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STUDY PROTOCOL NO. SM 11-01

EFFECT OF A TRADITIONAL SWEDISH SMOKELESS
TOBACCO PRODUCT (“SNUS”) ON THE QUIT RATE AMONG
CIGARETTE SMOKERS WHO WISH TO STOP SMOKING. A
META-ANALYSIS OF RESULTS FROM TWO RANDOMIZED
CLINICAL TRIALS

Principal Investigator:

P. N. Lee, M.A.

LIST OF ADDRESSES

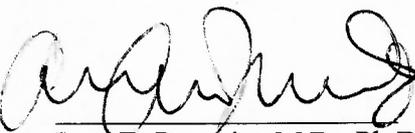
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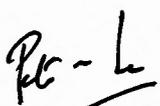
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Signature:  _____ Date: 16th February 2011
Name: P.N. Lee, M.A.
Director
P.N. Lee Statistics and Computing Ltd.

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

Signature: _____

Peter N Lee

Date: _____

16 Feb 2011

Name
(Print): _____

PETER N LEE

Investigator

SYNOPSIS

Title of Study	Effect of a traditional Swedish smokeless tobacco product (“snus”) on the quit rate among cigarette smokers who wish to stop smoking. a meta-analysis of results from two randomized clinical trials
Investigator	P N Lee, P.N. Lee Statistics and Computing Ltd., Sutton, Surrey, UK
Objectives	<p><i>Primary:</i> to examine if a traditional Swedish low-nitrosamine ST product (“snus”) compared to placebo can increase the quit rate among cigarette smokers motivated to change their smoking habits measured as continuous, complete smoking cessation over an approximate 20-week period following advice to quit smoking. For the US study, this is defined as complete abstinence during weeks 6 to 28 verified by expired air CO less than or equal to 8 ppm. For the Serbian study, this is defined as complete abstinence during weeks 24 to 48, verified by expired air CO less than or equal to 10 ppm.</p> <p><i>Secondary:</i></p> <ul style="list-style-type: none">• To examine continuous complete quit rates (biologically confirmed) during weeks 10 to 28 in the US study and weeks 30 to 48 in the Serbian study.• To examine point-prevalence (following week) quit rates (biologically confirmed) at the following defined pairs of times in the two studies; weeks 6 US and week 24 Serbia, week 16 US and week 36 Serbia, week 28 US and week 48 Serbia.
Design	P.N. Lee Statistics and Computing Ltd. will be provided with individual subject data in electronic form from the two clinical trials on site, sex, age, smoking history, date of randomization, product used, results of all CO tests, results of Fagerström tests at baseline, details of self-reported smoking status at each week, usage of study product and date of completion or withdrawal. The data will be transferred to a single database and the transfer checked, after which the statistical analyses will be conducted and a report prepared.
Populations	<p><i>Intention-to-treat subjects:</i> All eligible subjects who had a baseline evaluation were randomized to receive one of the study products, and used at least one dose of the assigned product, irrespective of compliance and protocol violations.</p> <p><i>Compliant subjects:</i> All subjects in the ITT population who</p>

used at least 1 sachet of their allocated study product per day in weeks 1 to 6 inclusive (US) or weeks 1 to 24 inclusive (Serbia).

Outcomes

Primary outcome: For the US study the primary outcome will be based on continuous cessation during weeks 6 to 28 inclusive, based on diary readings relevant to that period and confirmed by CO values of <8 ppm at all visits during the period. For the Serbian study, the corresponding period will be weeks 24 to 48, with confirmation by CO values of <10 ppm.

Secondary outcomes:

1. Based on CO confirmed continuous cessation during weeks 10 to 28 inclusive for the US study. For the Serbian study, the corresponding period will be weeks 30 to 48.
2. Based on CO confirmed point prevalence of being smoke free at week 6 (US) and week 24 (Serbia).
3. Based on CO confirmed point prevalence of being smoke free at week 16 (US) and week 36 (Serbia).
4. Based on CO confirmed point prevalence of being smoke free at week 28 (US) and week 48 (Serbia).

Statistical Analyses

Preliminary analyses will test for possible failures of randomization by comparing, within each study, the distribution of five potential confounding variables (site, sex, age, average cigarette consumption in the month before baseline, and baseline Fagerström nicotine dependence score) according to product used. Differences seen which are significant at $p < 0.05$ will be taken account of in the meta-analyses.

Descriptive analyses will test for variation in outcome by level of each of the five potential confounding variables after adjustment for study and study product used.

Fixed-effect and random-effects meta-analysis will be used for each outcome to combine individual study relative risk estimates. Where the preliminary analyses identified failures of randomization for a study, the relative risk estimate will be adjusted for the potential confounding variable.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

CO	Carbon monoxide
DF	Degrees of freedom
ITT	Intention-to-treat
NRT	Nicotine replacement therapy
RR	Relative risk
ST	Smokeless tobacco

INTRODUCTION

BACKGROUND AND RATIONALE

Two randomized placebo-controlled, double blind clinical trials have been conducted to test whether *ad lib* provision of 0.5 or 1.0 g sachets of low nitrosamine snus, as compared to placebo sachets with no tobacco or nicotine, affects subsequent smoking habits. One (SM 08-01) was conducted in five sites in the USA (Daytona Beach, Austin, Fort Worth, Portland and Evansville). The other (SM 07-01) was conducted in two centres in Belgrade, Serbia. Both studies involved subjects in a similar age range (USA: 25-65 years; Serbia: 20-65 years). Both studies were restricted to subjects who had smoked daily for >1 year, with a similar minimum average consumption level in the preceding month (USA: 9 cigs/day; Serbia: 10 cigs/day). Both studies were restricted to subjects who were in good health and who were motivated to change their smoking habits (USA: motivated to quit smoking by a smokeless tobacco (ST) product; Serbia: motivated to substantially reduce or quit smoking). Both studies effectively excluded current users of ST, in the US by a specific exclusion criterion, in Serbia by ST not being available on the market. Both studies excluded subjects who had used any type of pharmaceutical or other product for smoking cessation in the preceding 3 months, who had oral conditions that could be worsened by treatment, who abused alcohol or drugs, who had a history of cardiovascular disease, and who were pregnant or lactating. Both studies collected self-reported tobacco status data in a diary completed by the subject, and recorded exhaled carbon monoxide (CO) levels at intervals, as well as conducting a Fagerström test for nicotine dependence.

The US study involved four periods, a screening period of two weeks to evaluate eligibility, a study product test period (weeks 1 to 4 post-randomization) during which the subjects were instructed to use the study products when they felt an urge to smoke, initially without any requirement for complete abstinence from cigarettes, an intervention phase (weeks 5 to 16) during which subjects were encouraged to stop smoking completely and to use their allocated study product instead of smoking if they felt an urge to smoke, and a follow-up phase (weeks 17 to 28). Note that the product was supplied only up to week 16, with subjects instructed to cut down on product use during weeks 14 to 16 to avoid too abrupt an ending of nicotine

intake. The objectives of the US study included comparison of smoking quit rates measured by complete abstinence during weeks 6 to 28, verified by CO \leq 8 ppm (the primary objective), comparison of verified quit rates measured by complete abstinence during weeks 6 to 16, and comparison of verified quit rates specifically at weeks 16 and 28.

The Serbian study involved a baseline visit, a smoking reduction stage (weeks 1 to 24 post-randomization) and a smoking cessation stage (weeks 25 to 48). During the first 24 weeks subjects were instructed to cut down on smoking by taking a sachet of snus when they felt an urge to smoke, though if they still wished to smoke after 20-30 minutes they could do so. Subjects were also informed that although smoking cessation was preferable, the primary objective of the first 24 weeks of the study was smoking reduction. Subjects who failed to achieve smoking reduction at 24 weeks (as judged by a 50% reduction in the self-reported number of cigarettes smoked daily in weeks 20 to 24, and a reduction of at least 1 ppm CO relative to baseline) were withdrawn from the study at week 24. Continuing subjects were instructed to quit smoking completely by use of the sachets. While the primary objective of the Serbian study related to smoking reduction, other objectives related to smoking cessation, both at weeks 12 and 24, and at weeks 36 and 48.

