
NRT	nicotine replacement therapy
ppm	parts per million
SAE	serious adverse event
ST	smokeless tobacco
TD	target day
US	United States
WHO	World Health Organization

INTRODUCTION

BACKGROUND AND RATIONALE

Tobacco, which is usually smoked, has well documented detrimental effects on health. Before the mass production of cigarettes, it was common to use tobacco in non-smoked forms, such as a dry, fine-grained powder for nasal sniffing or moist grained tobacco for oral use usually held between check and upper gum. Smokeless tobacco (ST) is still a common form of tobacco used in countries such as India, Sudan, Sweden, and the United States (US).

Smokeless tobacco has been classified by the World Health Organization (WHO) as a carcinogen; however ST products vary widely in tobacco used, curing, production (pasteurization or fermentation), additives, and storage. Because ST is not burned and carcinogenic pyrolysis by-products are not formed, ST has been advocated by many health protection institutions and scientists as a possible harm reduction tool.[1-4]. While the Indian and Sudanese products (e.g., Guthka and Tombak) have been found to be carcinogenic, evidence for the much researched Swedish ST product commonly called "snus" has not been definitive.

Swedish "snus" is different in many significant respects from American moist snuff. It is manufactured using a heat-treatment technique which renders the finished product virtually sterile. This technique has contributed to the fact that "snus" historically and today have much lower levels of potentially carcinogenic nitrosamines than American moist snuff which is a fermented product. Swedish Match has also introduced an industrial standard for its snus products (GothiaTek) which includes limits for potentially toxic compounds. The guiding principle for these limits has been those set for common food-stuffs.

Traditionally "snus" is used in the upper sulcus (under the upper lip) which reduces salivation so there is no need to spit while using the product.

ORAL CANCER

The use of ST use has been associated with oral cancer for many decades, and there is a strong, widespread belief in this association. However, a recent review concluded that the use of chewing tobacco and moist snuff were associated with only minimally elevated risks, while other types of ST conferred higher risks.[5] Two of seven studies reviewed tested Swedish snus and demonstrated no oral cancer risk.[6,7] These results formed the basis for the European Union's decision in the year 2000 to remove the cancer warning from snus products. In a recent study, 1,115 snus users were followed for 29 years. Snus-induced lesions were common but oral cancer rarely occurred at the site of these lesions ;[8] there are, however, some anecdotal reports of oral cancer in long term snus users. [9]

CARDIOVASCULAR AND OTHER DISEASE

Epidemiological studies have examined the role of snus in cardiovascular disease (five studies), myocardial infarction (four studies), and stroke (one study). In three of the four studies on myocardial infarction, no increased risk was seen in snus users.[10-12] In the fourth study a significant increase in risk was noted but it was lower than that of smoking.[13] There was no association noted with use of snus and the occurrence of stroke.[14]

Two studies have examined the impact of snus as a risk factor for adult-onset diabetes, as some have hypothesised that ST could change glucose tolerance or insulin concentrations. One of these studies [15] found that snus users had a slightly elevated risk while the other reported that the risk of diabetes was not increased.[16]

OTHER CANCERS

No association with the use of snus and gastrointestinal or urinary tract cancer has been found.[17]

RESPIRATORY DISEASE

As there is no plausible causal mechanism whereby snus could cause respiratory disease, there are no studies available that have examined the effect snus has on respiratory disease.

PREGNANCY

One study has examined the effect of snus on pregnancy, and found snus was associated with increased risk of preterm delivery and preeclampsia.[18] Given that animal studies have implicated nicotine as a cause of some of the widely known adverse effects of tobacco exposure during pregnancy it follows that snus use during pregnancy is likely to incur some of the risks associated with smoking.

EPIDEMIOLOGY OF SNUS USE IN SWEDEN

In 2005, 22% of adult males in Sweden were daily snus users and 13% smoked cigarettes.[19] For women the figures were very different, 4% used snus and 17% smoked. Among young boys (age 15), 14% were daily or almost daily users of snus and 5% smoked. For girls the figures were 3% and 13 %.[19]

It is increasingly evident that snus can replace cigarettes among former smokers. In 2001, 47% of current snus users were found to have been smokers previously, according to a study commissioned by Swedish Match.[20] In another study commissioned by The Swedish Cancer Society and Pharmacia Corporation,[21] 1,000 Swedish ex-smokers were asked about their quitting methods. Fifty percent had not used any help to stop, 33% had replaced their cigarettes with snus, and 17% used nicotine replacement therapy (NRT) during some quit attempt. Twenty-eight percent of men reported having used snus during their last quit attempt. Ramström[22] found that among males using a product on their last quit attempt, 55% used snus. For females the figure was 15%. The rate of complete cigarette replacement with use of snus was 65% for males and 52% for females. For nicotine gum and patch, non-smoking rates were 46% and 32% for males and 37% and 30% for females, respectively. That

many Swedish smokers have switched completely to snus is also supported by data from local studies in northern and southern parts of Sweden.[23, 24]

In Sweden, snus is used at least as often as NRT at quit attempts and the rates of total cigarette replacement with snus are at least as high as the smoking cessation rates seen with NRT. Ramström and Foulds recently found that 55% of men attempting to completely replace cigarettes had used snus. A total of 26% used NRT in their latest quit attempt.[25] In a cross-sectional study in southern Sweden, 30% of men and 9% of women had used snus at attempts to replace cigarettes occurring between 2000 and 2004.[26]. In a recent study on Swedish twins it was found that snus use was strongly linked with complete cigarette replacement, particularly among more dependent cigarette smokers.[27]

Interpreting data on the acceptability and safety of snus to replace cigarettes is unclear to most tobacco control advocates, who have voiced fears that promotion of use of ST to replace cigarettes may be harmful because snus could be a "gateway" to later smoking as a more effective tool for nicotine delivery.[28-32] Several studies from Sweden [22, 25, 29] and the US [30, 31] however show that early ST use does not increase, but rather prevents later cigarette smoking. A few studies have found the opposite effect.[32, 33]

SNUS AND NICOTINE YIELD

Use of NRT to replace cigarettes typically has an under-dosing effect that results in low blood nicotine concentrations due to the low nicotine delivery of several products. NRT is also associated with poor compliance, in part because they are not very consumer friendly. Generally NRT users have 50 to 80% of the blood nicotine concentrations compared to smokers. ST delivers nicotine concentrations much closer to those of the cigarette than NRT.[34] In fact, Swedish snus can deliver blood levels similar to that of cigarettes although the nicotine absorption is slower and there is no "bolus" that results from inhalation of nicotine.[35] In a pharmacokinetic study, administration of nicotine gum (2 mg administered hourly for 12 hours) was compared with snus products in two sachet sizes: 0.5 g and 1.0 g. After 12 hours, the blood nicotine concentrations were 11 ng/ml with a 0.5 g snus sachet, 13 ng/ml for nicotine gum 2 mg, and 21-29 ng/ml with 1.0 g sachets of different snus brands commonly used in Sweden. [36]

SMOKELESS TOBACCO AS A SUBSTITUTE FOR CIGARETTES

Data previously described have spurred an interest in testing ST as a substitute for cigarettes among smokers interested in an alternative, smokeless tobacco product[37] including the Task Force of the European Respiratory Society [38]. The first smoking cessation study with ST, although uncontrolled, obtained a one year smoking cessation rate of 35% in heavily dependent smokers.[39] In a more recent study with 50 head and neck cancer patients, smoking cessation advice was repeatedly given by nurses at radiation therapy visits. Nicotine patches were chosen by 89% and snus was chosen by 50% of these smokers, often in combination. At 1 year, 68% were carbon monoxide (CO)-verified smokefree.[40]. Although both of these studies produced quit rates that are much higher than those typically seen in formal smoking cessation studies,[49] they were uncontrolled studies.

ETHICAL CONSIDERATIONS

Cigarette smoking is a significant public health problem in most countries. The number of smokers in the U. S. has not decreased substantially during the past 10-15 years. The addictive nature of cigarette smoking and the limited success of traditional anti-smoking measures represent a significant challenge to public health. In conclusion, there is a great need for further research on effective strategies for smoking cessation.

The current trial aims to determine the acceptability of Swedish snus among adult U.S. smokers, and to evaluate if use of snus can increase quit rates among cigarette smokers who want to quit smoking. The trial thus has considerable interest both from a scientific and public health point of view.

It might be viewed as problematic from an ethical point of view that the study does not entail treatment with products that have been demonstrated to be effective to achieve smoking cessation in the context of controlled clinical trials, such as, NRT, bupropion or varenicline. However, there are extensive epidemiological data from Sweden suggesting that snus has been used by many smokers to quit smoking and that it might even be more effective than NRT in achieving complete, long-term smoking cessation. All participants will also be informed about all available, evidence-based methods for smoking cessation.

There are extensive data from epidemiological studies demonstrating that smokeless tobacco, particularly low-nitrosamine Swedish snus, is associated with dramatically reduced health risks compared to cigarette smoking. The risk profile with snus thus appears closer to that of no tobacco use, than to cigarette smoking. So, switching from cigarettes to snus, albeit another tobacco product can be expected to be associated with significantly reduced health risks. Moreover, the trial design implies exposure to snus during only 16 weeks.

The addiction to cigarettes may not entirely be a result of the physical addiction to nicotine, but also in part a psychological phenomenon related to the stimuli and attributes of cigarette smoking. It is therefore essential to include a placebo control arm in studies of smoking cessation, and to conduct such trials with a randomized, double-blind technique, even though such study features may be viewed as problematic from an ethical point of view.

The clinical tests in the trial involve invasive methods (blood sampling), but such tests are part of routine medical care and are associated with minimal risks. Individual test results will be treated confidentially and will only be revealed to the study participants to minimize problems related to personal integrity. All participants will provide written informed consent to participate in the trial.

The participants will receive economic compensation for their participation in the study. However, the compensation is moderate and does not exceed what is typical in studies of this complexity so there is no reason to assume that the compensation *per se* will act as a pressure on potential participants to accept participation or on participants to continue in the trial should they wish to terminate their participation prematurely.Conduct of the study

will be approved by an appropriately constituted institutional review board (IRB) or independent ethics committee (IEC). No study products will be shipped to a site until written IRB/IEC authorization has been obtained.

STUDY PURPOSE

The current study will be the first randomized, placebo-controlled, double-blind clinical trial to test if use of a low-nitrosamine, Swedish snus product can increase the smoking cessation rate among cigarette smokers who wish to quit smoking.

STUDY OBJECTIVES

PRIMARY OBJECTIVE

The primary objective of this study is to examine if a traditional Swedish low-nitrosamine smokeless tobacco product ("snus") compared to placebo can increase the quit rate among cigarette smokers who wish to stop smoking measured as continuous, complete smoking cessation during Week 6 through Week 28 documented by subjects and biologically confirmed by expired air CO less than or equal to 8 ppm.

SECONDARY OBJECTIVES

The secondary objectives of this study are:

- To examine continuous complete quit rates (biologically confirmed) during Week 6 through Week 16,
- To examine point-prevalence (preceding week) quit rates (biologically confirmed) at the clinical visits during Week 10, 16, and 28
- To examine the withdrawal symptoms and cravings of snus compared to placebo as measured by the Minnesota Nicotine Withdrawal Scale at Weeks 6, 10, 16, and 28. Additionally, tobacco dependence will be measured by the Fagerström Test for Nicotine Dependence at Week 16 and 28.
- To examine the safety of snus compared to placebo as measured by adverse events, change from baseline in body weight, oral cavity health, physical examinations, and vital sign measurements.
- To collect blood samples at baseline and at week 6, 16, and 28 which will be used for exploratory analyses of nicotine metabolites and biomarkers of exposure and/or disease related to tobacco use.

INVESTIGATIONAL PLAN

DESCRIPTION OF OVERALL STUDY DESIGN AND PLAN

This is a multicenter, randomized, double-blind, placebo-controlled trial designed to examine the ability of snus compared to placebo to increase the quit rate among cigarette smokers who wish to stop smoking. A total of 250 subjects who are habitual cigarette smokers aged 25 through 65 years will be randomly assigned to be offered tobacco-based, nicotine-containing snus or matching placebo snus (without tobacco and nicotine).

The study consists of three phases: Screening (up to 2 weeks), Study Product Test Period (4 weeks), Intervention Phase (12 weeks), and a Follow-Up Phase (12 weeks).

Potential subjects will be invited to the clinic to attend an Information Session and Screening visit for further evaluation of eligibility.

During the Baseline Visit, subjects will be randomly assigned in a 1:1 ratio to receive either snus or placebo. Over the next 4 weeks, subjects will be acclimatized to the allocated product and will be instructed to try to refrain from cigarettes through the use of the product when they feel or expect an urge to smoke. If subjects still feel an urge to smoke after c. 15-20 minutes, they may do so. Subjects will be encouraged to gradually substitute as many cigarettes as possible and to refrain from all cigarettes at the latest by the first day of Week 5 (or sooner if they can manage to do so). Use of study product will continue for a total of 12 weeks. The participants will be instructed to cut down on product use during the last 3 weeks of the intervention to avoid a too abrupt ending of nicotine intake.

Cigarette replacement will be assessed by self-report and exhaled CO. Subjects will be provided with an education booklet on the hazards of cigarettes (the National Cancer Institute's "Cleaning the Air" booklet) and will be provided with brief (< 10 minutes) counseling at each visit following Agency for Healthcare Research and Quality guidelines (Appendix 4).

After the intervention phase all subjects will be followed-up for an additional 12 weeks. Subjects will come to the clinic for a total of 6 visits, with 8 additional telephone visits. The maximum duration for individual subject participation is 30 weeks, including the 2 week screening phase.

The amount of nicotine needed to prevent withdrawal symptoms among cigarette smokers varies considerably. The amount of study product used by subjects is therefore also expected to vary and is dependent on the extent to which the products actually replace cigarettes. Subjects will therefore be instructed to use the products *ad libitum*, and will be informed that one 1.0 g snus sachet typically can replace one cigarette. Subjects will be instructed to use at least 10 1.0 g sachets per day (or 20 sachets if the subject has elected to use the 0.5 g sachets).

Recommended maximum number of 1.0 g sachets per day is 24. However, among those who are heavy smokers (≥ 15-20 cigarettes per day), or who are strongly nicotine dependent as evidenced by a Fagerström score of 7 or higher at baseline, and who try to replace all cigarettes with study product, total number of sachets needed per day may be higher

BIOMARKER BLOOD TESTS

In addition to the lab tests used to assess eligibility, blood will be drawn for biomarkers on all participants during screening, and at weeks 6, 16, and 28. The total amount of blood drawn on each occasion will be approximately 40 ml with equal amounts of serum and plasma samples. The research samples will be used for exploratory analyses of nicotine metabolites and biomarkers of exposure and/or disease related to use of tobacco.

SCREENING (UP TO 2 WEEKS, WEEK -2 TO BASELINE)

The Screening Phase will consist of an Information Session and Screening Visit (which may be scheduled consecutively at one occasion at the discretion of the Investigator). During the Information Session potential subjects will receive information on the health risks associated with the range of nicotine products including cigarettes, non-snus smokeless, snus and NRT, and their relative harm. Possible alternative treatments will also be outlined. The physiological effects of nicotine will be described, and an account given of experience with Swedish snus, including potential health risks associated with different types of smokeless tobacco products.

The Screening Visit will include an explanation of the purpose and nature of the study and subjects will provide voluntary written informed consent. A complete medical history will be taken (including assessment of smoking status; i.e., age of initiation of daily smoking; average number of cigarettes smoked per day during the past year; history of previous quit attempts; desire to quit cigarettes & smoking; history of previous use of NRT, other pharmaceutical, or other smoking cessation aids, history of previous ST use), along with a physical examination, blood tests, ECG (supine position for at least 5 minutes), oral cavity examination, and vital sign assessment. Subjects will also be provided with an education booklet (the National Cancer Institute's "Cleaning the Air" booklet) and will be provided with brief (<10 minutes) counseling following Agency for Healthcare Research and Quality guidelines.

STUDY PRODUCT TEST PERIOD (BASELINE THROUGH WEEK 4)

Baseline Visit

Qualifying subjects will return to the clinic for a Baseline assessment and random allocation to study product (snus or placebo). Assessments will be completed as outlined in *Schedule of Events).*

Subjects will be given a diary to record their use of study product consumption, including number and size of sachets used, and number of cigarettes smoked, if any.

Usage of study products including how it is placed in the mouth will be demonstrated to the participants.

Week 1 through Week 4

During this phase, subjects will undergo acclimatization to treatment and will be instructed to try to refrain from cigarettes by the use of allocated study product when they feel an urge to smoke. Each subject will be provided with blinded study products of two sachet sizes. Preferred sachet size and the number of sachets consumed per day are determined by the participants themselves and will vary based on individual preferences and smoking habits. One 1.0-gram sachet delivers roughly the same amount of nicotine as one cigarette. If subjects still feel an urge to smoke after c. 15-20 minutes, they can do so provided sachets of study product are removed to avoid nicotine overdosage.

Subjects will be encouraged to gradually substitute as many cigarettes as possible with the study products. The recommended number of 1.0 g sachets to be used per day is 10-24 unless the subject habitually have smoked >15-20 cigarettes per day, or are highly nicotine dependent as evidenced by a score on the Fagerström scale of 7 or more, and attempts to replace all cigarettes with study products. Among such individuals the number of sachets needed per day may be higher than 24. The goal is to replace all cigarettes completely no later than the first day of Week 5 (start of the Intervention Phase).

Subjects will also be instructed that no other source of nicotine (other than cigarettes) or study product should be used during the Test Period, and that NRT or any other pharmaceutical smoking cessation aid is not allowed.

Each week during this period sites will contact each subject by telephone to monitor progress and to assess compliance and adverse events. Brief behavioral counseling will also be included. Subjects will be reminded about the complete switch from cigarettes no later than the first day of Week 5.

INTERVENTION PHASE (WEEK 5 THROUGH WEEK 16)

Clinic visits will occur at Week 6, Week 10, and 16. These visits will include monitoring of each subjects progress (including self-reported smoking status and measurement of CO in exhaled air), brief behavioral counseling, and vital sign assessment. Clinic visits must be performed +/- 3 days from the target date of the visit. Other assessments will be completed as outlined in *Schedule of Events.*

At the Week 6 and 10 visits, subjects will receive continued supply of study product in their preferred size. Subjects will be provided with a sufficient quantity of the study product to last until the next clinic visit, or to the end of the Intervention Phase.

Telephone contacts will be completed at Weeks 8 and 13 to monitor each participant's progress, to assess compliance and any adverse events, and to provide brief behavioral counseling. At the week 13 contact, the participants will be instructed to cut down on product use during the last 3 weeks of the intervention to avoid a too abrupt ending of nicotine intake.