It should be noted that while snus and placebo were only available to week 16 in the US study, snus and placebo were available to the subjects during the whole period post-randomization (weeks 1 to 48) in the Serbian study. This difference arose because, while nicotine replacement therapy (NRT) and various smokeless tobacco products are both readily available to all participants at a cost comparable to cigarettes in the USA, smokeless tobacco is not available in Serbia and the cost of NRT there is considerably more than that of cigarettes.

Although there are differences between the two studies, there seem to be enough similarities to make it worthwhile combining the evidence from the studies to allow a more powerful test of whether use of low nitrosamine snus vs placebo sachets affects the rate of quitting smoking. Both studies are relatively small (USA 125 in each group; Serbia 158 snus and 161

placebo) and a meta-analysis of appropriately defined endpoints should allow an improved test of the main hypothesis of interest.

In deriving endpoints, it seems appropriate to consider the period following when the advice given to subjects concentrated on quitting, i.e. from week 5 in the US study and from week 25 in the Serbian study. To avoid bias, it is also appropriate to base the analyses on all the subjects randomized initially, so including those withdrawn at week 24 in the Serbian study because they failed to achieve a 50% reduction in the number of cigarettes smoked daily by them, and were assumed not to be going to quit had they continued in the study.

STUDY PURPOSE

To combine evidence from available randomized, placebo-controlled, double blind clinical trials to test whether use of a low-nitrosamine, Swedish snus product can increase the smoking cessation rate among cigarette smokers motivated to change their smoking habits.

STUDY OBJECTIVES

PRIMARY OBJECTIVE

The primary objective of the meta-analysis is to examine if a traditional Swedish low-nitrosamine ST product (“snus”) compared to placebo can increase the quit rate among cigarette smokers motivated to change their smoking habits measured as continuous, complete smoking cessation over an approximate 20-week period following advice to quit smoking. For the US study, this is defined as complete abstinence during weeks 6 to 28 verified by expired air CO less than or equal to 8 ppm. For the Serbian study, this is defined as complete abstinence during weeks 24 to 48, again verified by expired air CO less than or equal to 10 ppm.

SECONDARY OBJECTIVES

The secondary objectives of this study are:

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- To examine continuous complete quit rates (biologically confirmed) during weeks 10 to 28 in the US study and weeks 30 to 48 in the Serbian study.
- To examine point-prevalence (preceding week) quit rates (biologically confirmed) at the defined pairs of times in the two studies; weeks 6 US and week 24 Serbia, week 16 US and week 36 Serbia, week 28 US and week 48 Serbia.

INVESTIGATIONAL PLAN

The protocols of the individual studies (Protocols SM 08-01 for US study and SM 07-01 for Serbian study) are attached as Appendices A and B.

P N Lee Statistics and Computing Ltd. will be supplied by Swedish Match with electronic data files (e.g. SAS or EXCEL) for each of the two studies containing at least the following information for each subject randomized.

Site where subject attended

Sex

Age

Smoking history

Date at which subject randomized

Whether randomized to snus or placebo

Results of CO Exhaled air test (weeks 0, 6, 10, 16 and 28 for US study; weeks 0, 2, 6, 12, 18, 24, 30, 36, 42 and 48 for Serbian study)

Results of Fagerström test conducted at baseline

Self-reported smoking status for each week of the study

Whether the subject used the study product (snus or placebo) for each week of the study

Whether the subject completed the study or was withdrawn

Date of completion or withdrawal

They will also be supplied with corresponding data listings and summary tables.

P.N. Lee Statistics and Computing Ltd. will then carry out the data management and statistical analysis as described in the next section of this report and will prepare a report for the sponsors presenting the findings.

DATA MANAGEMENT AND STATISTICAL ANALYSIS

SUPPLY OF DATA

The relevant individual subject data supplied by the two studies will be transferred onto a single ROELEE database for statistical analysis.

Data listings and summary tables will then be run off to ensure the data transfer has not produced errors. Any data items that are unclear, or missing without adequate explanation, will be referred back to Swedish Match.

The rest of 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 report of this study.

INTERIM ANALYSES

No interim analyses are planned.

SUBJECT POPULATION FOR ANALYSIS

Outcome analysis will be carried out using the intention-to-treat (ITT) population.

INTENTION-TO-TREAT POPULATION (ITT)

All eligible subjects who had a baseline evaluation were randomized to receive one of the study products, and used at least one dose of the assigned product, irrespective of compliance and protocol violations.

ANALYSIS

PRIMARY OUTCOME ENDPOINT

For the US study the primary outcome measure will be continuous smoking cessation during weeks 6 to 28 inclusive based on diary readings reviewed at weeks 6, 10, 16, and 28 confirmed by exhaled air CO values of less than 8 ppm at these times.

For the Serbian study the primary outcome measure will be continuous smoking cessation during weeks 24 to 48 inclusive based on diary readings reviewed at weeks 24, 30, 42 and 48 confirmed by CO values from exhaled air of less than 10 ppm at weeks 24, 36 and 48.

SECONDARY OUTCOME ENDPOINTS

Secondary outcome measures are:

- For the US study continuous smoking cessation during weeks 10 to 28 inclusive based on diary readings reviewed at weeks 10, 16, and 28 confirmed by CO values ≤ 8 ppm at these times. For the Serbian study continuous smoking cessation during weeks 30 to 48 inclusive based on diary readings reviewed at weeks 30, 42 and 48 confirmed by CO values ≤ 10 ppm at weeks 36 and 48.
- The point prevalence of smoke-free subjects (self-reported and confirmed by CO measurement) at week 6 in the US study and at week 24 in the Serbian study.
- The point prevalence of smoke-free subjects (self-reported and confirmed by CO measurement) at week 16 in the US study and at week 36 in the Serbian study.
- The point prevalence of smoke-free subjects (self-reported and confirmed by CO measurement) at week 28 in the US study and at week 48 in the Serbian study.

Missing values for smoking status or CO measurement will be taken as indicating that the subject smoked on that occasion.

POTENTIAL CONFOUNDING VARIABLES

Variables other than study treatment (snus or placebo) to be considered as possibly affecting outcome include the following:

Site where subject attended
Sex
Age
Average cigarettes smoked per day in month before baseline
Fagerström nicotine dependence score at baseline

TESTING FOR FAILURE OF RANDOMIZATION

Within each study, the distribution of each potential confounding variable will be summarized according to product used (snus or placebo) and differences investigated using Fisher exact tests for variables with two possible values, and the Wilcoxon test for continuous or semi-continuous variables Conover, 2003.

Variables showing differences between snus and placebo that are significant at $p < 0.05$ will be adjusted for in the meta-analyses that follow.

META-ANALYSES

Where no potential confounding variables need to be adjusted for, the logit method (see e.g. Fleiss et al., 1991) will be used to provide fixed-effect and random-effects estimates of the relative risk of the outcome in snus compared to placebo in the two studies combined. The method is summarized briefly below.

For a particular outcome the data to be analyzed for each study ($i = 1,2$) are as follows:

<u>Subjects</u>	<u>Snus</u>	<u>Placebo</u>
Outcome successful (quit smoking)	A_i	B_i
At risk	C_i	D_i

The relative risk in study i , RR_i , is estimated by

$$RR_i = (A_i D_i) / (B_i C_i)$$

and the variance of $\log RR_i$, V_i , is estimated by

$$V_i = \text{var}(\log_e RR_i) = 1/A_i + 1/B_i - 1/C_i - 1/D_i$$

To meta-analyze results from the two studies, a combined fixed-effect estimate of $\log_e RR_i$ is calculated as a weighted average of the individual estimates using inverse-variance weighting. Thus, we have

$$Y_T = \log_e RR_T = \left(\sum_{i=1}^2 w_i \log_e RR_i \right) / \sum_{i=1}^2 w_i$$

where w_i , the weight, equals $1/V_i$.

Thus the overall estimate RR_i is given by $\exp(Y_T)$.

The variance of $\log_e RR_T$, V_T , is then estimated by

$$V_T = \text{var}(\log_e RR_T) = 1 / \sum_{i=1}^2 w_i$$

A 95% confidence interval for the overall estimate of RR_T is then given by

$$\exp(Y_T \pm Z \sqrt{V_T})$$

Where Z is the value of the standard normal distribution corresponding to the 97.5% percentile (i.e. approximately 1.96).

The heterogeneity of the two studies is tested by taking the statistic

$$Q = \sum_{i=1}^2 w_i (Y_i - Y_T)^2$$

as having a chi-squared distribution with degrees of freedom (DF) equal to one less than the number of studies (S). Here S = 2, so DF = 1.

Q plays a central role in the random-effects estimate. If $Q \leq S-1 = 1$ the fixed- and random-effects estimates are the same. If $Q > 1$ we calculate

$$D = \frac{(Q-1) \sum_{i=1}^2 w_i}{\left(\sum_{i=1}^2 w_i\right)^2 - \sum_{i=1}^2 w_i^2}$$

and revised weighting factors, w_i^* , are calculated as

$$w_i^* = (D + 1/w_i)^{-1}$$

Random-effects estimates and their 95% confidence limits are then calculated using the revised weighting factors.

Where one or more potential confounding variables need to be adjusted for, fixed-effects meta-analysis is first used within each study to combine independent RR estimates from separate strata defined by the variable(s) to be adjusted for (e.g. age 20-39, 40-65). The weaker levels of the strata will be kept small so as to avoid loss of power arising if zero cases of a successful outcome appear within a stratum. The stratified RR estimates for each study will then be combined over the two studies using fixed-effect and random-effects estimates as before. The primary meta-analyses will be conducted based on the ITT population, though results based on compliant subjects will also be reported.

ADDITIONAL ANALYSES

Analyses will also be carried out testing for variation in outcome by level of each of the potential confounding variables with adjustment for study and study product used. For each

variable up to 5 levels will be defined and a stratified trend test will be used to test whether the probability of the outcome varies by level of the variable Breslow et al., 1987.

CHECKING

All statistical analyses will be independently checked by qualified members of P.N.Lee Statistics and Computing Ltd.

REPORTING

A report on the study will be provided which will include the following sections:

- Index
- Summary of the designs of the two studies and objectives
- Data provided for statistical analysis
- Populations
- Data processing
- Outcomes
- Statistical methods
- Description of listings of data and statistical tables
- Variation in outcome by site, sex, age, cigarettes per day and Fagerström score
- Testing for possible failure of randomization
- Meta-analyses
- Discussion
- Summary (equivalent to the Executive Summary)
- References

REFERENCES

- Breslow, N.E., Day, N.E., 1987. The design and analysis of cohort studies, Vol. 2. Statistical methods in cancer research, International Agency for Research on Cancer, Lyon. (IARC Scientific Publication No. 82.)
- Conover, W.J., 2003. Practical nonparametric statistics, 3rd edition. Wiley series in probability and mathematical statistics, R.A. Bradley, J.S. Hunter, D.G. Kendall, G.S. Watson (Eds.). John Wiley & Sons, New York, Chichester, Brisbane, Toronto.
- Fleiss, J.L., Gross, A.J., 1991. Meta-analysis in epidemiology, with special reference to studies of the association between exposure to environmental tobacco smoke and lung cancer: a critique. *J. Clin. Epidemiol.* 44, 127-139.

APPENDIX 1.

STUDY PROTOCOL no. SM 08-01 (final version dated Nov 12, 2008
including an amendment dated Jan 13, 2009)

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Swedish Match AB
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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.

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Swedish Match Approval:

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

Covance Approval:

Signature: _____ Date: _____
Name: [Name]
[Department, Title]

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: _____

Name
(print): _____

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	<p><i>Primary:</i> 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 abstinence 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.</p> <p><i>Secondary:</i></p> <ul style="list-style-type: none"> • To examine the extent of continuous complete abstinence 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	<p>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).</p> <p>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 abstinence 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.</p>
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

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	<p>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.</p>
Diagnosis And Key Subject Selection Criteria	<p><i>Key Inclusion Criteria:</i></p> <ul style="list-style-type: none"> • 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 <p><i>Key Exclusion Criteria:</i></p> <ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Traditional, low nitrosamine Swedish snus in 0.5 or 1.0 g sachets <i>ad libitum</i> • Matching placebo (without tobacco or nicotine)
Main Outcome Parameters	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Adverse events • Vital sign measurements, including body weight • Oral cavity health • Physical examinations
Statistical Methods	<p>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.</p> <p>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).</p> <p>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</p>

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	<p>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.</p> <p>Refer to Section 4.8 for analysis of safety variables.</p>
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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 cheek 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:

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- 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 cardboard 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 ^f 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

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^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

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- 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 smoked, 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.

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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, p_1 , of 0.270 and the placebo group proportion, p_2 , of 0.120 (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.

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 ≥ 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 ≥ 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.

REFERENCES

1. Royal College of Physicians. Nicotine addiction in Britain. A report of the Tobacco Advisory Group of the Royal College of Physicians. London: Royal College of Physicians, 2000.
2. Rodu B, Godshall WT. Tobacco harm reduction: an alternative cessation strategy for inveterate smokers. *Harm Reduct J.* 2006;3:1-23.
3. Foulds J, Ramström LM, Burke M, et al. The effects of smokeless tobacco (snus) on smoking and public health in Sweden. *Tob Control.* 2003;12:349-359.
4. Martinet Y, Bohadana A, Wirth N, et al. Would alternate tobacco products use be better than smoking? *Lung Cancer.* 2006;53:1-4.
5. Rodu B, Cole P. Smokeless tobacco use and cancer of the upper respiratory tract. *Oral Surgical Oral Med Oral Pathol.* 2002;5:511-515.
6. Lewin F, Norell SE, Johansson H, et al. Smoking tobacco, oral snuff, and alcohol in the etiology of squamous cell carcinoma of the head and neck. *Cancer.* 1988;82:1367-1374.
7. Schildt EB, Eriksson M, Hardell L, et al. Oral snuff, smoking habits and alcohol consumption in relation to oral cancer in a Swedish case-control study. *J Cancer.* 1988;77:341-346.
8. Roosar A, Johansson AL, Borgh-Englund G, et al. A long term follow up study on the natural course of snus-induced lesions among Swedish snus users. *Int J Cancer.* 2006;119:392-397.
9. Zatterstrom UK, Svensson M, Sand L, et al. Oral cancer after using Swedish snus for 70 years – a case report. *Oral Dis.* 2004;10:50-53.
10. Huhtasaari F, Asplund K, Lundberg V, et al. Tobacco and myocardial infarction: is snuff less dangerous than cigarettes? *British Med J.* 1992;305:1252-1256.
11. Huhtasaari F, Lundberg V, Eliasson M, et al. Smokeless tobacco as a possible risk factor for myocardial infarction: a population-based study in middle-aged men. *J Am Coll Cardiol.* 1999;34:1784-1790.
12. Hergens MP, Ahlbom A, Andersson T, et al. Swedish moist snuff and myocardial infarction among men. *Epidemiol.* 2005;16:12-16.
13. Bolinder G, Alfredsson L, Englund A, et al. Smokeless tobacco use and increased cardiovascular mortality among Swedish construction workers. *Am J Public Health.* 1994;84:399-404.
14. Asplund K, Nasic S, Janlert U, et al. Smokeless tobacco as a possible risk factor for stroke in men. A nested case control study. *Stroke.* 2003;34:1-6.
15. Persson PG, Carlsson S, Svanström L, et al. Cigarette smoking, oral moist snuff use, and glucose intolerance. *J Intern Med.* 2002;248:103-110.
16. Eliasson M, Asplund K, Evrin PE. Relationship of cigarette smoking and snuff dipping to plasma fibrinogen, fibrinolytic variables and serum insulin. The Northern Sweden MONICA Study. *Atherosclerosis.* 1995;113:41-53.
17. Waterbor J, Adams R, Robinson J, et al. Disparities between public health educational materials and scientific evidence that smokeless tobacco use causes cancer. *J Cancer Educ.* 2004;19:17-28.
18. Englund LJ, Levin RJ, Mills JL, et al. Adverse pregnancy outcomes in snuff users. *Am J Obstet Gynecol.* 2003;189:939-943.
19. Statens Folkhälsoinstitut. Minskat bruk av tobak– var står vi idag? Del av folkhälsomål 11. Statistik, 2005. Accessed at www.fhi.se/upload/ar2005/ovrigt/Tobaksfaktanov05.pdf.