At Week 16, subjects will return to the clinic to assess smoking cessation (based on self-report and measurement of CO in exhaled air), study product use and compliance, vital sign assessment, and assessment of adverse events. Other assessments will be completed as outlined in the *Schedule of Events.*

FOLLOW-UP PHASE (WEEK 17 THROUGH WEEK 28)

All subjects will be encouraged to continue in the study for follow-up independent of smoking status. Use of study product will be discontinued. Telephone contacts will occur during Weeks 20 and 24, with a final clinic visit at Week 28. Assessments at the Week 28 visit will include review of subjects' self-reported tobacco status relative to the use of cigarettes, verified by CO in exhaled air. Other assessments as described on the *Schedule of Events* will also be completed at the final visit.

If a subject has managed to quit cigarettes during the *Intervention Phase* with the help of their allocated study product and at the 16 wk visit or anytime thereafter there is an imminent danger of smoking relapse during the *Follow-Up Phase*, that subject should be informed that use of NRT or a smokeless tobacco product is a better option in terms of health risks than a smoking relapse.

If a subject discontinues participation during the *Intervention Phase*, the procedures that would be done at Week 16 will be completed at the time of discontinuation. If a subject discontinues participation during the *Follow-Up Phase*, the procedures that would be done at Week 28 will be completed at the time of discontinuation.

SELECTION OF STUDY POPULATION

Subjects will be identified from clinic data bases and/or through advertisements. A total of 250 male and female smokers aged between 25 and 65 years who are otherwise healthy will be eligible for study entry. It is anticipated that approximately 6 sites in the United States with sufficient experience and access to the desired subject population will participate.

INCLUSION CRITERIA

Subjects meeting all of the following inclusion criteria at screening should be considered for admission to the study:

1. The subject is male or female, between 25 and 65 years of age, inclusive. If female, the subject has a negative urine pregnancy test and is not lactating, or has not been of childbearing potential for at least 3 months prior to use of study product. To be considered to be not of childbearing potential, the subject must be postmenopausal for at least 2 years; have had a hysterectomy or bilateral tubal ligation, or be proven to be otherwise incapable of pregnancy. If of childbearing potential, the subject must have been practicing one of the following methods of contraception consistently for at least 1 month prior to study entry and agree to continue practicing it during the study: hormonal contraceptives, intrauterine device, spermicide and barrier, spouse/partner sterility; or is practicing abstinence and agrees to continue abstinence or to start an acceptable method of contraception from the above list if sexual activity commences.
2. The subject smokes > 9 cigarettes per day (average daily consumption during past month)
3. The subject has smoked daily for > 1 year.
4. The subject is motivated to quit smoking with the help of a smokeless tobacco alternative
5. The subject is in good general health as evidenced by medical history, physical examination, routine blood chemistry (Hb, total WBC, transaminases, creatinine, electrolytes) , and an ECG
6. The subject practices, by self-report, good oral hygiene (including brushing teeth at least twice per day and having regular dental check-ups).
7. The subject is able and willing to provide written informed consent.
8. The subject agrees to comply with the requirements of the protocol and complete study measures.
9. The subject has stable residence and telephone.

EXCLUSION CRITERIA

Subjects meeting any of the following exclusion criteria at screening will not be enrolled in the study.

1. The subject is a current user of ST (defined as daily usage during more than 1 week within past 6 months) or is unable to refrain from NRT or any other non-protocol treatment during the study. Use of pipes, cigars, cigarillos, snuff, and chewing tobacco is also prohibited during the study.
2. The subject is a female who is pregnant or lactating.
3. The subject has oral conditions that could potentially be made worse by use of study product, for instance, exposed dental cervices in the upper sulcus.
4. The subject has used any type of pharmaceutical (including some psychotropics, e.g., wellbutrin) or other products for smoking cessation within the past 3 months.
5. The subject has a history of clinically significant renal, hepatic, neurological, or chronic pulmonary disease that in the judgment of the investigator precludes participation

6. The subject has a history of cardiovascular disease, including myocardial infarction within the last 3 months, significant cardiac arrhythmias, or poorly controlled hypertension (defined as a diastolic pressure of more than 90 mm Hg or a systolic pressure of more than 140 mm Hg) that in the judgment of the investigator precludes participation
7. The subject has a history of alcohol or substance abuse or dependence other than cigarette smoking within the past year
8. Use of any illicit drug or smoked marijuana in the last 3 months.
9. The subject is unwilling to be randomized into active or placebo conditions, or be available for follow-up assessments.
10. The subject resides in a household where another member is currently participating in the study.

REMOVAL OF SUBJECTS FROM THERAPY OR ASSESSMENT

A subject will be considered to have completed the study when he completes the final assessment visit at Week 28. If a subject discontinues study procedures at any time after entering the study, the Investigator will make every effort to contact the subject and complete the termination case report form (CRF).

A termination case report form (CRF) page should be completed for every randomized subject, whether or not the subject completed the study. The reason for any early discontinuation should be indicated on this form. The primary reason for a subject withdrawing prematurely should be selected from the following standard categories of early termination:

- *Protocol Violation*: The subject's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements Every effort should be made to establish contact with participants who fail to show up for scheduled visits to determine the cause of the non-compliance.
- *Lost to Follow-Up*: The subject stopped coming for visits and study personnel were unable to contact the subject.
- *Withdrawal of consent*: The subject desired to withdraw from further participation in the study in the absence of an investigator-determined medical need to withdraw. If the subject gave a reason for withdrawing, it should be recorded in the CRF.
- *Adverse Event (Adverse Reaction)*: Clinical events occurred that in the medical judgment of the Investigator for the best interest of the subject are grounds for discontinuation. This includes serious and nonserious adverse events regardless of relation to study product. Clinical events that are reported by the subject and result in the subject choosing to withdraw from further participation are recorded as a discontinuation due to adverse event (not withdrawal of consent).
- *Death:* The subject died.
- *Other*: The subject was terminated for a reason other than those listed above

INTERVENTIONS

DESCRIPTION OF STUDY PRODUCTS

For comprehensive information about the study products, refer to protocol Appendix 1. Snus and matching placebo sachets will be provided to the study sites by the sponsor or its representative as white sachets weighing 0.5 or 1.0 g. Placebo sachets will include herbal material with flavoring without tobacco and nicotine. Additional details are provided in Table 1 below.

TABLE 1: DETAILS OF STUDY TREATMENTS

	Preparations to be Administered	
	Snus	**Placebo**
Active Substance	Nicotine	None
Manufacturer	Swedish Match	Swedish Match
Dose(s)	Ad libitum	Ad libitum
Route	Oral	Oral
Sachet Weight	0.5 mg and 1.0 mg	0.5 mg and 1.0 mg

DOSAGE, ADMINISTRATION, AND BLINDING

Subjects will be randomly assigned to receive snus or matching placebo in a 1:1 ratio at the Baseline Visit. Each subject will be given products at baseline, and at the clinic visits at Week 6 and 10. The amount of products given at each occasion is estimated to cover the need of a smoker who completely switches from cigarettes to snus during the entire *Intervention Phase*.

The sachets are placed under the upper lip (upper sulcus) which reduces salivation compared to placement in the lower part of the mouth. This means that there no need to spit while using the products. As the products have a relatively high pH, subjects may initially feel a slight burning sensation at the location of the sachet. This sensation is alleviated if the location of the sachet in the upper sulcus is changed.

The number of sachets consumed per day is determined by the participants themselves and will vary based on smoking habits. The amount of nicotine needed to prevent withdrawal symptoms among smokers varies considerably, therefore the amount of study product used by subjects is expected to vary and is dependent on the extent to which the products actually can replace cigarettes. Subjects will be instructed to use the products *ad libitum* with a recommended maximum number of 24 large sachets per day (recommended maximum number is 30 for those who smoke more than 15-20 cigarettes per day or have a Fagerström score of 7 or higher), and will be informed that one 1.0 g snus sachet typically can replace one cigarette. Recommended maximum number of small sachets is double that of large sachets, that is, 48-60 per day. When subjects feel or expect an urge to smoke, they will be instructed to try their allocated study product for at least 15-20 minutes. Subjects will also be

informed that nicotine overdose may occur with excessive use of the product, particularly with concomitant smoking, but those symptoms (typically nausea, tachycardia, etc.) quickly subside upon cessation of smoking or use of the product. The average snus consumption among snus users in Sweden who do not smoke is about 10 to 15 large sachets per day.

During the *Study Product Test Period* subjects will be instructed to replace as many cigarettes as possible with their allocated study product in order to achieve smoking cessation at the latest by the first day of week 5. The participants will be instructed to cut down on product use during week 14-16 to avoid a too abrupt ending of nicotine intake. Use of study product will be discontinued at the Week 16 visit.

If a subject has managed to quit cigarettes with the help of their allocated study product and there is an imminent danger of smoking relapse during the *Follow-Up Phase*, that subject should be informed that use of NRT or a smokeless tobacco product is a better option in terms of health risks than a smoking relapse.

UNBLINDING

Only in case of an emergency, when knowledge of the study product is essential for the clinical management or welfare of the subject, the investigator may unblind a subject's treatment assignment. If the blind is broken for any other reason, the investigator must notify the sponsor's medical representative immediately, and discontinue the subject from study product. If the investigator breaks the blind for a subject, the data and reason must be recorded in the CRF.

METHOD OF RANDOM ASSIGNMENT

Subjects will be randomly assigned chronologically in the order in which they are enrolled into the study stratified by treatment center and will be assigned a unique study number. The random sequence determining the allocation will be generated using a computer-based algorithm based on the permuted block technique with a block size of six.

Each participating center will be provided with four product "bins" that are uniquely numbered. Two bins at each center will include placebo products (large and small sachets), and two bins will include snus products. Each unique study number will be linked to bin numbers from which the participant shall receive study products (placebo or snus).

The trialist will document which products were provided to each participant and study product labeling will ensure that it can be verified that correct products according to the random allocation were issued to each participant.

PRODUCT PACKAGING AND LABELING

Study products will be supplied in "bins" (=for each study site uniquely numbered card-board boxes). Products are routinely packed in stacks of ten boxes ("logs"). All products will be labeled according to applicable laws and regulations and ICH-GCP Guidelines.

STORAGE AND HANDLING OF STUDY PRODUCTS

Receipt of product supplies

Product supplies will not be provided to the Investigator until Institutional Review Board (IRB) approval has been obtained.

The Investigator or his/her designees will inventory all supply shipments upon receipt, acknowledge possession by signing the certificate of delivery, and return the form to the sponsor or its representative.

Storage

Study products should be kept refrigerated at 2-8 centigrades in a securely locked or in a limited access, secure area. Neither the Investigator nor designees may provide the study product to individuals not participating in this protocol.

Return of study product

Throughout the study, the sponsor or designee will make arrangements for the Investigator to return all unused study product to the sponsor or its representative. This shipment will be documented on the product accountability form. The Investigator must provide an explanation for any missing study product.

Responsibilities

In addition to responsibilities upon receipt previously outlined, the Investigator or his/her designees must maintain an inventory record of administered products to assure regulatory authorities and the sponsor that the investigational study product will not be administered to any person who is not participating in this study under the terms and conditions set forth in this protocol.

The inventory record will include:

- Name of the sponsor
- Protocol name and number
- Product name and description
- Study site and name of the Investigator
- Number of snus boxes dispensed and study participant identifier to whom study product was dispensed
- Product balance
- Name and signature of the qualified individual dispensing study product

Representatives of the sponsor will review these records.

Compliance

Self-reported number of cigarettes smoked daily and snus sachets used per day will be recorded in the subject's diary. The recommended number of 1.0 g and 0.5 g sachets to be used per day is 10-30 and 20-60, respectively.

PRIOR AND CONCOMITANT ILLNESSES AND TREATMENTS

Prior and concomitant illnesses

As this study is to be performed in healthy subjects, there should be no significant concomitant illnesses at the time of entry into the study. Illnesses first occurring or detected during the study, or a significant deterioration of a pre-existing condition will be documented as adverse events in the CRF. All data on medical history etc. collected as part of this trial will be based on the subject's self-reported information.

Prior and concomitant medications

Any concomitant medication is acceptable except NRT or other treatments used for smoking cessation, for instance, bupropion or varenicline. Other psychotropics (e.g., antidepressants other than bupropion) should also not be used. If a subject has used such treatments previously, they must be discontinued at least 3 months prior to randomization.

Use of any other product containing tobacco (e.g., pipes, cigars, cigarillos, snuff, and chewing tobacco) is prohibited throughout the study.

SUBJECT EVENTS

SCHEDULE OF EVENTS

The procedures to be performed throughout the study are outlined in Table 2, Schedule of Events, and the text following.

Table 2. Schedule of Events

	Screening	Baseline	Study Product Test Period (Week 1-4)				Intervention Phase (Week 5-16)					Follow-Up (Week 17-28)		
Study Week	-2, -1	0	1	2	3	4	6	8	10	13	16	20	24	28
Clinical Visit[a]	X	X					X		X		X[e]			X[e]
Telephone Contact[a]			X	X	X	X		X		X[d]		X	X	
Visit/Contact Window			± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 1 wk	± 1 wk	± 1 wk	± 1 wk
Interventions/Evaluations:														
Information Session	X													
Written Informed Consent	X													
Assessment of Eligibility	X	X												
Medical and Smoking History, ECG	X													
Physical & Oral[c] Examination	X[b]										X			X
Biomarkers (blood tests)	X						X				X			X
Screening tests (urine & blood tests)	X													
Vital Signs, including weight	X						X		X		X			X
CO Exhaled Air Test		X					X		X		X			X
Fagerström Test for Nicotine Dependence		X									X			X
Minnesota Nicotine Withdrawal Scale		X					X		X		X			X
Brief behavioral counseling	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X												
Dispense study product		X					X		X					
Review self-reported tobacco status		X	X	X	X	X	X	X	X	X	X	X	X	X
Assess AEs			X	X	X	X	X	X	X	X	X	X	X	X
Assess Compliance, Review & Dispense diary		X	X	X	X	X	X	X	X	X	X	X	X	X

[a] All clinical visits and telephone contacts (except those during screening and at baseline) to be scheduled at the end of the designated week

[b] Includes height

[c] Additional unscheduled exams may be done at any clinic visit, if needed.

[d] At the week 13 contact the participants will be instructed to cut down on product use during week 14-16 to avoid a too abrupt ending of nicotine intake.

[e] If a subject discontinues prior to Week 16, the procedures that would be done at Week 16 should be completed at the time of discontinuation. If a subject discontinues after Week 16, the procedures that would be done at Week 28 should be completed at the time of discontinuation.

ASSESSMENTS BY VISIT

SCREENING (WEEK -2, WEEK -1)

During a preliminary Information Session, potential subjects will receive information on the health risks associated with cigarettes as well as possible alternatives. The physiological effects of nicotine will be outlined, and an account given of experience with Swedish snus, including potential health risks associated with different types of smokeless tobacco products. Potential subjects will be invited to the clinic for a Screening Visit (Visit 1), for an explanation of the purpose and nature of the study. Written informed consent will be obtained and the following evaluations will be completed:

- Evaluation of entry criteria
- Complete medical and smoking history, including assessment of tobacco use and smoking status (i.e., age at initiation of daily smoking, average number of cigarettes smoked per day during the past year, history of previous quit attempts, desire to quit cigarettes and smoking, history of use of smokeless tobacco products), history of psychiatric disorders, and history of previous use of NRT or other pharmaceutical or other smoking cessation aids)
- Oral examination
- Vital signs, including weight
- Urine pregnancy test for females of childbearing potential
- Investigators will verify post-menopausal status with a Follicular Stimulating Hormone (FSH) test for women between the ages of 45 and 55.
- Physical examination, including height and ECG (supine position for at least 5 minutes)
- Blood chemistry (Hb, total WBC, transaminases, creatinine, electrolytes)
- Biomarker blood tests
- Urine test for illicit drugs (amphetamine, opioids, cocaine, cannabis)
- Brief behavioral counseling in the form of educational materials on smoking cessation, the National Cancer Institute's "Cleaning the Air" booklet

The Information Session and Screening Visit may occur on the same day.

STUDY PRODUCT TEST PERIOD (WEEK 1 THROUGH WEEK 4)

Baseline Visit

After Screening procedures have been completed and results reviewed, qualifying subjects will return to the clinic (at any time within 2 weeks from the Screening Visit date) for a Baseline assessment and random allocation to study product (snus or placebo). The following assessments will be completed:

- Confirmation of eligibility criteria
- CO exhaled air test

- Fagerström Nicotine Dependence test
- Minnesota Nicotine Withdrawal Scale
- Brief counseling following Agency for Healthcare Research and Quality guidelines (see Appendix 5)
- Randomization
- Dispense study product with instructions on use
- Dispense subject diary with instructions to record number and size of study product used
- Instruct subjects to gradually decrease the daily number of smoked cigarettes through the use of study products
- Instruct subjects to refrain totally from cigarettes no later than the first day of Week 5

Week 1 through 4

Telephone contacts will occur at Weeks 1, 2, 3, 4, and will include a review of the subject's smoking status, use of study products, and brief behavioral counseling. Adverse events will also be assessed.

INTERVENTION PHASE (WEEK 5 THROUGH WEEK 16)

Week 5 through Week 16

Throughout the Intervention Phase, clinic visits and telephone contacts will be completed. Telephone contacts will occur at Weeks 8, and 13 and will include a review of the subject's smoking status, and brief behavioral counseling. Adverse events and compliance with study product will also be assessed. At the telephone contact scheduled at week 13 the participants will be instructed to cut down on product use during week 14 through 16 to avoid a too abrupt ending of nicotine intake.

Clinic visits will be scheduled at Week 6, as well as during Weeks 10, and 16. They will include the following assessments:

Week 6 and Week 10

- Vital signs, including weight
- CO exhaled air test
- Biomarker blood tests (Week 6 only)
- Minnesota Nicotine Withdrawal Scale
- Provision of brief counseling following Agency for Healthcare Research and Quality guidelines
- Dispense study product
- Review self-reported smoking status
- Assess adverse events
- Review diary information regarding product use and assess compliance. Dispense new diary.

Week 16

- Vital signs, including weight
- Physical examination
- Oral examination
- CO exhaled air test
- Fagerström Nicotine Dependence test
- Minnesota Nicotine Withdrawal Scale
- Biomarker blood tests
- Brief counseling following Agency for Healthcare Research and Quality guidelines
- Review self-reported smoking status
- Assess adverse events
- Review diary information regarding product use and assess compliance.

If a subject discontinues prematurely, the procedures that would be done at Week 16 should be completed at the time of discontinuation.

FOLLOW-UP PHASE (WEEK 17 THROUGH WEEK 28)

Throughout the Follow-Up Phase, clinic visits and telephone visits will be completed. Telephone visits will occur at Weeks 20 and 24 and will include a review of the subject's smoking status and brief behavioral counseling. Adverse events will also be assessed.

A final clinic visit will occur at Week 28 and will include the following assessments:

- Physical examination
- Oral examination
- Vital signs, including weight
- CO exhaled air test
- Fagerström Nicotine Dependence test
- Minnesota Nicotine Withdrawal Scale
- Biomarker blood tests
- Brief counseling following Agency for Healthcare Research and Quality guidelines
- Review self-reported smoking status
- Assess adverse events
- Use of OTC NRT, smoking cessation services, smokeless tobacco, or smoking products other than cigarettes since week 16.