20. TEMO (a public pool institute). 2002. Svenska Folkets Tobaksvanor. Commissioned by Swedish Match.
21. TEMO (a public pool institute). 2001. Rökare Och Slutare [Smokers and Quitters]. Commissioned by the Cancer Society and Pharmacia Corporation. Snus better than nicotine preparations. Published in Svenska Dagbladet.
22. Ramström, L. Patterns of use: a gate leading to smoking, or a way to give up. In: Proceedings of the 4th Annual Meeting of the Society for Research on Nicotine and Tobacco; 2002; Santander, Spain.
23. Rodu R, Stegmayr B, Nasic S, et al. Impact of smokeless tobacco use on smoking in northern Sweden. *J Intern Med.* 2002;252:398-404.
24. Lindström M, Isacson SO, and the Malmö Shoulder-Neck Study Group. Smoking cessation among daily smokers, aged 45-69 years: a longitudinal study in Malmö, Sweden. *Addict.* 2001;97:205-215.
25. Ramstrom LM, Foulds J. Role of snus in initiation and cessation of tobacco smoking in Sweden. *Tob Control.* 2006;15:210-214.
26. Lindstrom M. Nicotine replacement therapy, professional therapy, snuff use and tobacco smoking: A study of smoking cessation studies in southern Sweden. *Tob Control.* In press.
27. Furberg H, Bulik C, Sullivan P. Snus use and other correlates of smoking cessation in the Swedish twin registry. Poster presented at: 13th Annual Meeting of the Society for Research on Nicotine and Tobacco; Feb 21-24, Austin, USA.
28. Tomar SL, Connolly G, Wilkenfeld J, et al. Declining smoking in Sweden: Is Swedish Match getting the credit for Swedish tobacco control's efforts? *Tob Control.* 2003;12:368-371.
29. Furberg H, Lichtenstein P, Pedersen N, et al. Cigarettes and oral snuff use in Sweden: prevalence and transitions. *Addict.* 2006;101:1509-1515.
30. Kozlowski LT, O'Connor RJ, Edwards BQ, et al. Most smokeless tobacco use is not a causal gateway to cigarettes: using order of product use to evaluate causation in a national US sample. *Addict.* 2003;98:1077-85.
31. O'Connor RJ, Kozlowski LT, Flaherty BP, et al. Most smokeless tobacco use does not cause cigarette smoking: results from the 2000 National Household Survey on Drug Abuse. *Addict Behav.* 2005;30:325-36.
32. Haddock CK, Weg MV, DeBon M, et al. Evidence that smokeless tobacco use is a gateway for smoking initiation in young adult males. *Prev Med.* 2001;32:262-7.
33. Tomar SL. Smokeless tobacco use is a significant predictor of smoking when appropriately modeled. *Nicotine Tob Res.* 2003;5:571-3.
34. Balfour D, Fagerström KO. Pharmacology of nicotine and its therapeutic use in smoking cessation and neurodegenerative disorders. *Pharmacol and Therapeutics.* 1996;72:51-58.
35. Holm H, Jarvis MJ, Russel MA, et al. Nicotine intake and dependence in Swedish snuff takers. *Psychopharmacol.* 1992;108:507-511.
36. Lunell E, Lunell M. Steady-state nicotine plasma levels following use of four different types of Swedish snus compared with 2-mg Nicorette chewing gum: A crossover study. *Nicotine Tob Res.* 2005;7(3):397-403.
37. Gartner CE, Hall WD, Vos T, et al. Assessment of Swedish Snus as a tobacco harm reduction intervention. *The Lancet.* In press.
38. Tonnesen P, Carrozzi L, Fagerstrom KO, et al. Smoking cessation in patients with respiratory diseases: a high priority, integral component of therapy. *Eur Respir J.* 2007;29:390-417.

39. Tilashalski K, Rodu B, Cole P. A pilot study of smokeless tobacco in smoking cessation. *Am J Med.* 1998;1004:456-458.
40. Sharp L, Lewin F, Johansson H, et al. Smoking cessation among patients with head and neck cancer. *Eur J Can Nursing.* In press.
41. Jarvis MJ, Russell MAH, 1980. Expired air carbon monoxide: a simple breath test of tobacco smoke intake. *Br Med J.* 1980;281(6238):484-5.
42. Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. The Fagerström Test for Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire. *Br J Addict* 1991;86:1119-27.
43. Hughes JR, Hatsukami DK. Signs and symptoms of tobacco withdrawal. *Arch Gen Psychiatr* 1986; 43:289-294.
44. Cox LS, Tiffany ST, Christen AG. Evaluation of the brief questionnaire of smoking urges (QSU-brief) in laboratory and clinical settings. *Nicotine Tob Res* 2001;3:7-16.
45. Tiffany ST, Drobes DJ. The development and initial validation of a questionnaire on smoking urges. *Br J Addict* 1991;86:1467-76.
46. Cappelleri JC, Bushmakin AG, Baker CL, et al. Confirmatory factor analyses and reliability of the modified cigarette evaluation questionnaire. *Addict Behav.* 2006 Jul 26.
47. Jorenby DE et al., 2007. Efficacy of varenicline, an $\alpha 4\beta 2$ nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA* 296 (1): 56-63.

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 thus 1-2 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
<u>Nitrite</u> (mg/kg)	3.5	1.1 (<0.5 - 1.9)	<u>Cadmium</u> (mg/kg)	0.5	0.2 (0.1 - 0.3)
<u>TSNA</u> (mg/kg)	5	0.8 (0.4 - 1.1)	<u>Lead</u> (mg/kg)	1.0	0.2 (0.1 - 0.2)
<u>NDMA</u> (µg/kg)	5	0.6 (<0.5 - 1.1)	<u>Arsenic</u> (mg/kg)	0.25	0.08 (<0.03 - 0.13)
<u>BaP</u> (µg/kg)	10	0.9 (<0.5 - 1.8)	<u>Nickel</u> (mg/kg)	2.25	0.8 (0.3 - 1.2)
<u>Pesticides</u>	According to the Swedish Match pesticide policy		<u>Chromium</u> (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
<p>Recognize danger situations. Identify events, internal states, or activities that increase the risk of cigarette use</p>	<ul style="list-style-type: none"> • Negative affect. • Being around other smokers. • Drinking alcohol. • Experiencing urges. • Being under time pressure.
<p>Develop coping skills. Identify and practice coping or problem-solving skills. Typically, these skills are intended to cope with danger situations.</p>	<ul style="list-style-type: none"> • 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).
<p>Provide basic information. Provide basic information about smoking and successful methods to switch to a non-smoking behavior</p>	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none">• 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.	<ul style="list-style-type: none">• 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: <ul style="list-style-type: none">• 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>

APPENDIX 2.

STUDY PROTOCOL no. SM 07-01 (dated May 15, 2007) and protocol amendments 1-3

Sponsor: Swedish Match AB
SE-118 85, Stockholm, Sweden

Serbian Smoking Reduction/Cessation Trial (2SRT)

Clinical Study Protocol SM 07-01

CONFIDENTIAL

This document and its contents are confidential. Any unauthorized copying or use of this document is prohibited.

SIGNATURE PAGE

Sponsor Approval:

Signature:

Date:

Name:

Investigator Agreement: I have read the protocol and agree to conduct the study as outlined herein.

Signature:

Date:

Name:

Signature:

Date:

Name (print):

Signature:

Date:

Name (print):

Signature:

Date:

Name (print):

Signature:

Date:

Name (print):

SYNOPSIS

TITLE OF STUDY	Serbian Smoking Reduction/Cessation Trial (2SRT)
INVESTIGATORS & STUDY CENTERS	Professor Robert Nilsson, Stockholm, International Coordinating Investigator Dr Ruza Antic, Belgrade, Principal National Investigator Participants will be recruited at four centers in the city of Belgrade, Serbia
PHASE OF DEVELOPMENT	Phase III
OBJECTIVES	To assess the efficacy of a traditional Swedish smokeless tobacco product (“snus”) to reduce smoking among adult smokers in Serbia
DESIGN	Randomized, placebo-controlled, double-blind trial
PLANNED SAMPLE SIZE	500
DIAGNOSIS AND KEY SUBJECT SELECTION CRITERIA	Males and females in good general health aged 20-65 years regularly smoking >10 cigarettes per day for more than 1 year, who are motivated to reduce or quit smoking
TREATMENTS	<ol style="list-style-type: none"> 1. Traditional, low-nitrosamine Swedish snus in 0.5 or 1.0 g sachets ad libitum 2. Placebo snus (without tobacco or nicotine)
MAIN PARAMETERS OF EFFICACY	<p>Primary end-point:</p> <ul style="list-style-type: none"> • “Smoking reduction” at 24 weeks, defined as a self-reported reduction of $\geq 50\%$ compared to baseline in the average number of smoked cigarettes per day during week 20-24, verified by a reduced concentration of carbon monoxide (CO) in exhaled air of at least 1 ppm <p>Secondary end-points:</p> <ul style="list-style-type: none"> • “Smoking reduction” at 12 weeks • Smoking cessation at 12 and 24 weeks defined as self-reported total abstinence from cigarettes during the preceding 4-week period verified by a concentration of CO in exhaled air of <10 ppm • Smoking cessation at 36 and 48 weeks among those who achieved smoking reduction at 24 weeks (cessation here defined as self-reported total abstinence from cigarettes during the preceding 4, 12, or 24-week period, verified by a CO-concentration in exhaled air of <10 ppm) • Clinical tests and biomarkers at 12 and 24 weeks among all participants, and at 36 and 48 weeks among those who achieved smoking reduction at 24 weeks, including body weight, blood pressure, CO in exhaled air, measures of lung function, total S-WBC, S-CRP, total S-cholesterol, S-HDL, S-LDL, S-fibrinogen, S-cotinine

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
BMI	body mass index
CRF	case report form
CRP	C-reactive protein
CRO	contract research organization
GCP	good clinical practice
GothiaTek [®]	Industrial standard under which snus products are manufactured
EU	European Union
FEV%	FEV _{1.0} /FVC
FEV _{1.0}	forced expiratory lung volume during the first second
FVC	forced vital capacity
HDL	high-density lipoprotein
IEC	independent research ethics committee
IRB	institutional review board
ITT	intent-to-treat
LDL	low-density lipoprotein
NCS	not clinically significant
NRT	nicotine replacement therapy
ppm	parts per million
TSNA	tobacco specific nitrosamines
WBC	white blood cell count
WHO	World Health Organization
WHOART	World Health Organization Adverse Reaction Terms

INTRODUCTION

In developed countries (e.g. Europe, North America, Japan, Australia, and New Zealand) tobacco-related disease is the single most important avoidable cause of premature death among males. In these countries an average of about 25% percent of male deaths has been attributed to tobacco smoking (Peto et al, 2003). It follows that policies to reduce smoking-related disease would have a considerable potential for reducing future morbidity and mortality. In this context it is of special importance to assess country-specific data for Serbia in comparison with other European countries, where Serbia shares with Croatia top positions for male all-cause mortality attributable to smoking (Peto et al., 2003).

Sweden, on the other hand, demonstrates a unique pattern in terms of smoking-related disease. Not only are male smoking-related deaths radically fewer than in other European countries, but Sweden is also the only country where males have a lower overall risk of smoking-related death than women (IARC, 1997). This finding can be explained by the fact that during the last decades male smoking has decreased to a considerably larger extent in men than in women, largely due to the prevalent use in men of “snus”, a traditional Swedish oral tobacco product, as a smoking cessation aid or replacement for cigarettes (Henningfield & Fagerström, 2001). The use of low-nitrosamine smokeless tobacco of the Swedish type is associated with health risks that are only a fraction of those caused by smoking (Kozlowski, L.T, 2002; Foulds, Ramström, Burke, Fagerström. 2003; Levy et al., 2004).

Other types of smokeless tobacco products extensively used in India and parts of Africa have been associated with substantial risks of both oral cancer and cardiovascular disease (IARC, 1985, Idris et al, 1994). However, these products are distinctly different from Swedish snus in that they typically contain much higher levels of TSNA:s, and are often combined with betel and areca nuts which contain non-tobacco substances that are highly carcinogenic.

The manufacture of Swedish snus is regulated according to Swedish laws for food-stuffs and according to an industrial standard (GothiaTek[®]) that includes limits for tobacco-specific substances, such as TSNA:s, as well as for potentially toxic substances present in all food-stuffs, such as, heavy metals, pesticide residues, and mycotoxins (www.gothiatek.com). In addition, Swedish snus is traditionally manufactured using a heating process similar to pasteurization which renders the product virtually sterile, which helps to ensure product stability during storage.

During the last years, the public health authorities in Serbia have initiated antismoking campaigns and bans on smoking in public places. However, due to the difficult financial situation after the Balkan wars, the funding for such campaigns have been limited, as well as for modern pharmaceutical smoking cessation products. An alternative nicotine delivery device providing aid in smoking cessation is lacking that is both acceptable from the point of efficacy and cost.

In summary, in Serbia a reduction of the smoking-related burden of disease is an important public health issue. The experience from Sweden and other countries indicates that substantial risk reduction due to smoking related disease - tobacco harm reduction - is achievable, despite limited financial resources.

Main attempts to reduce smoking related disease are directed towards prevention of onset of smoking in young people, and cessation/reduction of smoking among adult, current smokers. Obviously, both approaches are important, but differ with respect to their short-term versus long-term impact. Most of the smoking-related deaths for the next 50 years will occur among existing smokers as cancer, cardiovascular disease and lung disease related to smoking typically occur after several decades of smoking. Consequently, prevention of onset of smoking among young people will not have a major influence on mortality until today's teenagers reach the age where smoking-related disease becomes a significant cause of death, i.e. towards the mid of this century. On the other hand, cessation of smoking starts influencing death risk already after a few years (Peto et al, 2003).

Many smokers, in particular heavy smokers, have great problems quitting smoking, and the use of alternative nicotine delivering devices may be of considerable assistance to promote abstinence as evidenced by numerous controlled clinical trials of the role of NRT:s in smoking cessation (George & O'Malley, 2004). However, the low success rate for alternative nicotine delivering devices such as nicotine chewing gum, nicotine patch and nicotine spray are well documented. This observation seems to be due to the fact that the kinetics of nicotine absorption differs greatly from that associated with smoking (Fant et al., 1999). Also, the cost of these nicotine sources is high. More recently, other pharmaceutical smoking cessation aids have been introduced, such as, bupropion and varenicline (Schnoll & Lerman, 2006). Although the long-term success rates associated with these new therapies appear marginally better than with NRT, the drug costs are prohibitively high for a Serbian public health setting. In addition, due to the potential side effects of these new therapies including neuropsychological problems and nausea, they probably remain prescription drugs with a limited impact on smoking cessation from a public health perspective.