If a subject discontinues during the Follow-Up Phase, the procedures that would be done at Week 28 should be completed at the time of discontinuation.

DESCRIPTION OF ASSESSMENTS

All assessments to be used in this study are common, standard measurements frequently used in smoking cessation studies. Descriptions of outcome and safety assessments completed during the study are described below.

MEDICAL AND SMOKING HISTORY

Investigators should document all significant acute illnesses that the subject has experienced within 90 days of Screening. Additional acute or chronic illnesses present at the time informed consent is given are to be regarded as concomitant illnesses. Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study are to be documented as AEs on the CRF.

OUTCOME ASSESSMENTS

Smoking Status/Product Use Diary

Self-reported smoking status will be determined by a simple "yes/no" question on smoking cessation (i.e., "Have you smoked a cigarette since the last visit?"). Subjects will also record study product consumption each day (number and size of product) and number of cigarettes smokes, and will return the diary at each clinic visit.

CO Exhaled Air Test

The amount of carbon monoxide in end-expired alveolar air provides a rapid and accurate measure of carboxyhemoglobin.[41] CO in exhaled air will be analyzed using Micro Smokerlyser EC-50® (Bedfont Scientific Ltd, U. K.).

Fagerström Nicotine Dependence Test

The Fagerström Test for Nicotine Dependence is a standard instrument for assessing the intensity of this physical addiction.[42] The higher the Fagerström score, the more intense the physical dependence on nicotine. Higher scores indicate that treatment of withdrawal symptoms, usually with nicotine replacement therapy, will be an important factor in the participant's plan of care. A total score of 7 to 10 points indicates highly dependent, 4 to 6 points indicates moderately dependent, and less than 4 points indicates minimally dependent (refer to Appendix 2).

Minnesota Nicotine Withdrawal Scale (MNWS)

The MNWS [43] features two separate measures for examining the severity of nicotine withdrawal symptoms in a subject: a self-report scale and an observer scale. Only the self-report scale will be used in this trial. Nine items are included that assess urge to smoke (craving); depressed mood; irritability, frustration, or anger; anxiety; difficulty concentrating; restlessness; increased appetite; difficulty going to sleep; and difficulty staying asleep. Each item is rated by a subject on an ordinal scale from 0 (not at all) to 4 (extreme) relative to symptoms experienced over the past week. A total withdrawal discomfort score is obtained by summing the 9 items, with higher scores indicating more withdrawal symptoms. Refer to Appendix 3.

SAFETY ASSESSMENTS

Physical Examinations

Physical examinations will include examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, heart, lungs, abdomen, lymph nodes, extremities, and nervous system. An AE form must be completed for all changes identified as clinically noteworthy. Height without shoes will be recorded in inches at Baseline.

Oral Examinations

Examinations of the oral cavity will be performed to identify tobacco-and snus-related oral conditions. Exams are scheduled at Screening, and at Weeks 16 and 28 (or final) visits. Unscheduled exams may be conducted at the discretion of the Investigator at any time during the study. An AE form must be completed for all changes identified as clinically noteworthy.

Vital Signs

Vital signs (body temperature, heart rate, respiratory rate, and blood pressure) will be assessed according to the Schedule of Events. Blood pressure will be measured after subjects have been in the seated position for at least 5 minutes.

Temperature will be measured by either the oral or tympanic route, also consistent throughout the study for a particular subject. Body weight without shoes will be recorded in pounds whenever vital signs are recorded. An AE form must be completed for all changes identified as clinically noteworthy.

Concomitant Medications

Medications taken by or administered to the subject for 30 days before the Screening Visit will be recorded in the CRF. Any medication or therapy that is taken by or administered to the subject during the course of the study must be recorded in the CRF. The entry must include the dose, regimen, route, indication, and dates of use.

Adverse Events

An adverse event (AE) is any symptom, physical sign, syndrome, or disease that either emerges during the study or, if present at screening, worsens during the study, regardless of the suspected cause of the event. All medical and psychiatric conditions (except those related to the indication under study, that is, nicotine addiction) present at screening will be documented on the Prior Illnesses CRF. Changes in these conditions and new symptoms, physical signs, syndromes, or diseases should be noted on the AE CRF during the rest of the study.

AEs may be volunteered spontaneously by the subject, or discovered as a result of general questioning by the study staff. At each visit the subject will be asked, "Have you experienced any problems since your last visit?" All AEs will be recorded on the CRF. For all AEs, the Investigator must pursue and obtain information adequate both to determine

the outcome of the AE and to assess whether it meets the criteria for classification as a serious AE requiring immediate notification. Follow-up of the AE, even after the date of discontinuation of study products, is required if the AE persists until the event resolves or stabilizes at a level acceptable to the Investigator.

In order to avoid vague, ambiguous, or colloquial expressions, all AEs should be recorded in standard medical terminology rather than the subject's own words. Each AE will also be described in terms of duration, frequency, intensity, association with the study product, assessment of possible causes, actions taken, and outcome, using choices given on the CRF. Specific guidelines for classifying AEs by intensity and relationship to study product are given in the tables below.

CLASSIFICATION OF ADVERSE EVENTS BY INTENSITY	
MILD:	The symptom is barely noticeable to the subject and does not influence performance or functioning. Prescription drug treatment is not ordinarily needed for relief of mild AEs but may be given because of personality of subject.
MODERATE:	The symptom is of sufficient severity to make the subject uncomfortable, and performance of daily activities is influenced. Treatment for the symptom may be needed.
SEVERE:	The symptom causes severe discomfort, sometimes of such severity that the subject cannot continue in the study. Treatment for the symptom may be necessary.

CLASSIFICATION OF ADVERSE EVENTS BY RELATIONSHIP TO STUDY PRODUCT	
UNRELATED:	This category applies to those AEs that are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.).
UNLIKELY:	This category applies to those AEs that are judged to be unrelated to the test product, but for which no extraneous cause may be found. An AE may be considered unlikely to be related to study product if or when it meets 2 of the following criteria: (1) it does not follow a reasonable temporal sequence from administration of the test product; (2) it could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it does not follow a known pattern of response to the test product; or (4) it does not reappear or worsen when the product is re-administered.
POSSIBLY:	This category applies to those AEs for which a connection with the test product administration appears unlikely but cannot be ruled out with certainty. An AE may be considered possibly related if or when it meets 2 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the product; (2) it could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; or (3) it follows a known pattern of response to the test product.
PROBABLY:	This category applies to those AEs that the Investigator feels with a high degree of certainty are related to the test product. An AE may be considered probably related if or when it meets 3 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the product; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it disappears or decreases on cessation or reduction in dose (note that there are exceptions when an AE does not disappear upon discontinuation of the product, yet product-relatedness clearly exists; for example, as in bone marrow depression, fixed drug eruptions, or tardive dyskinesia); or (4) it follows a known pattern of response to the test product.
DEFINITELY:	This category applies to those AEs that the Investigator feels are incontrovertibly related to test product. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence from administration of the product; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it disappears or decreases on cessation or reduction in dose and recurs with re-exposure to product (if rechallenge occurs); and (4) it follows a known pattern of response to the test product.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the experience should be noted. If the intensity category changes

over a number of days, then those changes should be recorded separately (with distinct onset dates).

Serious Adverse Events

A serious adverse event (SAE) is defined as any AE that meets one or more of the following criteria:

- The event is fatal or life-threatening.
- The event is permanently disabling (incapacitating or interfering with the ability to resume usual life patterns).
- The event results in unplanned inpatient hospitalization or prolongation of existing hospitalization.
- The event is a congenital anomaly.
- The event requires medical intervention of any kind in order to prevent any of the aforementioned outcomes.

A death occurring during the study or within 1 week of discontinuing use of study product must be reported to the trial safety coordinator. A serious AE is not necessarily severe; for example, an overnight hospitalization for a diagnostic procedure must be reported as a serious AE even though the occurrence is not medically serious. By the same token, a severe AE is not necessarily serious: nausea of several hours' duration may be rated as severe but may not be considered serious.

Any serious adverse event due to any cause that occurs during the investigation, whether or not related to the study product, must be reported within 24 hours of occurrence or when the Investigator becomes aware of the event. The Investigator must send a preliminary report of any SAE encountered during the study and for 1 month after a subject has discontinued or completed the study to the trial safety coordinator by fax within 24 hours using an SAE Report Form. The event must also be recorded on the standard AE CRF. Preliminary reports of SAEs must be followed by detailed descriptions later on, including clear photocopies of hospital case reports, consultant reports, autopsy reports, and other documents when requested and applicable. SAE reports must be made whether or not the Investigator considers the event to be related to the investigational product.

Appropriate remedial measures should be taken to treat the SAE and the response should be recorded. Subjects must be closely followed until sufficient information is obtained to indicate a return to normal status or until the event stabilizes at a level acceptable to the Investigator. Clinical, laboratory, and diagnostic measures should be employed as needed in order to determine the etiology of the problem. The results will be reported promptly to the sponsor.

Other Significant Adverse Events

To ensure subject safety, the Investigator should also notify the safety coordinator should any AE occur that is considered significant but does not meet criteria for an SAE, or that is considered unexpected. In addition, any field monitor who notes a significant AE or medical condition while reviewing the CRFs or source documents at the site must immediately convey this information to the trial safety coordinator.

OTHER PROCEDURES OR ASSESSMENTS

Behavioral Counseling

At each clinic and telephone visit, subjects will be provided with brief counseling following Agency for Healthcare Research and Quality guidelines (refer to Appendix 5). Counseling should last no more than 10 minutes per visit. In addition, subjects will be provided with an education booklet (the National Cancer Institute's "Cleaning the Air" booklet) at the Screening Visit.

Biomarker blood tests

Blood tests will be taken on all participants at screening, and periodically during the study for exploratory purposes. A total of 30-50 ml of blood will be sampled at each occasion.

DATA MANAGEMENT AND STATISTICAL ANALYSIS

Completed CRFs for this study will be forwarded to Covance where editing and construction of a quality-assured database will occur. All data will be listed and summary tables will be provided. Summary statistics will be presented by treatment group.

This section describes the statistical analysis as it is foreseen at the time of planning the study. Any major deviations from this plan, the reasons for such deviations, and all alternative or additional statistical analyses that may be performed will be described in the Statistical Analysis Plan (SAP), which gives a detailed technical description of all statistical analyses prior to the unblinding of the randomization codes. Because of the unpredictability of some problems, it may be necessary to decide the manner with which irregularities will be dealt in a blind data review meeting before breaking the blind.

INTERIM ANALYSIS

No interim analyses are planned.

DETERMINATION OF SAMPLE SIZE

The primary endpoint is the quit rate among cigarette smokers who wish to stop smoking. The quit rate is examined between subjects randomized to snus as compared to subjects randomized to placebo. Assuming a rate of 12% in the placebo group and 27% in the active snus group, a two group continuity corrected χ^2 test with a 0.050 two-sided significance level will have 80% power to detect the difference between the active group proportion, p1, of 0.270 and the placebo group proportion, p2, of 0.120 (odds ration of 0.369) when the sample size in each group is 122 (total sample size of 244). The study is therefore intended to include a total of 250 participants. Treatment assignments will be balanced between active and placebo groups. The ITT population will be used for all statistical analyses of treatment efficacy.

RANDOMIZATION

A listing of subjects and treatment group assignments will be provided. All analyses of efficacy in terms of smoking cessation will be by allocated product (snus or placebo). Analyses of safety will both be done both by allocated product and by product actually received.

SUBJECT POPULATIONS FOR ANALYSIS

Three populations are defined for outcome analyses: the intention-to-treat (ITT) population, compliant subjects, and the fully evaluable population.

INTENTION-TO-TREAT POPULATION (ITT)

ITT is defined as all eligible subjects who had a baseline evaluation, were randomized to receive one of the study products, and used at least one dose of assigned product, irrespective of compliance and protocol violations. The ITT population will be used for analyses of smoking cessation, as well as compliance and safety.

COMPLIANT SUBJECTS

These are defined as those within the intention-to-treat population who used $\geq$ 1 sachets of their allocated study product per day during week 1 through 6. This population will be used, in addition to the ITT population, to evaluate the secondary end-points of point-prevalence of smoking cessation at week 16 and week 28

FULLY EVALUABLE POPULATION

These are defined as all subjects who completed the full 16 weeks of double-blind intervention. This population will be used, in addition to the ITT population, to assess compliance and safety.

DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Subject characteristics, demographics, and other baseline measurements will be described in terms of age, previous smoking history and quit attempts, previous use of NRT or other pharmaceutical smoking cessation aids, Fagerström score, medical history, and other relevant data collected at Baseline. Descriptive statistics (mean, median, standard deviation, minimum, maximum) will be summarized by treatment group and overall, for continuous variables, and numbers and percentages of subjects for categorical variables. The differences in the baseline characteristics of the two groups will be assessed.

COMPLIANCE

Number of cigarette smoked daily and snus or placebo sachets used per day during the past week will be tabulated from self-reported data.

OUTCOME ANALYSES

PRIMARY OUTCOME ENDPOINT

The primary outcome measure will be continuous smoking cessation during Week 6 through Week 28 (at all measurement points/visits) as reported by subjects and corroborated by objective verification using the CO value from exhaled air of less than 8 ppm at all visits during the specified time period.

SECONDARY OUTCOME ENDPOINTS

Secondary outcome measures are:

- Continuous smoking cessation during Week 6 through Week 16 (at all measurement points/visits) as reported by subjects and corroborated by objective verification using the CO value from exhaled air of less than 8 ppm at all visits during the specified time period.
- Point prevalence of smoke-free subjects at Week 6, 16, and 28 will be summarized as the rate during the preceding week (self-reported and confirmed by CO measurement).
- Withdrawal symptoms during the study will be measured by the Minnesota Nicotine Withdrawal Scale. The differences in the average daily overall symptom score and the score for craving between the two treatment groups will be analyzed.
- CO in exhaled air levels will be summarized at Baseline and subsequent applicable visits and the change from baseline will be tabulated by overall and by the two treatment groups.

- Scores on the Fagerström Nicotine Dependence Test will be calculated at Baseline, Week 15, and Week 27 and will be summarized at each time point. The change from the baseline will be tabulated for the two treatment group and for overall population.

- Point-prevalence of smoking cessation at week 16 and week 28 (self-reported and confirmed by CO measurement) will be analyzed among compliant subjects (defined as those within the intention-to-treat population who used $\geq$ 1 sachets of their allocated study product per day during week 1 through 6)

In general, missing responses to any questions will be imputed by using the last observation carried forward method (LOCF). If participant did not respond to a question at any of the previous visits, a worst score will be assigned for that question and this score will be carried forward until the time participant responded or completed the study. Missing responses or missing data relating to smoking status will be interpreted as though the participant had smoked on that occasion.

SAFETY ANALYSES

Safety analyses will be performed on the ITT population as well as the fully evaluable population on the basis of treatment actually received.

ADVERSE EVENTS

The subject incidence (%) and number of reports of AEs will be calculated and presented for each treatment by MedDRA term and body system. Individual subject listings of all AEs will be provided. AEs will also be presented by severity and relationship to treatment. The number of subjects who withdrew because of an AE or who died will also be summarized. SAEs will be summarized.

VITAL SIGNS, PHYSICAL AND ORAL EXAMINATIONS

Vital signs will be listed by subject and will be summarized at each time point by treatment. Changes from baseline will also be reported at each time point by treatment. Clinically notable abnormalities will be summarized at each time point by treatment (as percentage of subjects). Summary statistics will be provided.

Status of oral cavity will be summarized at baseline and at the end of study (Week 27) and change from baseline will be tabulated.

PRIOR AND CONCOMITANT MEDICATIONS

Data on medications other than test products used by subjects prior to or during the course of study will be summarized for the overall population and for the two treatment groups.

PRIOR OR CONCOMITANT ILLNESSES

Subjects experiencing any prior or concomitant illness will be reported in subject listings.

WITHDRAWAL OF SUBJECTS FROM THE STUDY AND ANALYSIS

All subjects who discontinued from the allocated intervention will be listed and their reasons for discontinuation will be tabulated for the two treatment groups and for the overall population. Eligible subjects who discontinue after randomization will not be replaced.

STUDY MANAGEMENT

APPROVAL AND CONSENT

REGULATORY GUIDELINES

The study will be performed in accordance with the most recent guidelines of the World Medical Association Declaration of Helsinki, the guidelines of the International Conference on Harmonization (ICH), the Health Insurance Portability and Accountability Act of 1996 (HIPAA), and all other applicable laws and regulations.

INSTITUTIONAL REVIEW BOARD

Conduct of the study must be approved by an appropriately constituted IRB. IRB approval is required for the study protocol, protocol amendments, informed consent forms, subject information sheets, and advertising materials. No study product will be released for the site until written IRB authorization has been received by the Sponsor or its representative and communicated to the Investigator.

INFORMED CONSENT

For each study subject, signed written informed consent will be obtained prior to any protocol-related activities. As part of this procedure, the Investigator must explain orally and in writing the nature, duration, and purpose of the study, and the action of the product in such a manner that the subject is aware of the benefits, potential risks, inconveniences, or adverse effects that may occur as a result of their participation. Subjects should be informed that they may withdraw from the study at any time. Subjects will receive all information that is required by ICH guidelines. The Investigator will provide the Sponsor or its

representative with a copy of the IRB-approved informed consent form (ICF) prior to the start of the study.

DISCONTINUATION OF THE STUDY BY THE SPONSOR

The sponsor reserves the right to discontinue the study at this site or at multiple sites for safety or administrative reasons at any time. In particular, a site that does not recruit at a reasonable rate may be discontinued. Should the study be terminated and/or the site closed for whatever reason, all documentation and equipment pertaining to the study must be returned to the sponsor or its representative.

STUDY DOCUMENTATION

By signing page 2 of this protocol, the Investigator acknowledges that he/she has received appropriate information about the products being tested in the trial and assures the sponsor that he/she will comply with the protocol. No changes in this protocol can be made without the sponsor's written approval.

The Investigator will supply the sponsor with:

- Curricula vitae for all Investigators involved in the trial
- Signed protocol signature page

The sponsor or its representative will supply the Investigator with:

- Clinical study protocol
- Other relevant information about the study products
- Sample informed consent form
- Case report forms (CRFs)/instruction manual
- Equipment for clinical measurements of CO in exhaled air

STUDY MONITORING AND AUDITING

This study will be monitored at all stages of its development by the clinical research personnel employed by the sponsor or its representative. Monitoring will include personal visits and telephone communication to assure that the investigation is conducted according to protocol and in order to comply with guidelines of Good Clinical Practice. On-site review of CRFs will include a review of forms for completeness and clarity, and consistency with source documents available for each subject.

Source documents in this trial will be a variety of documents including clinical records, laboratory reports, participant diaries, and printouts from medical equipment. For machine readings of CO in exhaled air (for which there are no printouts) directly noted on the CRF, the CRF will serve as source document.

Medical advisors and clinical research associates or assistants may request to witness subject evaluations occurring as part of this protocol. The Investigator and appropriate personnel will be periodically requested to attend meetings/workshops organized by the sponsor to assure acceptable protocol execution. The study may be subject to audit by the sponsor or by regulatory authorities. If such an audit occurs, the Investigator must agree to allow access to required subject records. By signing this protocol, the Investigator grants permission to personnel from the sponsor, its representatives, and appropriate regulatory authorities for on-site monitoring of all appropriate study documentation, as well as on-site review of the procedures employed in CRF generation, where clinically appropriate.

DATA VALIDATION

Any data to be recorded directly on the CRFs (to be considered as source data) will be identified at the start of the trial.

All CRF entries must be made in black ink. The Investigator must ensure the accuracy, completeness, legibility, and timeliness of data reported in the CRF and all required reports. Any change or correction to a CRF must be dated, initialed, and explained (if necessary), and must not obscure the original entry. This process applies to both written and electronic changes.

Data reported on the CRF that are derived from source documents should be consistent with the source documents, or the discrepancies must be explained.

Within one week (or other agreed time frame) of completion of each subject, the Investigator should agree to have completed and signed CRFs available for inspection by the clinical monitor.

STUDY PROTOCOL, DOCUMENTATION, AND RETENTION OF RECORDS

Conduct of the study will strictly follow the protocol. However, if any changes become necessary, both the Investigator and the Sponsor must agree to any amendments made to the protocol. All amendments to the protocol must be signed by the Sponsor's Medical Director and the Investigator, except for those referring to organizational changes. Any amendment to the protocol cannot be implemented by the Investigator until an IRB has reviewed and approved the amendment. The Investigator must treat all of the information related to the study and the compiled data as strictly confidential. The Sponsor must approve any transfer of information not directly involved in the study. The Investigator

will be provided with a CRF for each subject to be filled in with all relevant data pertaining to the subject during the study. For each subject, a termination/discontinuation record must be completed. All screened subjects who either entered the study, or were considered ineligible, or were eligible but not enrolled into the study must be documented on a screening log along with the reason for screen failure if applicable.

CRF entries and corrections must be made in a way that does not obscure the original entry. The correct data must be inserted, dated, and initialed by the Investigator. All data entered into the CRF must also be available in the individual subject file either as printouts or as notes taken by either the Investigator or another responsible person assigned by the Investigator. The Investigator agrees to provide the Sponsor with the subject data and to discuss them with representatives of the Sponsor. The Investigator should take measures to prevent accidental or premature destruction of study documents. Subject identification codes have to be retained according to ICH GCP guidelines or for at least 15 years after the completion or discontinuation of the study, whichever is the longest period of time.

The Investigator must arrange for retention of study records at the site for 15 years. The Investigator should take measures to prevent accidental or premature destruction of these documents.

USE OF STUDY FINDINGS

By signing the study protocol, the Investigator agrees to the use of results of the study for the purposes of national and international regulatory authorities. If necessary, those authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement. Reports covering clinical and biometric aspects of the study will be prepared by the Sponsor or its representative.

It is the intention of the Sponsor that the results of the study based on subjects from all participating centers be published in a peer-reviewed international scientific journal irrespective of the study results. After such a joint publication, each investigator is free to present or publish any data based on this study provided the Sponsor is informed at least four weeks in advance.

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APPENDICES

1. Description of study products
2. Fagerström test of nicotine dependence
3. Minnesota Nicotine Withdrawal Scale (Self-Report)
4. Counseling guidelines (modified from Agency for Healthcare Research and Quality Guidelines, Treating Tobacco Use and Dependence: PHS Clinical Practice Guideline Counseling Participants to Quit)

APPENDIX 1. DETAILED DESCRIPTION OF STUDY PRODUCTS

TRADITIONAL SNUS

Active substance: Nicotine

Product name: Snus

Appearance: Paper sachets

Content : Snus is made from ground tobacco leaves, water, and food-allowed additives (salt, humidifier, acidity regulator, and flavor substances). The finished product adheres to an industrial standard which includes limits for undesired substances, see below. No nicotine is added or removed from the product which implies that the nicotine in the product solely comes from the tobacco.

Content (large sachets):	Tobacco	0.5 g
	Water	0.5 g
	Salt (NaCl)	6%
	Nicotine	8 mg
	Propylene glycol (E 1520)	
	Sodium carbonate (E 500)	
	Flavor substances	

Content (small sachets):	Tobacco	0.25 g
	Water	0.25 g
	Salt (NaCl)	6%
	Nicotine	4mg
	Propylene glycol (E 1520)	
	Sodium carbonate (E 500)	
	Flavor substances	

pH: 8.1 to 8.9 (accepted range)

Administration: The sachets are placed in the mouth between the upper gingiva and cheek (upper sulcus). Usage is *ad libitum*. Typically, the sachets are retained for 20 to 30 minutes up to 60 minutes. There is large individual variation in total number of sachets used per day, and the time the sachets are retained in the mouth, which reflects the wide variation in nicotine dose required by habitual users of nicotine products.

Nicotine absorption: 10 to 20% of the nicotine in the sachets is absorbed to the blood through the mucous membranes. The potential nicotine uptake is thus1-2 mg from the large sachets and 0.5 to 1.0 mg from the small sachets.

Side effects: The side effects of the nicotine in snus are the same as those from other sources of nicotine such as cigarettes, and are dose dependent. As is known by every habitual smoker, the side effects are reversible when the dose is reduced or when usage is interrupted.

Common side effects of nicotine include: *Cardiology*: Increased heart rate, slight elevation of blood pressure (typically 5-10 mm Hg), *Neurology*: Vertigo, head ache. *GI*: Nausea, stomach ache, heart burn

The content of sodium carbonate in the product makes it slightly alkaline. This may cause a burning sensation in the mouth at the location of the sachet, particularly among those unaccustomed to the product. Should this problem occur, it can be alleviated by changing the location of the sachet in the upper sulcus, e g by switching to the contralateral side.

Short term use of snus (months) is not associated with any known mucosal side effects. Long term use (several years) may be associated with a mucosal "snus lesion," that is, a whitish thickening of the mucosa. Such lesions are reversible if the placement of the snus sachet is changed, or usage stopped. Snus lesions are not associated with cellular atypia and do not have malignant potential. They are thus quite distinct from oral leukoplakias. Long term use (typically several years), particularly of loose snus products, has in some individuals been associated with exposed dental cervices.

Weight variation of study product: Sachet weight may vary between -10% and +20% of the labelled weight.

Undesired substances: Snus contains traces of undesired substances occurring naturally in tobacco and other agricultural products. The levels are well below the limits of the industrial standard GothiaTek®, and are listed in the table.

Component[1]	Limit[2]	Content[3]	Component[1]	Limit[2]	Content[3]
Nitrite (mg/kg)	3.5	1.1 (<0.5 - 1.9)	Cadmium (mg/kg)	0.5	0.2 (0.1 - 0.3)
TSNA (mg/kg)	5	0.8 (0.4 - 1.1)	Lead (mg/kg)	1.0	0.2 (0.1 - 0.2)
NDMA (µg/kg)	5	0.6 (<0.5 - 1.1)	Arsenic (mg/kg)	0.25	0.08 (<0.03 - 0.13)
BaP (µg/kg)	10	0.9 (<0.5 - 1.8)	Nickel (mg/kg)	2.25	0.8 (0.3 - 1.2)
Pesticides	According to the Swedish Match pesticide policy		Chromium (mg/kg)	1.5	0.5 (0.3 - 0.7)

1: Main undesired components defined by **GothiaTek®**, 2: According to **GothiaTek®**, 3: Results for batches produced by Swedish Match AB 2005, based on a water content of 50%

Packaging & storage: The snus sachets are distributed in round plastic containers. The packaging material is food allowed according to the Swedish Food Act. As the unique production method entails a heat treatment similar to pasteurization, the product is virtually sterile. However, snus should preferably be stored in a refrigerator (2 to 8 °C) to preserve the water content and freshness of the product.

The product is marked with a best-before date which is typically c. 20 weeks after production date. It should be noted that the levels of undesired, potentially toxic substances, such as, nitrosamines, do not increase during storage, even in room temperature. It is mainly the water content that decreases which affects the subjective freshness of the product. There is also a slight decline in the pH level during storage which decreases the amount of bio-available nicotine.

If the product is stored in a freezer (< -18 °C) the best before date is postponed almost indefinitely.

PLACEBO SNUS

Active ingredient/content: No active substance. The product only contains food-allowed constituents, ingredients and additives.

Appearance: Paper sachets. The physical appearance and flavoring is the same as that of the traditional snus.

Content (large sachets):	Cocoa bean fibers, oat fibers	0.5 g
	Water	0.5 g
	Salt (NaCl)	5.5%
	Sodium carbonate (E500)	
	Propylene glycol (E 1520)	
	Flavor substances	

Content (small sachets):	Cocoa bean fibers, oat fibers	0.25 g
	Water	0.25 g
	Salt (NaCl)	5.5%
	Sodium carbonate (E500)	
	Propylene glycol (E 1520)	
	Flavor substances	

pH: 8.1 to 8.9 (accepted range)

Weight variation of study products: Sachet weight may vary between -10% and +20% of the labelled weight, the mean weight is: 1.0 g (large sachets) and 0.5 g (small sachets)

Administration and usage: Same as with traditional snus

Side effects: None reported during short-term usage (a few weeks to months). However, because the product is slightly alkaline just as traditional snus, users may initially experience a burning sensation in the oral mucosa at the location of the sachet, particularly among those unaccustomed to the product. As a result of the pH, long term use (several years) may theoretically be associated with mucosal "snus lesions," just as traditional snus. Such lesions, should they occur, are of minor

clinical significance and are expected to be infrequent among participants in the current study.

Packaging & storage: The sachets come in round plastic containers identical to those used for traditional snus. The packaging material is food allowed according to the Swedish Food Act. The product is marked with a best-before date which is typically c. 20 weeks after production date. Water content and freshness is best preserved if the product is stored in a refrigerator (2 to 8^{o}C).

If the product is stored in a freezer (< -18^{o}C) the best before date is postponed almost indefinitely.

APPENDIX 2. FAGERSTRÖM TEST FOR NICOTINE DEPENDENCE

1. How soon after waking do you smoke your first cigarette?

a) Less than five minutes (3p)
b) 5-30 minutes (2p)
c) 31-60 minutes (1p)
d) More than an hour (0p)

2. Do you find it difficult to refrain from smoking in places where it is forbidden?

a) Yes (1p)
b) No (0p)

3. Which cigarette would you most hate to give up?

a) First one in the morning (1p)
b) Any other (0p)

4. How many cigarettes do you smoke per day?

a) More than 30 per day (3p)
b) 21-30 per day (2p)
c) 11-20 per day (1p)
d) 10 or less per day (0p)

5. Do you smoke more frequently during the first hours after waking than during the rest of the day?

a) Yes (1p)
b) No (0p)

6. Do you smoke if you are so ill that you are in bed most of the day?

a) Yes (1p)
b) No (0p)

APPENDIX 3. MINNESOTA NICOTINE WITHDRAWAL SCALE (SELF-REPORT)

Behavior Rating Scale Self-Report

Please rate yourself for the period for the last 24 hours:

0 = none, 1 = slight, 2 = mild, 3 = moderate, 4 = severe

1. Angry, irritable, frustrated	0 1 2 3 4
2. Anxious, nervous	0 1 2 3 4
3. Depressed mood, sad	0 1 2 3 4
4. Desire or craving to smoke	0 1 2 3 4
5. Difficulty concentrating	0 1 2 3 4
6. Increased appetite, hungry, weight gain	0 1 2 3 4
7. Insomnia, sleep problems, awakening at night	0 1 2 3 4
8. Restless	0 1 2 3 4
9. Impatient	0 1 2 3 4

Hughes JR, Hatsukami DK. Signs and symptoms of tobacco withdrawal. Arch Gen Psychiatr 1986; 43:289-294.

Scale available at http://www.uvm.edu/~hbpl/minnesota/2005/Behavior%20Rating%20Scale%20-%20Self%20Report.pdf

APPENDIX 4: COUNSELING GUIDELINES

Modified from Agency for Healthcare Research and Quality Guidelines, Treating Tobacco Use and Dependence: PHS Clinical Practice Guideline Counseling Participants to Quit

The counseling can be divided into practical and supportive counseling advice.

Practical counseling advice (problem-solving/skills training)	Examples
Recognize danger situations. Identify events, internal states, or activities that increase the risk of cigarette use	• Negative affect. • Being around other smokers. • Drinking alcohol. • Experiencing urges. • Being under time pressure.
Develop coping skills. Identify and practice coping or problem-solving skills. Typically, these skills are intended to cope with danger situations.	• Learning to anticipate and avoid temptation. • Learning cognitive strategies that will reduce negative moods. • Accomplishing lifestyle changes that reduce stress, improve quality of life, or produce pleasure. • Learning cognitive and behavioral activities to cope with smoking urges (e.g., distracting attention).
Provide basic information. Provide basic information about smoking and successful methods to switch to a non-smoking behavior	• Any smoking (even a single puff) increases the likelihood of failure. • Withdrawal typically peaks within 1-3 weeks after switching from cigarettes • Withdrawal symptoms include negative mood, urges to smoke, and

	difficulty concentrating.

Supportive counseling advice	Examples
Encourage the smoker	• Communicate belief in the participant's ability to replace cigarettes • Note that effective alternatives are now available. • Note that half of all people who have ever smoked have stopped using cigarettes
Communicate caring and concern.	• Ask how the participant feels about replacing cigarettes • Directly express concern and willingness to help. • Be open to the participant's expression of fears of not using cigarettes, difficulties experienced, and ambivalent feelings.
Encourage the participant to talk about the process.	Ask about: • Reasons the participant wants to switch from cigarettes • Concerns or worries about the switch from cigarettes • Success the participant has achieved. • Difficulties encountered with the switch

Internet Citation:

Counseling Patients To Quit. U.S. Public Health Service. Agency for Healthcare Research and Quality. Rockville, MD. http://www.ahrq.gov/clinic/tobacco/counsel.htm

Final Clinical Protocol (12 November 2008)

Swedish Match AB
SWEDEN

Covance

3402 Kinsman Boulevard, Madison, Wisconsin 53704

STUDY PROTOCOL No. SM 08-01:

A CONTROLLED STUDY OF THE ABILITY OF A TRADITIONAL SWEDISH SMOKELESS TOBACCO PRODUCT ("SNUS") TO INCREASE THE QUIT RATE AMONG CIGARETTE SMOKERS WHO WISH TO STOP SMOKING

Principal Investigator:

Karl Fagerström, Ph. D.

LIST OF ADDRESSES

SPONSOR:	**SWEDISH MATCH AB** **ROSENLUNDSGATAN 36** **SE-118 85 STOCKHOLM** **SWEDEN**
SPONSOR'S RESPONSIBLE MEDICAL DIRECTOR:	**LARS E. RUTQVIST, M. D., PH. D.**
COVANCE STUDY MANAGER:	**JASMINE ROPERS** **3402 KINSMAN BOULEVARD** **MADISON, WI 53704**
COVANCE COORDINATOR:	**LEANNE MCGANN** **3402 KINSMAN BOULEVARD** **MADISON, WI 53704**
COVANCE DATA MANAGEMENT:	**CHRISTY SEAHOLM** **3402 KINSMAN BOULEVARD** **MADISON, WI 53704**
INSTITUTIONAL REVIEW BOARD (IRB):	**INDEPENDENT INVESTIGATIONAL REVIEW BOARD LLC.** **6738 WEST SUNRISE BLVD, SUITE 102** **PLANTATION, FLORIDA 33313**

SIGNATURE PAGE

SWEDISH MATCH APPROVAL:

Signature: _____ Date: 2013-01-28

Name: Lars E. Rutqvist, M.D., Ph. D
Vice President – Scientific Affairs
Swedish Match AB

COVANCE APPROVAL:

Signature: Jasmine Ropers Date: 1 Feb 2013

Name: [Name] Jasmine Ropers
[Department, Title] Early Clinical Dev, Project Manager

INVESTIGATOR PROTOCOL AGREEMENT PAGE

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by the sponsor.
- Not to implement any changes to the protocol without written agreement from the sponsor and prior review and written approval from the Institutional Review Board (IRB) except where necessary to eliminate an immediate hazard to subjects.
- That I am thoroughly familiar with the appropriate use of the study product, as described in this protocol and any other information provided by the sponsor including, but not limited to, the current protocol.
- That I am aware of, and will comply with, "good clinical practices" (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the study product and of their study-related duties and functions as described in the protocol.

Signature: H Frank Farmer JR Date: 13 Nov 2008

Name (print): H Frank Farmer JR MD
Investigator

Site Number: 01

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Signature: Carter MD Date: 17 Nov 2008

Name (print): David C. Carter, MD
Investigator

Site Number: 02

INVESTIGATOR PROTOCOL AGREEMENT PAGE

I agree:

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Signature: _____ Date: 17 Nov 2008

Name (print): Keith Klatt, MD
Investigator

Site Number: 04

INVESTIGATOR PROTOCOL AGREEMENT PAGE

I agree:

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- To ensure that all persons assisting me with the study are adequately informed about the study product and of their study-related duties and functions as described in the protocol.