Oral snuff (smokeless tobacco), for which the kinetics of nicotine delivery is more similar to that of smoking compared to NRT, offers another possibility for nicotine replacement therapy. The Swedish experience provides strong indirect support to the notion that snus with low levels of nitrosamines, provides an effective aid in smoking cessation (Bates et al., 2003). According to the Swedish National Board of Health (2005) subjects who used snuff for the purpose of smoking cessation had a 50% higher probability of remaining non-smokers than those who quit without any alternative nicotine source. The cost for one days' consumption of Swedish low-nitrosamine snus is not higher than for one package of cigarettes.

Clinical experience on smoking cessation from the Nicotine Institute in Vienna (Kunze, personal communication) indicates that recruitment to smoking cessation programs is more successful if the goal proposed to the subjects entering a smoking cessation program is focused on reducing smoking rather than emphasizing total cessation. Many smokers have previously made unsuccessful attempts to stop smoking, and therefore might abstain from participating in a program if the requirement is total abstinence. However, for several subjects treatment with a cigarette substitute containing nicotine will reduce smoking drastically, and eventually to such a low level that smoking cessation is facilitated. The current trial will, therefore, adopt this general philosophy.

Considerations as those presented above constitute the rationale for conducting a controlled clinical trial in Serbia among adult smokers with the goal to reduce smoking, and eventually stop smoking, using low-nitrosamine snus manufactured according to the Swedish GothiaTek® standard.

Some types of oral smokeless tobacco have been associated with the induction of cancers in the head/neck region (Winn et al, 1986, IARC, 1985; Idris et al., 1994). Consequently, the EU tobacco directive previously required that packages of snuff should carry a cancer warning. However, the European Commission decided that the cancer warning be dropped in 2001, because large, Swedish epidemiological studies showed no increase of cancer risk associated with the use of Swedish snus (Lewin et al., 1998; Schildt et al., 1998).

A recent extensive public health report from the Swedish National Board of Health (2006) emphasized that:

“Although we cannot exclude health risks associated with snus...the conclusion is that these are very small in comparison with smoking”.

This conclusion has been supported by prestigious institutions like the Royal College of Physicians in Great Britain (2002) as well as by the Institute of Medicine of the National Academies of Sciences, Washington, D.C. (IOM, 2001).

The use of oral smokeless tobacco is virtually unknown in Serbia. A limited feasibility study was therefore conducted in Belgrade during 2005 where 21 smokers were offered different Swedish snus products, and 18 were offered the Nicorette® nicotine patch. The main objectives for this study were to assess the acceptability of various snus products in a Serbian setting, as well as to assess possible potential problems that could be expected in a full scale study. Out of the 21 participants who tried snus, a total of ten preferred an eucalyptus flavored brand, seven an liquorice flavored brand, four a menthol brand, and none liked the taste of a regular unflavored Swedish snus brand.

One main obstacle in conducting the feasibility study was poor motivation among some male participants, perhaps due to a low awareness of the health risks associated with smoking. For the whole group of smokers, however, there was a marked reduction of average CO levels in exhaled air at the end of the one month period indicating a substantial reduction of the number of cigarettes smoked. The study also clearly demonstrated that, if properly flavoured, oral moist tobacco like Swedish snus was acceptable to both Serbian male and female smokers.

This protocol has been developed in collaboration with an international advisory panel consisting of:

- Prof. Michael Kuntze, University of Vienna, Austria
- Dr. Karl-Olof Fagerström, Fagerström Consulting, Hälsingborg, Sweden
- Prof. Robert Nilsson, University of Stockholm, Sweden

Prof. Nilsson will function as International Coordinating Investigator in the trial, and Dr Ruza Antic, Belgrade, Serbia will be the National Principal Investigator.

STUDY OBJECTIVES

The primary objective of this study is to assess the efficacy of a traditional Swedish low nitrosamine smokeless tobacco product (“snus”) to help adult cigarette smokers in Serbia to substantially reduce their smoking or completely stop smoking.

The secondary objective of this study is to assess the effects of the intervention on clinical tests and biomarkers related to lung function, risk of cardiovascular disease, and other health outcomes.

INVESTIGATIONAL PLAN

Description of Overall Study Design and Plan

This multi-center, double-blind, placebo-controlled, randomized, clinical trial is designed to evaluate snus versus placebo as an aid to reduce smoking among adult cigarette smokers in Serbia.

The snus and the placebo product come in sachets (or pouches) that are to be placed in the mouth between the upper gingiva and cheek. The sachets are delivered in plastic containers each with 24 sachets. The participants can choose from two different sachet sizes (0.5 and 1 g) and two different flavors (liquorice and eucalyptus). The rationale for using different sachet sizes is that many individuals feel that the standard 1 g sachet is too big to be easily retained in the mouth. On the other hand, the smaller sachet contains less tobacco and may not deliver enough nicotine to alleviate nicotine abstinence in all smokers. The selected flavors were those favored by most participants in the mentioned feasibility study.

The contents of snus and the placebo product are described in detail in an appendix to this protocol. The content of both products complies with the industrial standard GothiaTek®.

It should be noted that the product used as placebo in this trial is a snus replacement product that does not contain nicotine, but is widely marketed in Sweden under the brand name "Onico".

The participants will be instructed to try to refrain from cigarettes through the use of their allocated study product when they feel an urge to smoke. The sachet should be retained in the mouth during at least 20-30 minutes (at which time the blood nicotine levels reach a maximum). If the participants still feel an urge to smoke after 30 minutes, they can do so. The participants will be encouraged to substitute as many cigarettes as possible with the study products, although total abstinence from cigarettes is not a primary goal during the first 24 weeks. Those who are able to achieve a substantial reduction of their self-reported cigarette consumption at 24 weeks (verified by a decreased level of CO in exhaled air) will be encouraged to quit smoking during the ensuing 24-48 week follow-up. Those who cannot achieve a substantial reduction at 24 weeks are defined as treatment failures and will not be followed beyond 24 weeks.

The amount of nicotine needed to prevent withdrawal symptoms among smokers varies considerably. The amount of study products used by the participants is therefore also expected to vary and is dependent on the extent to which the products actually can replace cigarettes. The participants will therefore be instructed to use the products ad libitum. They will be informed that one 1 g snus sachet typically can replace one cigarette. There is a possibility of nicotine overdose, particularly among those who both use cigarettes and snus since the participants, at least in the early phase of the trial period are unfamiliar with the effects of snus. However, such overdose is typically self-limiting since it will result in symptoms that are familiar to most habitual smokers, that is, nausea, tachycardia, cold sweat etc. The symptoms are quickly reversible upon cessation of smoking or use of snus.

Selection of Study Population: Information Seminar & Baseline Visit

Potential participants will be invited (through posters and ads, see appendix) to an information seminar with c. 10-20 attendees where the goals of the study as well as the means of its achievement are explained. Information is provided about health risks associated with smoking, as well as about possible alternative aids available for smoking cessation. The physiological effects of nicotine will be outlined, and an account given of the Swedish experience with snus including potential health risks associated with different types of smokeless tobacco products. The trial inclusion and exclusion criteria will be mentioned.

A few days-weeks after the seminar, potential trial participants are invited to a baseline visit during which written informed consent to participate will be obtained. Other activities at the baseline visit are described in detail in section 3.4 Assessments.

Participants are healthy, adult cigarette smokers aged 20-65 years who habitually smoke >10 cigarettes per day, who have smoked daily for >1 year, and who are motivated to substantially reduce or completely stop smoking but who are unable to do so without help.

Specific entry criteria are detailed in Sections 3.2.1 and 3.2.2.

Inclusion Criteria

Subjects meeting all of the following inclusion criteria can be considered for admission to the study.