Signature: _____ Date: 13 NOV 2008

Name (print): RANDALL STOLTZ, MD
Investigator

Site Number: 05

SYNOPSIS

Title Of Study	A controlled study of the ability of a traditional Swedish smokeless tobacco product ("snus") to increase the quit rate among cigarette smokers who wish to stop smoking
Investigator/Study Center	Multicenter; an estimated 6 sites in the United States
Phase Of Development	Phase III
Objectives	*Primary:* to examine the ability of a traditional Swedish low nitrosamine smokeless tobacco product ("snus") to increase the quit rate among cigarette smokers aged between 25-65 years who wish to stop smoking. This will be measured as continuous abstention from smoking during Week 6 through Week 28 documented by subjects and biologically confirmed by expired air carbon monoxide (CO) less than or equal to the cut off point of 8 ppm. The study is double-blind and placebo-controlled using a non-tobacco, non-nicotine snus-like product as placebo. *Secondary:* • To examine the extent of continuous complete abstention from smoking during Week 6 through Week 16 as well as point-prevalence rates of smoking cessation at week 16 and 28, biologically confirmed by expired air carbon monoxide (CO) less than or equal to 8 ppm • To examine the withdrawal symptoms and cravings of snus compared to placebo as measured by the Minnesota Nicotine Withdrawal Scale. Tobacco dependence will also be measured by the Fagerström Test for Nicotine Dependence. • To examine the safety of snus compared to placebo as measured by adverse events, change from baseline in body weight, oral cavity health, physical examinations, and vital sign measurements • To examine compliance to the allocated study product during the intervention period as well as use of OTC NRT and/or smokeless tobacco products during the follow-up • To examine smoking cessation measured as point-prevalence rates at week 16 and 28 (biologically confirmed by expired air carbon monoxide (CO) less than or equal to 8 ppm) among compliants defined as participants who used $\geq$ 1 sachets of their allocated study product per day during week 1 through 6.
Design	This is a multicenter, randomized, double-blind, placebo-controlled trial designed to examine the ability of snus to increase quit rates among cigarette smokers who wish to stop smoking. The study consists of four phases: pre-randomization screening (up to 2 weeks), Study product test period (4 weeks), Intervention Phase (12 weeks), and a Follow-Up Phase (12 weeks). Potential subjects will be invited to attend an Information Session and Screening visit for evaluation of eligibility. At randomization the participants will be randomly assigned in a 1:1 ratio to receive either snus or placebo snus for 16 weeks. During a 4-week test period the participants will be instructed to use the study products when they feel or expect an urge to

	smoke, initially without requirement of complete abstention from cigarettes. During the following 12-week intervention phase subjects are encouraged to completely stop smoking. If they feel an urge to smoke they are instructed to use their allocated study product instead of smoking. Participants will be continuously supplied with their allocated product. The participants will be instructed to cut down on product use during the last 3 weeks of the intervention to avoid a too abrupt ending of nicotine intake. After the intervention phase the subjects will be followed for an additional 12 weeks. Subjects will come to the clinic for a total of 6 visits, with 8 additional telephone visits. The maximum duration for individual subject participation (including pre-randomization screening) is 30 weeks.
Planned Sample Size	The primary endpoint is the quit rate among cigarette smokers who wish to stop smoking. The quit rate is examined between subjects randomized to snus as compared to subjects randomized to placebo. Assuming a rate of 12% in the placebo group and 27% in the active snus group, a two group continuity corrected χ^2 test with a 0.050 two-sided significance level will have 80% power to detect the difference between the active group proportion, p1, of 0.270 and the placebo group proportion, p2, of 0.0120 (odds ratio of 0.369) when the sample size in each group is 122 (total sample size of 244). The study is therefore intended to include a total of 250 participants. Treatment assignments will be balanced between active and placebo groups. The ITT population will be used for all statistical analyses of treatment efficacy.
Diagnosis And Key Subject Selection Criteria	*Key Inclusion Criteria*: • Subjects between 25 and 65 years of age, inclusive, who smoke > 9 cigarettes per day (average daily consumption during past month) • The subject has smoked daily >1 year • Subjects motivated to quit smoking using a smokeless tobacco product • Subjects in good general health *Key Exclusion Criteria:* • Use of smokeless tobacco during past 6 months or subjects unable to refrain from NRT during the study. • Current oral condition that could potentially be made worse by study treatment • Use of any type of pharmaceutical (including some psychotropics, e.g., wellbutrin) or other products for smoking cessation within the past 3 months • History of clinically significant renal, hepatic, neurological, or chronic pulmonary disease that in the judgment of the investigator precludes participation • History of significant cardiovascular disease, including myocardial infarction within the last 3 months, significant cardiac arrhythmias, or poorly controlled hypertension that in the judgment of the investigator precludes participation • History of alcohol or substance abuse other than cigarette smoking within the past year
Treatments	• Traditional, low nitrosamine Swedish snus in 0.5 or 1.0 g sachets *ad libitum* • Matching placebo (without tobacco or nicotine)
Main Outcome Parameters	• Continuous rates of smoking cessation by self-report and confirmed by expired air CO less than or equal to 8 ppm

	• Point-prevalence smoking cessation rates (during preceding week) confirmed by expired air CO less than or equal to 8 ppm • Minnesota Nicotine Withdrawal Scale • Fagerström Test for Nicotine Dependence
Main Safety Parameters	• Adverse events • Vital sign measurements, including body weight • Oral cavity health • Physical examinations
Statistical Methods	The primary outcome measure will be continuous complete smoking cessation from Week 6 through Week 28 (at all measurement points/visits) as reported by subjects and corroborated by objective verification using the CO value from exhaled air of less than 8 ppm at all relevant visits. Further exploratory analysis will be performed to assess the relationship between various baseline characteristics (age, gender, etc.) and the defined endpoints. For secondary outcome endpoints, point prevalence of smoke-free subjects at Week 16 and Week 28 will be summarized as the rate during the preceding week (self-reported and confirmed by CO measurement). Withdrawal symptoms measured by the Minnesota Nicotine Withdrawal Scale scores will be calculated and summarized by treatment group and overall. The analyses will be done both including all randomized subjects as well as restricted to those who actually managed to stop smoking The differences in the average daily symptom score between the two treatment groups will be analyzed. In addition, "Craving" will be analyzed separately. CO in exhaled air levels will be summarized at Baseline and subsequent applicable visits and the change from baseline will be tabulated by overall and by the two treatment groups. The difference in the change from baseline between the two treatment groups will be analyzed. Scores on the Fagerström Nicotine dependence will be calculated at Baseline, Week 16, and Week 28 and will be summarized at each time point. The change from the baseline in the Fagerström score will be tabulated for the two treatment group and for overall population. Incidence of SAE:s, discontinuation from the study because of an AE, and compliance to allocated study product will be analyzed by allocated treatment. Refer to Section 4.8 for analysis of safety variables.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
CFR	Code of Federal Regulations
CO	carbon monoxide
CRF	case report form
CRO	contract research organization
GCP	good clinical practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
IRB	Institutional Review Board
ITT	intention-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
NRT	nicotine replacement therapy
ppm	parts per million
SAE	serious adverse event
ST	smokeless tobacco
TD	target day
US	United States
WHO	World Health Organization

INTRODUCTION

BACKGROUND AND RATIONALE

Tobacco, which is usually smoked, has well documented detrimental effects on health. Before the mass production of cigarettes, it was common to use tobacco in non-smoked forms, such as a dry, fine-grained powder for nasal sniffing or moist grained tobacco for oral use usually held between check and upper gum. Smokeless tobacco (ST) is still a common form of tobacco used in countries such as India, Sudan, Sweden, and the United States (US).

Smokeless tobacco has been classified by the World Health Organization (WHO) as a carcinogen; however ST products vary widely in tobacco used, curing, production (pasteurization or fermentation), additives, and storage. Because ST is not burned and carcinogenic pyrolysis by-products are not formed, ST has been advocated by many health protection institutions and scientists as a possible harm reduction tool.[1-4]. While the Indian and Sudanese products (e.g., Guthka and Tombak) have been found to be carcinogenic, evidence for the much researched Swedish ST product commonly called "snus" has not been definitive.

Swedish "snus" is different in many significant respects from American moist snuff. It is manufactured using a heat-treatment technique which renders the finished product virtually sterile. This technique has contributed to the fact that "snus" historically and today have much lower levels of potentially carcinogenic nitrosamines than American moist snuff which is a fermented product. Swedish Match has also introduced an industrial standard for its snus products (GothiaTek) which includes limits for potentially toxic compounds. The guiding principle for these limits has been those set for common food-stuffs.

Traditionally "snus" is used in the upper sulcus (under the upper lip) which reduces salivation so there is no need to spit while using the product.

ORAL CANCER

The use of ST use has been associated with oral cancer for many decades, and there is a strong, widespread belief in this association. However, a recent review concluded that the use of chewing tobacco and moist snuff were associated with only minimally elevated risks, while other types of ST conferred higher risks.[5] Two of seven studies reviewed tested Swedish snus and demonstrated no oral cancer risk.[6,7] These results formed the basis for the European Union's decision in the year 2000 to remove the cancer warning from snus products. In a recent study, 1,115 snus users were followed for 29 years. Snus-induced lesions were common but oral cancer rarely occurred at the site of these lesions ;[8] there are, however, some anecdotal reports of oral cancer in long term snus users. [9]

CARDIOVASCULAR AND OTHER DISEASE

Epidemiological studies have examined the role of snus in cardiovascular disease (five studies), myocardial infarction (four studies), and stroke (one study). In three of the four studies on myocardial infarction, no increased risk was seen in snus users.[10-12] In the fourth study a significant increase in risk was noted but it was lower than that of smoking.[13] There was no association noted with use of snus and the occurrence of stroke.[14]

Two studies have examined the impact of snus as a risk factor for adult-onset diabetes, as some have hypothesised that ST could change glucose tolerance or insulin concentrations. One of these studies [15] found that snus users had a slightly elevated risk while the other reported that the risk of diabetes was not increased.[16]

OTHER CANCERS

No association with the use of snus and gastrointestinal or urinary tract cancer has been found.[17]

RESPIRATORY DISEASE

As there is no plausible causal mechanism whereby snus could cause respiratory disease, there are no studies available that have examined the effect snus has on respiratory disease.

PREGNANCY

One study has examined the effect of snus on pregnancy, and found snus was associated with increased risk of preterm delivery and preeclampsia.[18] Given that animal studies have implicated nicotine as a cause of some of the widely known adverse effects of tobacco exposure during pregnancy it follows that snus use during pregnancy is likely to incur some of the risks associated with smoking.

EPIDEMIOLOGY OF SNUS USE IN SWEDEN

In 2005, 22% of adult males in Sweden were daily snus users and 13% smoked cigarettes.[19] For women the figures were very different, 4% used snus and 17% smoked. Among young boys (age 15), 14% were daily or almost daily users of snus and 5% smoked. For girls the figures were 3% and 13 %.[19]

It is increasingly evident that snus can replace cigarettes among former smokers. In 2001, 47% of current snus users were found to have been smokers previously, according to a study commissioned by Swedish Match.[20] In another study commissioned by The Swedish Cancer Society and Pharmacia Corporation,[21] 1,000 Swedish ex-smokers were asked about their quitting methods. Fifty percent had not used any help to stop, 33% had replaced their cigarettes with snus, and 17% used nicotine replacement therapy (NRT) during some quit attempt. Twenty-eight percent of men reported having used snus during their last quit attempt. Ramström[22] found that among males using a product on their last quit attempt, 55% used snus. For females the figure was 15%. The rate of complete cigarette replacement with use of snus was 65% for males and 52% for females. For nicotine gum and patch, non-smoking rates were 46% and 32% for males and 37% and 30% for females, respectively. That

many Swedish smokers have switched completely to snus is also supported by data from local studies in northern and southern parts of Sweden.[23, 24]

In Sweden, snus is used at least as often as NRT at quit attempts and the rates of total cigarette replacement with snus are at least as high as the smoking cessation rates seen with NRT. Ramström and Foulds recently found that 55% of men attempting to completely replace cigarettes had used snus. A total of 26% used NRT in their latest quit attempt.[25] In a cross-sectional study in southern Sweden, 30% of men and 9% of women had used snus at attempts to replace cigarettes occurring between 2000 and 2004.[26]. In a recent study on Swedish twins it was found that snus use was strongly linked with complete cigarette replacement, particularly among more dependent cigarette smokers.[27]

Interpreting data on the acceptability and safety of snus to replace cigarettes is unclear to most tobacco control advocates, who have voiced fears that promotion of use of ST to replace cigarettes may be harmful because snus could be a "gateway" to later smoking as a more effective tool for nicotine delivery.[28-32] Several studies from Sweden [22, 25, 29] and the US [30, 31] however show that early ST use does not increase, but rather prevents later cigarette smoking. A few studies have found the opposite effect.[32, 33]

SNUS AND NICOTINE YIELD

Use of NRT to replace cigarettes typically has an under-dosing effect that results in low blood nicotine concentrations due to the low nicotine delivery of several products. NRT is also associated with poor compliance, in part because they are not very consumer friendly. Generally NRT users have 50 to 80% of the blood nicotine concentrations compared to smokers. ST delivers nicotine concentrations much closer to those of the cigarette than NRT.[34] In fact, Swedish snus can deliver blood levels similar to that of cigarettes although the nicotine absorption is slower and there is no "bolus" that results from inhalation of nicotine.[35] In a pharmacokinetic study, administration of nicotine gum (2 mg administered hourly for 12 hours) was compared with snus products in two sachet sizes: 0.5 g and 1.0 g. After 12 hours, the blood nicotine concentrations were 11 ng/ml with a 0.5 g snus sachet, 13 ng/ml for nicotine gum 2 mg, and 21-29 ng/ml with 1.0 g sachets of different snus brands commonly used in Sweden. [36]

SMOKELESS TOBACCO AS A SUBSTITUTE FOR CIGARETTES

Data previously described have spurred an interest in testing ST as a substitute for cigarettes among smokers interested in an alternative, smokeless tobacco product[37] including the Task Force of the European Respiratory Society [38]. The first smoking cessation study with ST, although uncontrolled, obtained a one year smoking cessation rate of 35% in heavily dependent smokers.[39] In a more recent study with 50 head and neck cancer patients, smoking cessation advice was repeatedly given by nurses at radiation therapy visits. Nicotine patches were chosen by 89% and snus was chosen by 50% of these smokers, often in combination. At 1 year, 68% were carbon monoxide (CO)-verified smokefree.[40]. Although both of these studies produced quit rates that are much higher than those typically seen in formal smoking cessation studies,[49] they were uncontrolled studies.

ETHICAL CONSIDERATIONS

Cigarette smoking is a significant public health problem in most countries. The number of smokers in the U. S. has not decreased substantially during the past 10-15 years. The addictive nature of cigarette smoking and the limited success of traditional anti-smoking measures represent a significant challenge to public health. In conclusion, there is a great need for further research on effective strategies for smoking cessation.

The current trial aims to determine the acceptability of Swedish snus among adult U.S. smokers, and to evaluate if use of snus can increase quit rates among cigarette smokers who want to quit smoking. The trial thus has considerable interest both from a scientific and public health point of view.

It might be viewed as problematic from an ethical point of view that the study does not entail treatment with products that have been demonstrated to be effective to achieve smoking cessation in the context of controlled clinical trials, such as, NRT, bupropion or varenicline. However, there are extensive epidemiological data from Sweden suggesting that snus has been used by many smokers to quit smoking and that it might even be more effective than NRT in achieving complete, long-term smoking cessation. All participants will also be informed about all available, evidence-based methods for smoking cessation.

There are extensive data from epidemiological studies demonstrating that smokeless tobacco, particularly low-nitrosamine Swedish snus, is associated with dramatically reduced health risks compared to cigarette smoking. The risk profile with snus thus appears closer to that of no tobacco use, than to cigarette smoking. So, switching from cigarettes to snus, albeit another tobacco product can be expected to be associated with significantly reduced health risks. Moreover, the trial design implies exposure to snus during only 16 weeks.

The addiction to cigarettes may not entirely be a result of the physical addiction to nicotine, but also in part a psychological phenomenon related to the stimuli and attributes of cigarette smoking. It is therefore essential to include a placebo control arm in studies of smoking cessation, and to conduct such trials with a randomized, double-blind technique, even though such study features may be viewed as problematic from an ethical point of view.

The clinical tests in the trial involve invasive methods (blood sampling), but such tests are part of routine medical care and are associated with minimal risks. Individual test results will be treated confidentially and will only be revealed to the study participants to minimize problems related to personal integrity. All participants will provide written informed consent to participate in the trial.

The participants will receive economic compensation for their participation in the study. However, the compensation is moderate and does not exceed what is typical in studies of this complexity so there is no reason to assume that the compensation *per se* will act as a pressure on potential participants to accept participation or on participants to continue in the trial should they wish to terminate their participation prematurely.Conduct of the study

will be approved by an appropriately constituted institutional review board (IRB) or independent ethics committee (IEC). No study products will be shipped to a site until written IRB/IEC authorization has been obtained.

STUDY PURPOSE

The current study will be the first randomized, placebo-controlled, double-blind clinical trial to test if use of a low-nitrosamine, Swedish snus product can increase the smoking cessation rate among cigarette smokers who wish to quit smoking.

STUDY OBJECTIVES

PRIMARY OBJECTIVE

The primary objective of this study is to examine if a traditional Swedish low-nitrosamine smokeless tobacco product ("snus") compared to placebo can increase the quit rate among cigarette smokers who wish to stop smoking measured as continuous, complete smoking cessation during Week 6 through Week 28 documented by subjects and biologically confirmed by expired air CO less than or equal to 8 ppm.

SECONDARY OBJECTIVES

The secondary objectives of this study are:

- To examine continuous complete quit rates (biologically confirmed) during Week 6 through Week 16,
- To examine point-prevalence (preceding week) quit rates (biologically confirmed) at the clinical visits during Week 10, 16, and 28
- To examine the withdrawal symptoms and cravings of snus compared to placebo as measured by the Minnesota Nicotine Withdrawal Scale at Weeks 6, 10, 16, and 28. Additionally, tobacco dependence will be measured by the Fagerström Test for Nicotine Dependence at Week 16 and 28.
- To examine the safety of snus compared to placebo as measured by adverse events, change from baseline in body weight, oral cavity health, physical examinations, and vital sign measurements.
- To collect blood samples at baseline and at week 6, 16, and 28 which will be used for exploratory analyses of nicotine metabolites and biomarkers of exposure and/or disease related to tobacco use.

INVESTIGATIONAL PLAN

DESCRIPTION OF OVERALL STUDY DESIGN AND PLAN

This is a multicenter, randomized, double-blind, placebo-controlled trial designed to examine the ability of snus compared to placebo to increase the quit rate among cigarette smokers who wish to stop smoking. A total of 250 subjects who are habitual cigarette smokers aged 25 through 65 years will be randomly assigned to be offered tobacco-based, nicotine-containing snus or matching placebo snus (without tobacco and nicotine).

The study consists of three phases: Screening (up to 2 weeks), Study Product Test Period (4 weeks), Intervention Phase (12 weeks), and a Follow-Up Phase (12 weeks).

Potential subjects will be invited to the clinic to attend an Information Session and Screening visit for further evaluation of eligibility.

During the Baseline Visit, subjects will be randomly assigned in a 1:1 ratio to receive either snus or placebo. Over the next 4 weeks, subjects will be acclimatized to the allocated product and will be instructed to try to refrain from cigarettes through the use of the product when they feel or expect an urge to smoke. If subjects still feel an urge to smoke after c. 15-20 minutes, they may do so. Subjects will be encouraged to gradually substitute as many cigarettes as possible and to refrain from all cigarettes at the latest by the first day of Week 5 (or sooner if they can manage to do so). Use of study product will continue for a total of 12 weeks. The participants will be instructed to cut down on product use during the last 3 weeks of the intervention to avoid a too abrupt ending of nicotine intake.

Cigarette replacement will be assessed by self-report and exhaled CO. Subjects will be provided with an education booklet on the hazards of cigarettes (the National Cancer Institute's "Cleaning the Air" booklet) and will be provided with brief (< 10 minutes) counseling at each visit following Agency for Healthcare Research and Quality guidelines (Appendix 4).

After the intervention phase all subjects will be followed-up for an additional 12 weeks. Subjects will come to the clinic for a total of 6 visits, with 8 additional telephone visits. The maximum duration for individual subject participation is 30 weeks, including the 2 week screening phase.