1. The subject is aged between 20 through 65 years
2. The subject smokes >10 cigarettes per day (average daily consumption during past month)
3. The subject has smoked daily for >1 year
4. The subject is motivated to substantially reduce or quit smoking
5. The subject is in good general health
6. The subject accepts not to take NRT or any other non-protocol treatment to facilitate smoking cessation during the study period

Exclusion Criteria

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

1. The subject has uncontrolled hypertension (systolic >140 mg Hg, diastolic >90 mg Hg)
2. The subject has a history of coronary heart disease or other significant heart condition
3. The subject has a history of another significant medical condition that may interfere with study procedures
4. The subject is a pregnant or nursing mother
5. The subject currently abuses alcohol or drugs
6. The subject has current active oral disease that may interfere with use of snus
7. The subject has significant psychiatric or psychosocial problems that may interfere with study procedures

8. The subject has used any type of pharmaceutical or other products for smoking reduction or cessation within the past 3 months

Removal of Subjects from Therapy or Assessment

A subject will be considered to have completed the study when he or she completes the final assessment visit at week 48. If a subject is discontinued at any time after entering the study, the investigator will make every effort to contact the subject and complete the Premature discontinuation form as shown in *Section 3.4.1, Schedule of Assessments*.

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:

- *Failure to achieve "smoking reduction" at 24 weeks (>50% reduction of self-reported number of smoked cigarettes during week 20-24, and CO in exhaled air <1 ppm, compared to baseline):* such subjects are unlikely to stop smoking during subsequent follow-up which is the aim of the study after 24 weeks.
- *Protocol Violation:* The subject's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements (e.g., treatment noncompliance, failure to return for defined number of visits). The violation necessitated premature termination from the study. Clinical visits are scheduled with a -1/+1 week window. Visits during this two-week window are not considered to be protocol violations. 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. Failure to complete one scheduled visit within the mentioned -1/+1 week window due to disease or other factors outside the participant's control is acceptable whereas failure to complete two consecutive visits shall be regarded as a protocol violation that necessitates premature study termination.
- *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 medication.
- *Death:* The subject died.
- *Other:* The subject was terminated for a reason other than those listed above

Treatments

Details of Study Treatments

Comprehensive information about the study products are given in an appendix to this protocol. All products used as part of the trial will be provided free of charge to the participants by the sponsor, and will be distributed by the central trial office. For participants who wish to continue with snus after completion of the study, the sponsor intends to make snus available from commercial retailers within the city of Belgrade,

unless this is made impossible by regulatory or other circumstances outside of the sponsor's control.

Dosage Schedule

Use of snus (or placebo) within the trial is ad libitum. When participants feel an urge to smoke, they are instructed to try their allocated study product for at least 20-30 minutes. If they still feel an urge to smoke, they can do so. Participants will be informed that one 1 g snus sachet typically can replace one cigarette. They will also be informed that nicotine overdosage 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 participants will be instructed to replace as many cigarettes as possible with their allocated study product. Those who achieve "smoking reduction" at 24 weeks will be encouraged to quit smoking totally. The average snus consumption among snus users in Sweden who do not smoke is about 10-15 sachets per day.

Treatment Assignment

After providing informed consent at the baseline visit, the subjects will be randomly allocated to either active snus or placebo snus. Stratification will be made according to treatment centre. Randomization will be done by telephone to a central office where participant's identifiers are recorded. The random allocation will be done according to a computer-based algorithm.

Product Packaging and Blinding

As this is a double-blind trial, the study products will be distributed from the central office and will be labeled with the participant's identifiers. Only the central office will have access to the key linking each participant to their allocated treatment.

Treatment Compliance

Self-reported number of cigarettes smoked daily and snus sachets used per day during the past week will be recorded each week. A simple participant diary will be used; a sample diary is enclosed as an appendix.

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 participant's self-reported information.

Prior and Concomitant Treatments

Any concomitant medication is acceptable except NRT or other treatments used for smoking cessation, for instance, bupropion or varenicline. If a subject has used such treatments previously, they must have been stopped more than three months ago.

Assessments

Schedule of Assessments

The procedures to be performed throughout the study are outlined in the flow chart of scheduled events which is enclosed as an appendix to this protocol. A detailed description of each assessment may be found in Section 3.4.2, Description of Assessments.

Description of Assessments

Unless otherwise indicated, all assessments listed below will be performed by the investigator or other regular study personnel. If the subject terminates the study or drops out before week 48, the premature discontinuation form in the CRF should be filled in.

Clinical visit at baseline: Individuals who are interested to participate and are deemed eligible for inclusion are invited to a base-line visit which includes assessment of eligibility criteria.

Eligible individuals who provide written informed consent are randomly allocated to one of the two study groups (active snus or placebo snus). The baseline visit will also include medical history, assessment of smoking status (age of initiation of daily smoking, average number of cigarettes smoked per day during the past year, history of previous quit attempts, and intention to participate: “want to quit smoking” versus “want to reduce smoking”, history of previous use of NRT or other pharmaceutical or other smoking cessation aids), blood samples, a lung function test, CO in exhaled air, measurement of blood pressure, height and weight, and Fagerström test of nicotine dependence. At selected study sites the participants will be asked to provide extra 30-50 ml of blood and a sample of buccal cells obtained with a tooth brush, to allow exploratory analyses of adducts. These analyses are not part of this protocol.

The participants are given a diary to register, on a weekly basis, their average daily cigarette and snus consumption during the preceding week, as well as any untoward subjective symptoms should such arise.

Participants are instructed to cut down on smoking by taking a sachet of snus when they feel an urge to smoke. If they still want to smoke after 20-30 minutes, they can do so (although they should then remove the snus sachet to avoid nicotine overdose). They are also informed that although smoking cessation is preferable, the primary objective of the first 24 weeks of the study is smoking reduction, which in itself is worthwhile since it may have beneficial health effects, and that it might be a first step towards complete smoking cessation.

The number of snus sachets consumed per day is determined by the participants themselves. The fact that one sachet delivers roughly the same amount of nicotine as one cigarette implies that individuals who replace all of their cigarettes with snus will consume about 10-25 sachets per day, that is, the same number as their previous cigarette consumption. The participant is provided with a sufficient quantity of the study product to last until the next visit. Information is given that no other source of nicotine than cigarettes or snus should be used, and that NRT or any other pharmaceutical smoking cessation aid is not allowed.

Week 1: telephone contact to establish preferences for flavors and sachet size (to direct further distribution of study products), to assess compliance and any adverse events, and to monitor each participant's progress.

Clinical visit at week 2 and week 6: Monitoring of each participant's progress including self-reported smoking status according to the participant diary, measurement of CO in exhaled air, blood pressure, and weight (weight only at week 6).

Week 9: telephone contact to monitor each participant's progress, to assess compliance and any adverse events,

Clinical visit at week 12: Clinical visit including measurements of primary and secondary end-Points (based on CO in exhaled air, lung function test, blood tests, self-reported smoking status and snus consumption according to diary, weight, blood pressure, assessment of compliance and adverse events)

Weeks 13-16: Information to participants by mail about test results.

Clinical visit at week 18: Monitoring of each participant's progress (including self-reported smoking status and snus consumption according to diary) & measurement of CO in exhaled air, assessment of compliance and adverse events

Clinical visit at week 24: Clinical visit including measurements of primary and secondary end-Points (based on CO in exhaled air, lung function test, blood tests, self-reported smoking status and snus consumption according to diary, weight, blood pressure, assessment of compliance and adverse events).

Participants who have achieved "smoking reduction" are asked to continue with their allocated treatment, and to come back for further follow-up. No unblinding of the allocated treatment will be done.

Main messages to participants during the first 24 weeks:

"The best thing you can do for your health is to reduce, or preferably quit, smoking..."

"Try to cut down on cigarettes as much as possible by using a sachet every time you feel an urge to smoke, if you still want to smoke after 20-30 min, you can do so, but take out the sachet..."