The amount of nicotine needed to prevent withdrawal symptoms among cigarette smokers varies considerably. The amount of study product used by subjects is therefore also expected to vary and is dependent on the extent to which the products actually replace cigarettes. Subjects will therefore be instructed to use the products *ad libitum*, and will be informed that one 1.0 g snus sachet typically can replace one cigarette. Subjects will be instructed to use at least 10 1.0 g sachets per day (or 20 sachets if the subject has elected to use the 0.5 g sachets).

Recommended maximum number of 1.0 g sachets per day is 24. However, among those who are heavy smokers (≥ 15-20 cigarettes per day), or who are strongly nicotine dependent as evidenced by a Fagerström score of 7 or higher at baseline, and who try to replace all cigarettes with study product, total number of sachets needed per day may be higher

BIOMARKER BLOOD TESTS

In addition to the lab tests used to assess eligibility, blood will be drawn for biomarkers on all participants during screening, and at weeks 6, 16, and 28. The total amount of blood drawn on each occasion will be approximately 40 ml with equal amounts of serum and plasma samples. The research samples will be used for exploratory analyses of nicotine metabolites and biomarkers of exposure and/or disease related to use of tobacco.

SCREENING (UP TO 2 WEEKS, WEEK -2 TO BASELINE)

The Screening Phase will consist of an Information Session and Screening Visit (which may be scheduled consecutively at one occasion at the discretion of the Investigator). During the Information Session potential subjects will receive information on the health risks associated with the range of nicotine products including cigarettes, non-snus smokeless, snus and NRT, and their relative harm. Possible alternative treatments will also be outlined. The physiological effects of nicotine will be described, and an account given of experience with Swedish snus, including potential health risks associated with different types of smokeless tobacco products.

The Screening Visit will include an explanation of the purpose and nature of the study and subjects will provide voluntary written informed consent. A complete medical history will be taken (including assessment of smoking status; i.e., age of initiation of daily smoking; average number of cigarettes smoked per day during the past year; history of previous quit attempts; desire to quit cigarettes & smoking; history of previous use of NRT, other pharmaceutical, or other smoking cessation aids, history of previous ST use), along with a physical examination, blood tests, ECG (supine position for at least 5 minutes), oral cavity examination, and vital sign assessment. Subjects will also be provided with an education booklet (the National Cancer Institute's "Cleaning the Air" booklet) and will be provided with brief (<10 minutes) counseling following Agency for Healthcare Research and Quality guidelines.

STUDY PRODUCT TEST PERIOD (BASELINE THROUGH WEEK 4)

Baseline Visit

Qualifying subjects will return to the clinic for a Baseline assessment and random allocation to study product (snus or placebo). Assessments will be completed as outlined in *Schedule of Events).*

Subjects will be given a diary to record their use of study product consumption, including number and size of sachets used, and number of cigarettes smoked, if any.

Usage of study products including how it is placed in the mouth will be demonstrated to the participants.

Week 1 through Week 4

During this phase, subjects will undergo acclimatization to treatment and will be instructed to try to refrain from cigarettes by the use of allocated study product when they feel an urge to smoke. Each subject will be provided with blinded study products of two sachet sizes. Preferred sachet size and the number of sachets consumed per day are determined by the participants themselves and will vary based on individual preferences and smoking habits. One 1.0-gram sachet delivers roughly the same amount of nicotine as one cigarette. If subjects still feel an urge to smoke after c. 15-20 minutes, they can do so provided sachets of study product are removed to avoid nicotine overdosage.

Subjects will be encouraged to gradually substitute as many cigarettes as possible with the study products. The recommended number of 1.0 g sachets to be used per day is 10-24 unless the subject habitually have smoked >15-20 cigarettes per day, or are highly nicotine dependent as evidenced by a score on the Fagerström scale of 7 or more, and attempts to replace all cigarettes with study products. Among such individuals the number of sachets needed per day may be higher than 24. The goal is to replace all cigarettes completely no later than the first day of Week 5 (start of the Intervention Phase).

Subjects will also be instructed that no other source of nicotine (other than cigarettes) or study product should be used during the Test Period, and that NRT or any other pharmaceutical smoking cessation aid is not allowed.

Each week during this period sites will contact each subject by telephone to monitor progress and to assess compliance and adverse events. Brief behavioral counseling will also be included. Subjects will be reminded about the complete switch from cigarettes no later than the first day of Week 5.

INTERVENTION PHASE (WEEK 5 THROUGH WEEK 16)

Clinic visits will occur at Week 6, Week 10, and 16. These visits will include monitoring of each subjects progress (including self-reported smoking status and measurement of CO in exhaled air), brief behavioral counseling, and vital sign assessment. Clinic visits must be performed +/- 3 days from the target date of the visit. Other assessments will be completed as outlined in *Schedule of Events.*

At the Week 6 and 10 visits, subjects will receive continued supply of study product in their preferred size. Subjects will be provided with a sufficient quantity of the study product to last until the next clinic visit, or to the end of the Intervention Phase.

Telephone contacts will be completed at Weeks 8 and 13 to monitor each participant's progress, to assess compliance and any adverse events, and to provide brief behavioral counseling. At the week 13 contact, the participants will be instructed to cut down on product use during the last 3 weeks of the intervention to avoid a too abrupt ending of nicotine intake.

At Week 16, subjects will return to the clinic to assess smoking cessation (based on self-report and measurement of CO in exhaled air), study product use and compliance, vital sign assessment, and assessment of adverse events. Other assessments will be completed as outlined in the *Schedule of Events.*

FOLLOW-UP PHASE (WEEK 17 THROUGH WEEK 28)

All subjects will be encouraged to continue in the study for follow-up independent of smoking status. Use of study product will be discontinued. Telephone contacts will occur during Weeks 20 and 24, with a final clinic visit at Week 28. Assessments at the Week 28 visit will include review of subjects' self-reported tobacco status relative to the use of cigarettes, verified by CO in exhaled air. Other assessments as described on the *Schedule of Events* will also be completed at the final visit.

If a subject has managed to quit cigarettes during the *Intervention Phase* with the help of their allocated study product and at the 16 wk visit or anytime thereafter there is an imminent danger of smoking relapse during the *Follow-Up Phase*, that subject should be informed that use of NRT or a smokeless tobacco product is a better option in terms of health risks than a smoking relapse.

If a subject discontinues participation during the *Intervention Phase*, the procedures that would be done at Week 16 will be completed at the time of discontinuation. If a subject discontinues participation during the *Follow-Up Phase*, the procedures that would be done at Week 28 will be completed at the time of discontinuation.

SELECTION OF STUDY POPULATION

Subjects will be identified from clinic data bases and/or through advertisements. A total of 250 male and female smokers aged between 25 and 65 years who are otherwise healthy will be eligible for study entry. It is anticipated that approximately 6 sites in the United States with sufficient experience and access to the desired subject population will participate.

INCLUSION CRITERIA

Subjects meeting all of the following inclusion criteria at screening should be considered for admission to the study:

1. The subject is male or female, between 25 and 65 years of age, inclusive. If female, the subject has a negative urine pregnancy test and is not lactating, or has not been of childbearing potential for at least 3 months prior to use of study product. To be considered to be not of childbearing potential, the subject must be postmenopausal for at least 2 years; have had a hysterectomy or bilateral tubal ligation, or be proven to be otherwise incapable of pregnancy. If of childbearing potential, the subject must have been practicing one of the following methods of contraception consistently for at least 1 month prior to study entry and agree to continue practicing it during the study: hormonal contraceptives, intrauterine device, spermicide and barrier, spouse/partner sterility; or is practicing abstinence and agrees to continue abstinence or to start an acceptable method of contraception from the above list if sexual activity commences.
2. The subject smokes > 9 cigarettes per day (average daily consumption during past month)
3. The subject has smoked daily for > 1 year.
4. The subject is motivated to quit smoking with the help of a smokeless tobacco alternative
5. The subject is in good general health as evidenced by medical history, physical examination, routine blood chemistry (Hb, total WBC, transaminases, creatinine, electrolytes) , and an ECG
6. The subject practices, by self-report, good oral hygiene (including brushing teeth at least twice per day and having regular dental check-ups).
7. The subject is able and willing to provide written informed consent.
8. The subject agrees to comply with the requirements of the protocol and complete study measures.
9. The subject has stable residence and telephone and can provide the name of an outside household collateral family member or close friend.

EXCLUSION CRITERIA

Subjects meeting any of the following exclusion criteria at screening will not be enrolled in the study.

1. The subject is a current user of ST (defined as daily usage during more than 1 week within past 6 months) or is unable to refrain from NRT or any other non-protocol treatment during the study. Use of pipes, cigars, cigarillos, snuff, and chewing tobacco is also prohibited during the study.
2. The subject is a female who is pregnant or lactating.
3. The subject has oral conditions that could potentially be made worse by use of study product, for instance, exposed dental cervices in the upper sulcus.
4. The subject has used any type of pharmaceutical (including some psychotropics, e.g., wellbutrin) or other products for smoking cessation within the past 3 months.

5. The subject has a history of clinically significant renal, hepatic, neurological, or chronic pulmonary disease that in the judgment of the investigator precludes participation
6. The subject has a history of cardiovascular disease, including myocardial infarction within the last 3 months, significant cardiac arrhythmias, or poorly controlled hypertension (defined as a diastolic pressure of more than 90 mm Hg or a systolic pressure of more than 140 mm Hg) that in the judgment of the investigator precludes participation
7. The subject has a history of alcohol or substance abuse or dependence other than cigarette smoking within the past year
8. Use of any illicit drug or smoked marijuana in the last 3 months.
9. The subject is unwilling to be randomized into active or placebo conditions, or be available for follow-up assessments.
10. The subject resides in a household where another member is currently participating in the study.

REMOVAL OF SUBJECTS FROM THERAPY OR ASSESSMENT

A subject will be considered to have completed the study when he completes the final assessment visit at Week 28. If a subject discontinues study procedures at any time after entering the study, the Investigator will make every effort to contact the subject and complete the termination case report form (CRF).

A termination case report form (CRF) page should be completed for every randomized subject, whether or not the subject completed the study. The reason for any early discontinuation should be indicated on this form. The primary reason for a subject withdrawing prematurely should be selected from the following standard categories of early termination:

- *Protocol Violation*: The subject's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements Every effort should be made to establish contact with participants who fail to show up for scheduled visits to determine the cause of the non-compliance.
- *Lost to Follow-Up*: The subject stopped coming for visits and study personnel were unable to contact the subject.
- *Withdrawal of consent*: The subject desired to withdraw from further participation in the study in the absence of an investigator-determined medical need to withdraw. If the subject gave a reason for withdrawing, it should be recorded in the CRF.
- *Adverse Event (Adverse Reaction)*: Clinical events occurred that in the medical judgment of the Investigator for the best interest of the subject are grounds for discontinuation. This includes serious and nonserious adverse events regardless of relation to study product. Clinical events that are reported by the subject and result in the subject choosing to withdraw from further participation are recorded as a discontinuation due to adverse event (not withdrawal of consent).
- *Death:* The subject died.

- *Other*: The subject was terminated for a reason other than those listed above

INTERVENTIONS

DESCRIPTION OF STUDY PRODUCTS

For comprehensive information about the study products, refer to protocol Appendix 1. Snus and matching placebo sachets will be provided to the study sites by the sponsor or its representative as white sachets weighing 0.5 or 1.0 g. Placebo sachets will include herbal material with flavoring without tobacco and nicotine. Additional details are provided in Table 1 below.

TABLE 1: DETAILS OF STUDY TREATMENTS

	Preparations to be Administered	
	Snus	**Placebo**
Active Substance	Nicotine	None
Manufacturer	Swedish Match	Swedish Match
Dose(s)	Ad libitum	Ad libitum
Route	Oral	Oral
Sachet Weight	0.5 mg and 1.0 mg	0.5 mg and 1.0 mg

DOSAGE, ADMINISTRATION, AND BLINDING

Subjects will be randomly assigned to receive snus or matching placebo in a 1:1 ratio at the Baseline Visit. Each subject will be given products at baseline, and at the clinic visits at Week 6 and 10. The amount of products given at each occasion is estimated to cover the need of a smoker who completely switches from cigarettes to snus during the entire *Intervention Phase*.

The sachets are placed under the upper lip (upper sulcus) which reduces salivation compared to placement in the lower part of the mouth. This means that there no need to spit while using the products. As the products have a relatively high pH, subjects may initially feel a slight burning sensation at the location of the sachet. This sensation is alleviated if the location of the sachet in the upper sulcus is changed.

The number of sachets consumed per day is determined by the participants themselves and will vary based on smoking habits. The amount of nicotine needed to prevent withdrawal symptoms among smokers varies considerably, therefore the amount of study product used by subjects is expected to vary and is dependent on the extent to which the products actually can replace cigarettes. Subjects will be instructed to use the products *ad libitum* with a recommended maximum number of 24 large sachets per day (recommended maximum number is 30 for those who smoke more than 15-20 cigarettes per day or have a Fagerström score of 7 or higher), and will be informed that one 1.0 g snus sachet typically can replace

one cigarette. Recommended maximum number of small sachets is double that of large sachets, that is, 48-60 per day. When subjects feel or expect an urge to smoke, they will be instructed to try their allocated study product for at least 15-20 minutes. Subjects will also be informed that nicotine overdose may occur with excessive use of the product, particularly with concomitant smoking, but those symptoms (typically nausea, tachycardia, etc.) quickly subside upon cessation of smoking or use of the product. The average snus consumption among snus users in Sweden who do not smoke is about 10 to 15 large sachets per day.

During the *Study Product Test Period* subjects will be instructed to replace as many cigarettes as possible with their allocated study product in order to achieve smoking cessation at the latest by the first day of week 5. The participants will be instructed to cut down on product use during week 14-16 to avoid a too abrupt ending of nicotine intake. Use of study product will be discontinued at the Week 16 visit.

If a subject has managed to quit cigarettes with the help of their allocated study product and there is an imminent danger of smoking relapse during the *Follow-Up Phase*, that subject should be informed that use of NRT or a smokeless tobacco product is a better option in terms of health risks than a smoking relapse.

UNBLINDING

Only in case of an emergency, when knowledge of the study product is essential for the clinical management or welfare of the subject, the investigator may unblind a subject's treatment assignment. If the blind is broken for any other reason, the investigator must notify the sponsor's medical representative immediately, and discontinue the subject from study product. If the investigator breaks the blind for a subject, the data and reason must be recorded in the CRF.

METHOD OF RANDOM ASSIGNMENT

Subjects will be randomly assigned chronologically in the order in which they are enrolled into the study stratified by treatment center and will be assigned a unique study number. The random sequence determining the allocation will be generated using a computer-based algorithm based on the permuted block technique with a block size of six.

Each participating center will be provided with four product "bins" that are uniquely numbered. Two bins at each center will include placebo products (large and small sachets), and two bins will include snus products. Each unique study number will be linked to bin numbers from which the participant shall receive study products (placebo or snus).

The trialist will document which products were provided to each participant and study product labeling will ensure that it can be verified that correct products according to the random allocation were issued to each participant.

PRODUCT PACKAGING AND LABELING

Study products will be supplied in "bins" (=for each study site uniquely numbered card-board boxes). Products are routinely packed in stacks of ten boxes ("logs"). All products

will be labeled according to applicable laws and regulations and ICH-GCP Guidelines.

STORAGE AND HANDLING OF STUDY PRODUCTS

Receipt of product supplies

Product supplies will not be provided to the Investigator until Institutional Review Board (IRB) approval has been obtained.

The Investigator or his/her designees will inventory all supply shipments upon receipt, acknowledge possession by signing the certificate of delivery, and return the form to the sponsor or its representative.

Storage

Study products should be kept refrigerated at 2-8 centigrades in a securely locked or in a limited access, secure area. Neither the Investigator nor designees may provide the study product to individuals not participating in this protocol.

Return of study product

Throughout the study, the sponsor or designee will make arrangements for the Investigator to return all unused study product to the sponsor or its representative. This shipment will be documented on the product accountability form. The Investigator must provide an explanation for any missing study product.

Responsibilities

In addition to responsibilities upon receipt previously outlined, the Investigator or his/her designees must maintain an inventory record of administered products to assure regulatory authorities and the sponsor that the investigational study product will not be administered to any person who is not participating in this study under the terms and conditions set forth in this protocol.

The inventory record will include:

- Name of the sponsor
- Protocol name and number
- Product name and description
- Study site and name of the Investigator
- Number of snus boxes dispensed and study participant identifier to whom study product was dispensed
- Product balance
- Name and signature of the qualified individual dispensing study product

Representatives of the sponsor will review these records.

Compliance

Self-reported number of cigarettes smoked daily and snus sachets used per day will be recorded in the subject's diary. The recommended number of 1.0 g and 0.5 g sachets to be used per day is 10-30 and 20-60, respectively.

PRIOR AND CONCOMITANT ILLNESSES AND TREATMENTS

Prior and concomitant illnesses

As this study is to be performed in healthy subjects, there should be no significant concomitant illnesses at the time of entry into the study. Illnesses first occurring or detected during the study, or a significant deterioration of a pre-existing condition will be documented as adverse events in the CRF. All data on medical history etc. collected as part of this trial will be based on the subject's self-reported information.

Prior and concomitant medications

Any concomitant medication is acceptable except NRT or other treatments used for smoking cessation, for instance, bupropion or varenicline. Other psychotropics (e.g., antidepressants other than bupropion) should also not be used. If a subject has used such treatments previously, they must be discontinued at least 3 months prior to randomization.

Use of any other product containing tobacco (e.g., pipes, cigars, cigarillos, snuff, and chewing tobacco) is prohibited throughout the study.

SUBJECT EVENTS

SCHEDULE OF EVENTS

The procedures to be performed throughout the study are outlined in Table 2, Schedule of Events, and the text following.

Table 2. Schedule of Events

	Screening	Baseline	Study Product Test Period (Week 1-4)				Intervention Phase (Week 5-16)					Follow-Up (Week 17-28)		
Study Week	-2, -1	0	1	2	3	4	6	8	10	13	16	20	24	28
Clinical Visit[a]	X	X					X		X		X[e]			X[e]
Telephone Contact[a]			X	X	X	X		X		X[d]		X	X	
Visit/Contact Window			± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 1 wk	± 1 wk	± 1 wk	± 1 wk
Interventions/Evaluations:														
Information Session	X													
Written Informed Consent	X													
Assessment of Eligibility	X	X												
Medical and Smoking History, ECG	X													
Physical & Oral[c] Examination	X[b]										X			X
Biomarkers (blood tests)	X						X				X			X
Screening tests (urine & blood tests)	X													
Vital Signs, including weight	X						X		X		X			X
CO Exhaled Air Test		X					X		X		X			X
Fagerström Test for Nicotine Dependence		X									X			X
Minnesota Nicotine Withdrawal Scale		X					X		X		X			X
Brief behavioral counseling	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X												
Dispense study product		X					X		X					
Review self-reported tobacco status		X	X	X	X	X	X	X	X	X	X	X	X	X
Assess AEs			X	X	X	X	X	X	X	X	X	X	X	X
Assess Compliance, Review & Dispense diary		X	X	X	X	X	X	X	X	X	X	X	X	X

[a] All clinical visits and telephone contacts (except those during screening and at baseline) to be scheduled at the end of the designated week

[b] Includes height

[c] Additional unscheduled exams may be done at any clinic visit, if needed.

[d] At the week 13 contact the participants will be instructed to cut down on product use during week 14-16 to avoid a too abrupt ending of nicotine intake.

[e] If a subject discontinues prior to Week 16, the procedures that would be done at Week 16 should be completed at the time of discontinuation. If a subject discontinues after Week 16, the procedures that would be done at Week 28 should be completed at the time of discontinuation.

ASSESSMENTS BY VISIT

SCREENING (WEEK -2, WEEK -1)

During a preliminary Information Session, potential subjects will receive information on the health risks associated with cigarettes as well as possible alternatives. The physiological effects of nicotine will be outlined, and an account given of experience with Swedish snus, including potential health risks associated with different types of smokeless tobacco products. Potential subjects will be invited to the clinic for a Screening Visit (Visit 1), for an explanation of the purpose and nature of the study. Written informed consent will be obtained and the following evaluations will be completed:

- Evaluation of entry criteria
- Complete medical and smoking history, including assessment of tobacco use and smoking status (i.e., age at initiation of daily smoking, average number of cigarettes smoked per day during the past year, history of previous quit attempts, desire to quit cigarettes and smoking, history of use of smokeless tobacco products), history of psychiatric disorders, and history of previous use of NRT or other pharmaceutical or other smoking cessation aids)
- Oral examination
- Vital signs, including weight
- Urine pregnancy test for females of childbearing potential
- Physical examination, including height and ECG (supine position for at least 5 minutes)
- Blood chemistry (Hb, total WBC, transaminases, creatinine, electrolytes)
- Biomarker blood tests
- Urine test for illicit drugs (amphetamine, opioids, cocaine, cannabis)
- Brief behavioral counseling in the form of educational materials on smoking cessation, the National Cancer Institute's "Cleaning the Air" booklet

The Information Session and Screening Visit may occur on the same day.

STUDY PRODUCT TEST PERIOD (WEEK 1 THROUGH WEEK 4)

Baseline Visit

After Screening procedures have been completed and results reviewed, qualifying subjects will return to the clinic (at any time within 2 weeks from the Screening Visit date) for a Baseline assessment and random allocation to study product (snus or placebo). The following assessments will be completed:

- Confirmation of eligibility criteria
- CO exhaled air test
- Fagerström Nicotine Dependence test
- Minnesota Nicotine Withdrawal Scale

- Brief counseling following Agency for Healthcare Research and Quality guidelines (see Appendix 5)
- Randomization
- Dispense study product with instructions on use
- Dispense subject diary with instructions to record number and size of study product used
- Instruct subjects to gradually decrease the daily number of smoked cigarettes through the use of study products
- Instruct subjects to refrain totally from cigarettes no later than the first day of Week 5

Week 1 through 4

Telephone contacts will occur at Weeks 1, 2, 3, 4, and will include a review of the subject's smoking status, use of study products, and brief behavioral counseling. Adverse events will also be assessed.

INTERVENTION PHASE (WEEK 5 THROUGH WEEK 16)

Week 5 through Week 16

Throughout the Intervention Phase, clinic visits and telephone contacts will be completed. Telephone contacts will occur at Weeks 8, and 13 and will include a review of the subject's smoking status, and brief behavioral counseling. Adverse events and compliance with study product will also be assessed. At the telephone contact scheduled at week 13 the participants will be instructed to cut down on product use during week 14 through 16 to avoid a too abrupt ending of nicotine intake.

Clinic visits will be scheduled at Week 6, as well as during Weeks 10, and 16. They will include the following assessments:

Week 6 and Week 10

- Vital signs, including weight
- CO exhaled air test
- Biomarker blood tests (Week 6 only)
- Minnesota Nicotine Withdrawal Scale
- Provision of brief counseling following Agency for Healthcare Research and Quality guidelines
- Dispense study product
- Review self-reported smoking status
- Assess adverse events
- Review diary information regarding product use and assess compliance. Dispense new diary.

Week 16

- Vital signs, including weight

- Physical examination
- Oral examination
- CO exhaled air test
- Fagerström Nicotine Dependence test
- Minnesota Nicotine Withdrawal Scale
- Biomarker blood tests
- Brief counseling following Agency for Healthcare Research and Quality guidelines
- Review self-reported smoking status
- Assess adverse events
- Review diary information regarding product use and assess compliance.

If a subject discontinues prematurely, the procedures that would be done at Week 16 should be completed at the time of discontinuation.

FOLLOW-UP PHASE (WEEK 17 THROUGH WEEK 28)

Throughout the Follow-Up Phase, clinic visits and telephone visits will be completed. Telephone visits will occur at Weeks 20 and 24 and will include a review of the subject's smoking status and brief behavioral counseling. Adverse events will also be assessed.

A final clinic visit will occur at Week 28 and will include the following assessments:

- Physical examination
- Oral examination
- Vital signs, including weight
- CO exhaled air test
- Fagerström Nicotine Dependence test
- Minnesota Nicotine Withdrawal Scale
- Biomarker blood tests
- Brief counseling following Agency for Healthcare Research and Quality guidelines
- Review self-reported smoking status
- Assess adverse events
- Use of OTC NRT, smoking cessation services, smokeless tobacco, or smoking products other than cigarettes since week 16.

If a subject discontinues during the Follow-Up Phase, the procedures that would be done at Week 28 should be completed at the time of discontinuation.

DESCRIPTION OF ASSESSMENTS

All assessments to be used in this study are common, standard measurements frequently used in smoking cessation studies. Descriptions of outcome and safety assessments completed during the study are described below.

MEDICAL AND SMOKING HISTORY

Investigators should document all significant acute illnesses that the subject has experienced within 90 days of Screening. Additional acute or chronic illnesses present at the time informed consent is given are to be regarded as concomitant illnesses. Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study are to be documented as AEs on the CRF.

OUTCOME ASSESSMENTS

Smoking Status/Product Use Diary

Self-reported smoking status will be determined by a simple "yes/no" question on smoking cessation (i.e., "Have you smoked a cigarette since the last visit?"). Subjects will also record study product consumption each day (number and size of product) and number of cigarettes smokes, and will return the diary at each clinic visit.

CO Exhaled Air Test

The amount of carbon monoxide in end-expired alveolar air provides a rapid and accurate measure of carboxyhemoglobin.[41] CO in exhaled air will be analyzed using Micro Smokerlyser EC-50® (Bedfont Scientific Ltd, U. K.).

Fagerström Nicotine Dependence Test

The Fagerström Test for Nicotine Dependence is a standard instrument for assessing the intensity of this physical addiction.[42] The higher the Fagerström score, the more intense the physical dependence on nicotine. Higher scores indicate that treatment of withdrawal symptoms, usually with nicotine replacement therapy, will be an important factor in the participant's plan of care. A total score of 7 to 10 points indicates highly dependent, 4 to 6 points indicates moderately dependent, and less than 4 points indicates minimally dependent (refer to Appendix 2).

Minnesota Nicotine Withdrawal Scale (MNWS)

The MNWS [43] features two separate measures for examining the severity of nicotine withdrawal symptoms in a subject: a self-report scale and an observer scale. Only the self-report scale will be used in this trial. Nine items are included that assess urge to smoke (craving); depressed mood; irritability, frustration, or anger; anxiety; difficulty concentrating; restlessness; increased appetite; difficulty going to sleep; and difficulty staying asleep. Each item is rated by a subject on an ordinal scale from 0 (not at all) to 4 (extreme) relative to symptoms experienced over the past week. A total withdrawal discomfort score is obtained by summing the 9 items, with higher scores indicating more withdrawal symptoms. Refer to Appendix 3.

SAFETY ASSESSMENTS

Physical Examinations

Physical examinations will include examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, heart, lungs, abdomen, lymph nodes, extremities, and nervous system. An AE form must be completed for all changes identified as clinically noteworthy. Height without shoes will be recorded in inches at Baseline.

Oral Examinations

Examinations of the oral cavity will be performed to identify tobacco-and snus-related oral conditions. Exams are scheduled at Screening, and at Weeks 16 and 28 (or final) visits. Unscheduled exams may be conducted at the discretion of the Investigator at any time during the study. An AE form must be completed for all changes identified as clinically noteworthy.

Vital Signs

Vital signs (body temperature, heart rate, respiratory rate, and blood pressure) will be assessed according to the Schedule of Events. Blood pressure will be measured after subjects have been in the seated position for at least 5 minutes.

Temperature will be measured by either the oral or tympanic route, also consistent throughout the study for a particular subject. Body weight without shoes will be recorded in pounds whenever vital signs are recorded. An AE form must be completed for all changes identified as clinically noteworthy.

Concomitant Medications

Medications taken by or administered to the subject for 30 days before the Screening Visit will be recorded in the CRF. Any medication or therapy that is taken by or administered to the subject during the course of the study must be recorded in the CRF. The entry must include the dose, regimen, route, indication, and dates of use.

Adverse Events

An adverse event (AE) is any symptom, physical sign, syndrome, or disease that either emerges during the study or, if present at screening, worsens during the study, regardless of the suspected cause of the event. All medical and psychiatric conditions (except those related to the indication under study, that is, nicotine addiction) present at screening will be documented on the Prior Illnesses CRF. Changes in these conditions and new symptoms, physical signs, syndromes, or diseases should be noted on the AE CRF during the rest of the study.

AEs may be volunteered spontaneously by the subject, or discovered as a result of general questioning by the study staff. At each visit the subject will be asked, "Have you experienced any problems since your last visit?" All AEs will be recorded on the CRF. For all AEs, the Investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious AE requiring immediate notification. Follow-up of the AE, even after the date of

discontinuation of study products, is required if the AE persists until the event resolves or stabilizes at a level acceptable to the Investigator.

In order to avoid vague, ambiguous, or colloquial expressions, all AEs should be recorded in standard medical terminology rather than the subject's own words. Each AE will also be described in terms of duration, frequency, intensity, association with the study product, assessment of possible causes, actions taken, and outcome, using choices given on the CRF. Specific guidelines for classifying AEs by intensity and relationship to study product are given in the tables below.

CLASSIFICATION OF ADVERSE EVENTS BY INTENSITY	
MILD:	The symptom is barely noticeable to the subject and does not influence performance or functioning. Prescription drug treatment is not ordinarily needed for relief of mild AEs but may be given because of personality of subject.
MODERATE:	The symptom is of sufficient severity to make the subject uncomfortable, and performance of daily activities is influenced. Treatment for the symptom may be needed.
SEVERE:	The symptom causes severe discomfort, sometimes of such severity that the subject cannot continue in the study. Treatment for the symptom may be necessary.

CLASSIFICATION OF ADVERSE EVENTS BY RELATIONSHIP TO STUDY PRODUCT	
UNRELATED:	This category applies to those AEs that are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.).
UNLIKELY:	This category applies to those AEs that are judged to be unrelated to the test product, but for which no extraneous cause may be found. An AE may be considered unlikely to be related to study product if or when it meets 2 of the following criteria: (1) it does not follow a reasonable temporal sequence from administration of the test product; (2) it could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it does not follow a known pattern of response to the test product; or (4) it does not reappear or worsen when the product is re-administered.
POSSIBLY:	This category applies to those AEs for which a connection with the test product administration appears unlikely but cannot be ruled out with certainty. An AE may be considered possibly related if or when it meets 2 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the product; (2) it could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; or (3) it follows a known pattern of response to the test product.
PROBABLY:	This category applies to those AEs that the Investigator feels with a high degree of certainty are related to the test product. An AE may be considered probably related if or when it meets 3 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the product; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it disappears or decreases on cessation or reduction in dose (note that there are exceptions when an AE does not disappear upon discontinuation of the product, yet product-relatedness clearly exists; for example, as in bone marrow depression, fixed drug eruptions, or tardive dyskinesia); or (4) it follows a known pattern of response to the test product.
DEFINITELY:	This category applies to those AEs that the Investigator feels are incontrovertibly related to test product. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence from administration of the product; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it disappears or decreases on cessation or reduction in dose and recurs with re-exposure to product (if rechallenge occurs); and (4) it follows a known pattern of response to the test product.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the experience should be noted. If the intensity category changes

over a number of days, then those changes should be recorded separately (with distinct onset dates).

Serious Adverse Events

A serious adverse event (SAE) is defined as any AE that meets one or more of the following criteria:

- The event is fatal or life-threatening.
- The event is permanently disabling (incapacitating or interfering with the ability to resume usual life patterns).
- The event results in unplanned inpatient hospitalization or prolongation of existing hospitalization.
- The event is a congenital anomaly.
- The event requires medical intervention of any kind in order to prevent any of the aforementioned outcomes.

A death occurring during the study or within 1 week of discontinuing use of study product must be reported to the trial safety coordinator. A serious AE is not necessarily severe; for example, an overnight hospitalization for a diagnostic procedure must be reported as a serious AE even though the occurrence is not medically serious. By the same token, a severe AE is not necessarily serious: nausea of several hours' duration may be rated as severe but may not be considered serious.

Any serious adverse event due to any cause that occurs during the investigation, whether or not related to the study product, must be reported within 24 hours of occurrence or when the Investigator becomes aware of the event. The Investigator must send a preliminary report of any SAE encountered during the study and for 1 month after a subject has discontinued or completed the study to the trial safety coordinator by fax within 24 hours using an SAE Report Form. The event must also be recorded on the standard AE CRF. Preliminary reports of SAEs must be followed by detailed descriptions later on, including clear photocopies of hospital case reports, consultant reports, autopsy reports, and other documents when requested and applicable. SAE reports must be made whether or not the Investigator considers the event to be related to the investigational product.

Appropriate remedial measures should be taken to treat the SAE and the response should be recorded. Subjects must be closely followed until sufficient information is obtained to indicate a return to normal status or until the event stabilizes at a level acceptable to the Investigator. Clinical, laboratory, and diagnostic measures should be employed as needed in order to determine the etiology of the problem. The results will be reported promptly to the sponsor.

Other Significant Adverse Events

To ensure subject safety, the Investigator should also notify the safety coordinator should any AE occur that is considered significant but does not meet criteria for an SAE, or that is considered unexpected. In addition, any field monitor who notes a significant AE or medical condition while reviewing the CRFs or source documents at the site must immediately convey this information to the trial safety coordinator.

OTHER PROCEDURES OR ASSESSMENTS

Behavioral Counseling

At each clinic and telephone visit, subjects will be provided with brief counseling following Agency for Healthcare Research and Quality guidelines (refer to Appendix 5). Counseling should last no more than 10 minutes per visit. In addition, subjects will be provided with an education booklet (the National Cancer Institute's "Cleaning the Air" booklet) at the Screening Visit.

Biomarker blood tests

Blood tests will be taken on all participants at screening, and periodically during the study for exploratory purposes. A total of 30-50 ml of blood will be sampled at each occasion.

DATA MANAGEMENT AND STATISTICAL ANALYSIS

Completed CRFs for this study will be forwarded to Covance where editing and construction of a quality-assured database will occur. All data will be listed and summary tables will be provided. Summary statistics will be presented by treatment group.

This section describes the statistical analysis as it is foreseen at the time of planning the study. Any major deviations from this plan, the reasons for such deviations, and all alternative or additional statistical analyses that may be performed will be described in the Statistical Analysis Plan (SAP), which gives a detailed technical description of all statistical analyses prior to the unblinding of the randomization codes. Because of the unpredictability of some problems, it may be necessary to decide the manner with which irregularities will be dealt in a blind data review meeting before breaking the blind.

INTERIM ANALYSIS

No interim analyses are planned.

DETERMINATION OF SAMPLE SIZE

The primary endpoint is the quit rate among cigarette smokers who wish to stop smoking. The quit rate is examined between subjects randomized to snus as compared to subjects randomized to placebo. Assuming a rate of 12% in the placebo group and 27% in the active snus group, a two group continuity corrected χ^2 test with a 0.050 two-sided significance level will have 80% power to detect the difference between the active group proportion, p1, of 0.270 and the placebo group proportion, p2, of 0.120 (odds ration of 0.369) when the sample size in each group is 122 (total sample size of 244). The study is therefore intended to include a total of 250 participants. Treatment assignments will be balanced between active and placebo groups. The ITT population will be used for all statistical analyses of treatment efficacy.

RANDOMIZATION

A listing of subjects and treatment group assignments will be provided. All analyses of efficacy in terms of smoking cessation will be by allocated product (snus or placebo). Analyses of safety will both be done both by allocated product and by product actually received.

SUBJECT POPULATIONS FOR ANALYSIS

Three populations are defined for outcome analyses: the intention-to-treat (ITT) population, compliant subjects, and the fully evaluable population.

INTENTION-TO-TREAT POPULATION (ITT)

ITT is defined as all eligible subjects who had a baseline evaluation, were randomized to receive one of the study products, and used at least one dose of assigned product, irrespective of compliance and protocol violations. The ITT population will be used for analyses of smoking cessation, as well as compliance and safety.

COMPLIANT SUBJECTS

These are defined as those within the intention-to-treat population who used $\geq$ 1 sachets of their allocated study product per day during week 1 through 6. This population will be used, in addition to the ITT population, to evaluate the secondary end-points of point-prevalence of smoking cessation at week 16 and week 28

FULLY EVALUABLE POPULATION

These are defined as all subjects who completed the full 16 weeks of double-blind intervention. This population will be used, in addition to the ITT population, to assess compliance and safety.

DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Subject characteristics, demographics, and other baseline measurements will be described in terms of age, previous smoking history and quit attempts, previous use of NRT or other pharmaceutical smoking cessation aids, Fagerström score, medical history, and other relevant data collected at Baseline. Descriptive statistics (mean, median, standard deviation, minimum, maximum) will be summarized by treatment group and overall, for continuous variables, and numbers and percentages of subjects for categorical variables. The differences in the baseline characteristics of the two groups will be assessed.

COMPLIANCE

Number of cigarette smoked daily and snus or placebo sachets used per day during the past week will be tabulated from self-reported data.

OUTCOME ANALYSES

PRIMARY OUTCOME ENDPOINT

The primary outcome measure will be continuous smoking cessation during Week 6 through Week 28 (at all measurement points/visits) as reported by subjects and corroborated by objective verification using the CO value from exhaled air of less than 8 ppm at all visits during the specified time period.

SECONDARY OUTCOME ENDPOINTS

Secondary outcome measures are:

- Continuous smoking cessation during Week 6 through Week 16 (at all measurement points/visits) as reported by subjects and corroborated by objective verification using the CO value from exhaled air of less than 8 ppm at all visits during the specified time period.
- Point prevalence of smoke-free subjects at Week 6, 16, and 28 will be summarized as the rate during the preceding week (self-reported and confirmed by CO measurement).
- Withdrawal symptoms during the study will be measured by the Minnesota Nicotine Withdrawal Scale. The differences in the average daily overall symptom score and the score for craving between the two treatment groups will be analyzed.
- CO in exhaled air levels will be summarized at Baseline and subsequent applicable visits and the change from baseline will be tabulated by overall and by the two treatment groups.

- Scores on the Fagerström Nicotine Dependence Test will be calculated at Baseline, Week 15, and Week 27 and will be summarized at each time point. The change from the baseline will be tabulated for the two treatment group and for overall population.

- Point-prevalence of smoking cessation at week 16 and week 28 (self-reported and confirmed by CO measurement) will be analyzed among compliant subjects (defined as those within the intention-to-treat population who used $\geq$ 1 sachets of their allocated study product per day during week 1 through 6)

In general, missing responses to any questions will be imputed by using the last observation carried forward method (LOCF). If participant did not respond to a question at any of the previous visits, a worst score will be assigned for that question and this score will be carried forward until the time participant responded or completed the study. Missing responses or missing data relating to smoking status will be interpreted as though the participant had smoked on that occasion.

SAFETY ANALYSES

Safety analyses will be performed on the ITT population as well as the fully evaluable population on the basis of treatment actually received.

ADVERSE EVENTS

The subject incidence (%) and number of reports of AEs will be calculated and presented for each treatment by MedDRA term and body system. Individual subject listings of all AEs will be provided. AEs will also be presented by severity and relationship to treatment. The number of subjects who withdrew because of an AE or who died will also be summarized. SAEs will be summarized.

VITAL SIGNS, PHYSICAL AND ORAL EXAMINATIONS

Vital signs will be listed by subject and will be summarized at each time point by treatment. Changes from baseline will also be reported at each time point by treatment. Clinically notable abnormalities will be summarized at each time point by treatment (as percentage of subjects). Summary statistics will be provided.

Status of oral cavity will be summarized at baseline and at the end of study (Week 27) and change from baseline will be tabulated.

PRIOR AND CONCOMITANT MEDICATIONS

Data on medications other than test products used by subjects prior to or during the course of study will be summarized for the overall population and for the two treatment groups.

PRIOR OR CONCOMITANT ILLNESSES

Subjects experiencing any prior or concomitant illness will be reported in subject listings.

WITHDRAWAL OF SUBJECTS FROM THE STUDY AND ANALYSIS

All subjects who discontinued from the allocated intervention will be listed and their reasons for discontinuation will be tabulated for the two treatment groups and for the overall population. Eligible subjects who discontinue after randomization will not be replaced.

STUDY MANAGEMENT

APPROVAL AND CONSENT

REGULATORY GUIDELINES

The study will be performed in accordance with the most recent guidelines of the World Medical Association Declaration of Helsinki, the guidelines of the International Conference on Harmonization (ICH), the Health Insurance Portability and Accountability Act of 1996 (HIPAA), and all other applicable laws and regulations.

INSTITUTIONAL REVIEW BOARD

Conduct of the study must be approved by an appropriately constituted IRB. IRB approval is required for the study protocol, protocol amendments, informed consent forms, subject information sheets, and advertising materials. No study product will be released for the site until written IRB authorization has been received by the Sponsor or its representative and communicated to the Investigator.

INFORMED CONSENT

For each study subject, signed written informed consent will be obtained prior to any protocol-related activities. As part of this procedure, the Investigator must explain orally and in writing the nature, duration, and purpose of the study, and the action of the product in such a manner that the subject is aware of the benefits, potential risks, inconveniences, or adverse effects that may occur as a result of their participation. Subjects should be informed that they may withdraw from the study at any time. Subjects will receive all information that is required by ICH guidelines. The Investigator will provide the Sponsor or its

representative with a copy of the IRB-approved informed consent form (ICF) prior to the start of the study.

DISCONTINUATION OF THE STUDY BY THE SPONSOR

The sponsor reserves the right to discontinue the study at this site or at multiple sites for safety or administrative reasons at any time. In particular, a site that does not recruit at a reasonable rate may be discontinued. Should the study be terminated and/or the site closed for whatever reason, all documentation and equipment pertaining to the study must be returned to the sponsor or its representative.

STUDY DOCUMENTATION

By signing page 2 of this protocol, the Investigator acknowledges that he/she has received appropriate information about the products being tested in the trial and assures the sponsor that he/she will comply with the protocol. No changes in this protocol can be made without the sponsor's written approval.

The Investigator will supply the sponsor with:

- Curricula vitae for all Investigators involved in the trial
- Signed protocol signature page

The sponsor or its representative will supply the Investigator with:

- Clinical study protocol
- Other relevant information about the study products
- Sample informed consent form
- Case report forms (CRFs)/instruction manual
- Equipment for clinical measurements of CO in exhaled air

STUDY MONITORING AND AUDITING

This study will be monitored at all stages of its development by the clinical research personnel employed by the sponsor or its representative. Monitoring will include personal visits and telephone communication to assure that the investigation is conducted according to protocol and in order to comply with guidelines of Good Clinical Practice. On-site review of CRFs will include a review of forms for completeness and clarity, and consistency with source documents available for each subject.

Source documents in this trial will be a variety of documents including clinical records, laboratory reports, participant diaries, and printouts from medical equipment. For machine readings of CO in exhaled air (for which there are no printouts) directly noted on the CRF, the CRF will serve as source document.

Medical advisors and clinical research associates or assistants may request to witness subject evaluations occurring as part of this protocol. The Investigator and appropriate personnel will be periodically requested to attend meetings/workshops organized by the sponsor to assure acceptable protocol execution. The study may be subject to audit by the sponsor or by regulatory authorities. If such an audit occurs, the Investigator must agree to allow access to required subject records. By signing this protocol, the Investigator grants permission to personnel from the sponsor, its representatives, and appropriate regulatory authorities for on-site monitoring of all appropriate study documentation, as well as on-site review of the procedures employed in CRF generation, where clinically appropriate.

DATA VALIDATION

Any data to be recorded directly on the CRFs (to be considered as source data) will be identified at the start of the trial.

All CRF entries must be made in black ink. The Investigator must ensure the accuracy, completeness, legibility, and timeliness of data reported in the CRF and all required reports. Any change or correction to a CRF must be dated, initialed, and explained (if necessary), and must not obscure the original entry. This process applies to both written and electronic changes.

Data reported on the CRF that are derived from source documents should be consistent with the source documents, or the discrepancies must be explained.

Within one week (or other agreed time frame) of completion of each subject, the Investigator should agree to have completed and signed CRFs available for inspection by the clinical monitor.

STUDY PROTOCOL, DOCUMENTATION, AND RETENTION OF RECORDS

Conduct of the study will strictly follow the protocol. However, if any changes become necessary, both the Investigator and the Sponsor must agree to any amendments made to the protocol. All amendments to the protocol must be signed by the Sponsor's Medical Director and the Investigator, except for those referring to organizational changes. Any amendment to the protocol cannot be implemented by the Investigator until an IRB has reviewed and approved the amendment. The Investigator must treat all of the information related to the study and the compiled data as strictly confidential. The Sponsor must approve any transfer of information not directly involved in the study. The Investigator

will be provided with a CRF for each subject to be filled in with all relevant data pertaining to the subject during the study. For each subject, a termination/discontinuation record must be completed. All screened subjects who either entered the study, or were considered ineligible, or were eligible but not enrolled into the study must be documented on a screening log along with the reason for screen failure if applicable.

CRF entries and corrections must be made in a way that does not obscure the original entry. The correct data must be inserted, dated, and initialed by the Investigator. All data entered into the CRF must also be available in the individual subject file either as printouts or as notes taken by either the Investigator or another responsible person assigned by the Investigator. The Investigator agrees to provide the Sponsor with the subject data and to discuss them with representatives of the Sponsor. The Investigator should take measures to prevent accidental or premature destruction of study documents. Subject identification codes have to be retained according to ICH GCP guidelines or for at least 15 years after the completion or discontinuation of the study, whichever is the longest period of time.

The Investigator must arrange for retention of study records at the site for 15 years. The Investigator should take measures to prevent accidental or premature destruction of these documents.

USE OF STUDY FINDINGS

By signing the study protocol, the Investigator agrees to the use of results of the study for the purposes of national and international regulatory authorities. If necessary, those authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement. Reports covering clinical and biometric aspects of the study will be prepared by the Sponsor or its representative.

It is the intention of the Sponsor that the results of the study based on subjects from all participating centers be published in a peer-reviewed international scientific journal irrespective of the study results. After such a joint publication, each investigator is free to present or publish any data based on this study provided the Sponsor is informed at least four weeks in advance.

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APPENDICES

1. Description of study products
2. Fagerström test of nicotine dependence
3. Minnesota Nicotine Withdrawal Scale (Self-Report)
4. Counseling guidelines (modified from Agency for Healthcare Research and Quality Guidelines, Treating Tobacco Use and Dependence: PHS Clinical Practice Guideline Counseling Participants to Quit)

APPENDIX 1. DETAILED DESCRIPTION OF STUDY PRODUCTS

TRADITIONAL SNUS

Active substance: Nicotine

Product name: Snus

Appearance: Paper sachets

Content : Snus is made from ground tobacco leaves, water, and food-allowed additives (salt, humidifier, acidity regulator, and flavor substances). The finished product adheres to an industrial standard which includes limits for undesired substances, see below. No nicotine is added or removed from the product which implies that the nicotine in the product solely comes from the tobacco.

Content (large sachets):	Tobacco	0.5 g
	Water	0.5 g
	Salt (NaCl)	6%
	Nicotine	8 mg
	Propylene glycol (E 1520)	
	Sodium carbonate (E 500)	
	Flavor substances	

Content (small sachets):	Tobacco	0.25 g
	Water	0.25 g
	Salt (NaCl)	6%
	Nicotine	4mg
	Propylene glycol (E 1520)	
	Sodium carbonate (E 500)	
	Flavor substances	

pH: 8.1 to 8.9 (accepted range)

Administration: The sachets are placed in the mouth between the upper gingiva and cheek (upper sulcus). Usage is *ad libitum*. Typically, the sachets are retained for 20 to 30 minutes up to 60 minutes. There is large individual variation in total number of sachets used per day, and the time the sachets are retained in the mouth, which reflects the wide variation in nicotine dose required by habitual users of nicotine products.

Nicotine absorption: 10 to 20% of the nicotine in the sachets is absorbed to the blood through the mucous membranes. The potential nicotine uptake is thus1-2 mg from the large sachets and 0.5 to 1.0 mg from the small sachets.

Side effects: The side effects of the nicotine in snus are the same as those from other sources of nicotine such as cigarettes, and are dose dependent. As is known by every habitual smoker, the side effects are reversible when the dose is reduced or when usage is interrupted.

Common side effects of nicotine include: *Cardiology*: Increased heart rate, slight elevation of blood pressure (typically 5-10 mm Hg), *Neurology*: Vertigo, head ache. *GI*: Nausea, stomach ache, heart burn

The content of sodium carbonate in the product makes it slightly alkaline. This may cause a burning sensation in the mouth at the location of the sachet, particularly among those unaccustomed to the product. Should this problem occur, it can be alleviated by changing the location of the sachet in the upper sulcus, e g by switching to the contralateral side.

Short term use of snus (months) is not associated with any known mucosal side effects. Long term use (several years) may be associated with a mucosal "snus lesion," that is, a whitish thickening of the mucosa. Such lesions are reversible if the placement of the snus sachet is changed, or usage stopped. Snus lesions are not associated with cellular atypia and do not have malignant potential. They are thus quite distinct from oral leukoplakias. Long term use (typically several years), particularly of loose snus products, has in some individuals been associated with exposed dental cervices.

Weight variation of study product: Sachet weight may vary between -10% and +20% of the labelled weight.

Undesired substances: Snus contains traces of undesired substances occurring naturally in tobacco and other agricultural products. The levels are well below the limits of the industrial standard GothiaTek®, and are listed in the table.

Component[1]	Limit[2]	Content[3]	Component[1]	Limit[2]	Content[3]
Nitrite (mg/kg)	3.5	1.1 (<0.5 - 1.9)	Cadmium (mg/kg)	0.5	0.2 (0.1 - 0.3)
TSNA (mg/kg)	5	0.8 (0.4 - 1.1)	Lead (mg/kg)	1.0	0.2 (0.1 - 0.2)
NDMA (µg/kg)	5	0.6 (<0.5 - 1.1)	Arsenic (mg/kg)	0.25	0.08 (<0.03 - 0.13)
BaP (µg/kg)	10	0.9 (<0.5 - 1.8)	Nickel (mg/kg)	2.25	0.8 (0.3 - 1.2)
Pesticides	According to the Swedish Match pesticide policy		Chromium (mg/kg)	1.5	0.5 (0.3 - 0.7)

1: Main undesired components defined by **GothiaTek®**, 2: According to **GothiaTek®**, 3: Results for batches produced by Swedish Match AB 2005, based on a water content of 50%

Packaging & storage: The snus sachets are distributed in round plastic containers. The packaging material is food allowed according to the Swedish Food Act. As the unique production method entails a heat treatment similar to pasteurization, the product is virtually sterile. However, snus should preferably be stored in a refrigerator (2 to 8 °C) to preserve the water content and freshness of the product.

The product is marked with a best-before date which is typically c. 20 weeks after production date. It should be noted that the levels of undesired, potentially toxic substances, such as, nitrosamines, do not increase during storage, even in room temperature. It is mainly the water content that decreases which affects the subjective freshness of the product. There is also a slight decline in the pH level during storage which decreases the amount of bio-available nicotine.

If the product is stored in a freezer (< -18 °C) the best before date is postponed almost indefinitely.

PLACEBO SNUS

Active ingredient/content: No active substance. The product only contains food-allowed constituents, ingredients and additives.

Appearance: Paper sachets. The physical appearance and flavoring is the same as that of the traditional snus.

Content (large sachets):	Cocoa bean fibers, oat fibers	0.5 g
	Water	0.5 g
	Salt (NaCl)	5.5%
	Sodium carbonate (E500)	
	Propylene glycol (E 1520)	
	Flavor substances	

Content (small sachets):	Cocoa bean fibers, oat fibers	0.25 g
	Water	0.25 g
	Salt (NaCl)	5.5%
	Sodium carbonate (E500)	
	Propylene glycol (E 1520)	
	Flavor substances	

pH: 8.1 to 8.9 (accepted range)

Weight variation of study products: Sachet weight may vary between -10% and +20% of the labelled weight, the mean weight is: 1.0 g (large sachets) and 0.5 g (small sachets)

Administration and usage: Same as with traditional snus

Side effects: None reported during short-term usage (a few weeks to months). However, because the product is slightly alkaline just as traditional snus, users may initially experience a burning sensation in the oral mucosa at the location of the sachet, particularly among those unaccustomed to the product. As a result of the pH, long term use (several years) may theoretically be associated with mucosal "snus lesions," just as traditional snus. Such lesions, should they occur, are of minor

clinical significance and are expected to be infrequent among participants in the current study.

Packaging & storage: The sachets come in round plastic containers identical to those used for traditional snus. The packaging material is food allowed according to the Swedish Food Act. The product is marked with a best-before date which is typically c. 20 weeks after production date. Water content and freshness is best preserved if the product is stored in a refrigerator (2 to 8°C).

If the product is stored in a freezer (< -18°C) the best before date is postponed almost indefinitely.

APPENDIX 2. FAGERSTRÖM TEST FOR NICOTINE DEPENDENCE

1. How soon after waking do you smoke your first cigarette?

a) Less than five minutes (3p)
b) 5-30 minutes (2p)
c) 31-60 minutes (1p)
d) More than an hour (0p)

2. Do you find it difficult to refrain from smoking in places where it is forbidden?

a) Yes (1p)
b) No (0p)

3. Which cigarette would you most hate to give up?

a) First one in the morning (1p)
b) Any other (0p)

4. How many cigarettes do you smoke per day?

a) More than 30 per day (3p)
b) 21-30 per day (2p)
c) 11-20 per day (1p)
d) 10 or less per day (0p)

5. Do you smoke more frequently during the first hours after waking than during the rest of the day?

a) Yes (1p)
b) No (0p)

6. Do you smoke if you are so ill that you are in bed most of the day?

a) Yes (1p)
b) No (0p)

APPENDIX 3. MINNESOTA NICOTINE WITHDRAWAL SCALE (SELF-REPORT)

Behavior Rating Scale Self-Report

Please rate yourself for the period for the last 24 hours:

0 = none, 1 = slight, 2 = mild, 3 = moderate, 4 = severe

1. Angry, irritable, frustrated	0 1 2 3 4
2. Anxious, nervous	0 1 2 3 4
3. Depressed mood, sad	0 1 2 3 4
4. Desire or craving to smoke	0 1 2 3 4
5. Difficulty concentrating	0 1 2 3 4
6. Increased appetite, hungry, weight gain	0 1 2 3 4
7. Insomnia, sleep problems, awakening at night	0 1 2 3 4
8. Restless	0 1 2 3 4
9. Impatient	0 1 2 3 4

Hughes JR, Hatsukami DK. Signs and symptoms of tobacco withdrawal. Arch Gen Psychiatr 1986; 43:289-294.

Scale available at http://www.uvm.edu/~hbpl/minnesota/2005/Behavior%20Rating%20Scale%20-%20Self%20Report.pdf

APPENDIX 4: COUNSELING GUIDELINES

Modified from Agency for Healthcare Research and Quality Guidelines, Treating Tobacco Use and Dependence: PHS Clinical Practice Guideline Counseling Participants to Quit

The counseling can be divided into practical and supportive counseling advice.

Practical counseling advice (problem-solving/skills training)	Examples
Recognize danger situations. Identify events, internal states, or activities that increase the risk of cigarette use	• Negative affect. • Being around other smokers. • Drinking alcohol. • Experiencing urges. • Being under time pressure.
Develop coping skills. Identify and practice coping or problem-solving skills. Typically, these skills are intended to cope with danger situations.	• Learning to anticipate and avoid temptation. • Learning cognitive strategies that will reduce negative moods. • Accomplishing lifestyle changes that reduce stress, improve quality of life, or produce pleasure. • Learning cognitive and behavioral activities to cope with smoking urges (e.g., distracting attention).
Provide basic information. Provide basic information about smoking and successful methods to switch to a non-smoking behavior	• Any smoking (even a single puff) increases the likelihood of failure. • Withdrawal typically peaks within 1-3 weeks after switching from cigarettes • Withdrawal symptoms include negative mood, urges to smoke, and

	difficulty concentrating.

Supportive counseling advice	Examples
Encourage the smoker	• Communicate belief in the participant's ability to replace cigarettes • Note that effective alternatives are now available. • Note that half of all people who have ever smoked have stopped using cigarettes
Communicate caring and concern.	• Ask how the participant feels about replacing cigarettes • Directly express concern and willingness to help. • Be open to the participant's expression of fears of not using cigarettes, difficulties experienced, and ambivalent feelings.
Encourage the participant to talk about the process.	Ask about: • Reasons the participant wants to switch from cigarettes • Concerns or worries about the switch from cigarettes • Success the participant has achieved. • Difficulties encountered with the switch

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