"Quitting/reducing smoking is difficult; don't feel discouraged if you don't succeed at once..."

Weeks 25-28: Information to participants by mail about test results

Clinical visit at week 30: Monitoring of each participant's progress (including self-reported smoking status and snus consumption according to diary) & measurement of CO in exhaled air, assessment of compliance and adverse events

Main message to participants during 24-48 weeks.

“Quit cigarettes completely by using sachets instead!”

“Since you have been able to substantially reduce your smoking, you should be able to quit completely...”

“Quitting smoking is the best you can do for your health...”

Clinical visit at week 36: Clinical visit including measurements of primary and secondary end-Points (based on CO in exhaled air, lung function test, blood tests, self-reported smoking status and snus consumption according to diary, weight, blood pressure, assessment of compliance and adverse events).

Weeks 37-40: Information to participants by mail about test results

Clinical visit at week 42: Monitoring of each participant’s progress (including self-reported smoking status and snus consumption according to diary) & measurement of CO in exhaled air, assessment of compliance and adverse events

Week 48: Clinical visit including measurements of primary and secondary end-Points (based on CO in exhaled air, lung function test, blood tests, self-reported smoking status and snus consumption according to diary, weight, blood pressure, assessment of compliance and adverse events).

Weeks 49-52: Information to participants by mail about test results

EFFICACY ASSESSMENTS:

Primary Efficacy Assessments:

Smoking status will be assessed at 12 and 24 weeks. "Smoking reduction" at 24 weeks is the primary outcome measure. It is defined as a self-reported reduction of $\geq 50\%$ compared to baseline in the average number of smoked cigarettes per day during week 20-24, verified by a reduced concentration of carbon monoxide (CO) in exhaled air of at least 1 ppm

Secondary Efficacy Assessments:

Secondary efficacy assessments will be made at 12, 24, 36 and 48 weeks. Secondary end-points include

- "Smoking reduction" at 12 weeks
- Smoking cessation at 12 and 24 weeks defined as self-reported total abstinence from cigarettes during the preceding 4-week period verified by a concentration of CO in exhaled air of < 10 ppm
- Smoking cessation at 36 and 48 weeks among those who achieved smoking reduction at 24 weeks (cessation here defined as self-reported total abstinence from cigarettes during the preceding 4, 12, or 24-week period, verified by a CO-concentration in exhaled air of < 10 ppm at all measurements during the specified time period
- Clinical tests and biomarkers at 12 and 24 weeks among all participants, and at 36 and 48 weeks among those who achieved smoking reduction at 24 weeks including body weight, BMI, blood pressure, CO in exhaled air, measures of lung function (FEV_{1.0}, FVC, FEV%), total S-WBC, S-CRP, total S-cholesterol, S-HDL, S-LDL, S-fibrinogen, S-cotinine

SAFETY ASSESSMENTS:

Medical history: Prior to randomization the potential participants' medical history will be analyzed to determine eligibility.

Vital signs, Body Weight and Height: Vital signs will include supine systolic and diastolic blood pressures. Supine recordings will be made after the subject has been recumbent for 3 minutes. Body weight without shoes will be recorded in kg.

Laboratory Parameters: The following laboratory tests are to be performed as indicated by the schedule of assessments:

- Hematology: total S-WBC
- Chemistry: S-CRP, total S-cholesterol, S-HDL, S-LDL, S-fibrinogen, S-cotinine
- Other: CO in exhaled air, lung function tests

At selected study sites an additional 30-50 ml of blood will be sampled from participants at the baseline visit and during follow-up among those who manage to quit smoking. These individuals will also be asked to provide samples of buccal cells which will be obtained with a non-invasive technique similar to brushing the buccal mucosa with a tooth-brush. These samples are intended for exploratory analyses of potential novel biomarkers for cardiovascular disease and cancer risks, e.g. DNA adducts, as well as possible biomarkers for risk of other tobacco-related disease. These exploratory analyses are not part of this clinical protocol so there will be a separate protocol and informed consent form for participants eligible for these analyses.

CO in exhaled air will be analyzed using Micro Smokerlyser EC-50® (Bedfont Scientific Ltd, U. K.). Lung function will be assessed using Easy One Spirometer® (ndd Medizintechnik AG, Zurich, Switzerland) as FEV%, FVC, and FEV_{1.0}.

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 medication, 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 medication 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 MEDICATION	
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 drug 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 stopping the treatment 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 medication, 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.

Appropriateness of Measurements

All assessments to be used in this study are common, standard measurements frequently used in smoking reduction/cessation studies.

DATA MANAGEMENT AND STATISTICAL ANALYSIS

Completed CRFs for this study will be forwarded to the sponsor's representative where editing and construction of a quality-assured database will occur. There will be no interim analyses of treatment efficacy.

Determination of Sample Size

To reliably detect ($p < 0.05$, statistical power $> 80\%$) a more than two-fold increase in the odds of achieving smoking reduction at 24 weeks among the active versus placebo groups, and assuming a smoking reduction rate of 15% in the placebo group versus 25% in the active snus group (corresponding to an odds ratio of 1.9), the target sample size can be estimated at 250 per group, that is, a total size of 500 study participants.

In previous randomized studies of NRT versus placebo, NRT has resulted in an increased proportion of participants achieving short- to medium term smoking cessation with odds ratios in the order of 1.5-3. Epidemiological, cross-sectional studies from Sweden have indicated that snus might be more effective as an aid in smoking cessation than NRT. Against this background the mentioned target sample size should provide reasonable statistical power for current purposes.

Study Population

The statistical analysis will include all randomized, eligible subjects on an "intention to treat" (ITT) basis. Exploratory analyses will also be done on those who achieved "smoking reduction" at 24 weeks.

Background and Demographic Characteristics

The population will be described in terms of age, gender, previous smoking history & quit attempts, and use of NRT or other pharmaceutical smoking cessation aids, Fagerström score, medical history, and other relevant data collected at baseline.

Efficacy Analysis

Primary Efficacy Variable

The primary end-point, that is, the proportion achieving "smoking reduction" at 24 weeks, will be analyzed with logistic regression modeling among eligible subjects using intent-to treat criteria and with participants who terminated the study prematurely for any reason considered to be failures.

Secondary Efficacy Variables

Secondary end-points will be analyzed using parametric or non-parametric standard statistical methods. The proportion achieving "smoking reduction" or "smoking cessation" at the times and with the criteria specified in section 3.4.2 (Description of Assessments), will be analyzed with logistic regression modeling among eligible subjects using intent-to treat criteria and with participants who terminated the study prematurely for any reason considered to be failures. Exploratory analyses of secondary end-points will also be done on those who achieved "smoking reduction" at 24 weeks.

A priori hypotheses concerning secondary end-points include that allocation to active snus will result in beneficial effects on lung function and cardiovascular biomarkers. Such effects are hypothesized to be directly related to the level of smoking reduction. Overall

nicotine consumption (as measured by S-cotinine) is not expected to increase in the active snus group.

STUDY MANAGEMENT

Approval and Consent

Regulatory Guidelines

The study will be performed in accordance with local national laws (as applicable), the guidelines of the International Conference on Harmonisation (ICH), and the guidelines of the Declaration of Helsinki adopted by the 18th World Medical Assembly in Helsinki, Finland in 1964 and amended by subsequent assemblies in Tokyo, Japan in 1975; Venice, Italy in 1983; Hong Kong in 1989; Somerset West, South Africa in 1996, and in Edinburgh, Scotland, October 2000.

Research ethics and approval by IRB/IEC

Cigarette smoking is a significant public health problem in Serbia. The prevalence of daily smoking in Serbia is one of the highest in Europe. Serbian health authorities are aware of the problem and have started to take measures against smoking. However, the high smoking prevalence, low public awareness of the health hazards with smoking, and economic problems to fund smoking reduction/cessation programs, represent a significant challenge to all anti-smoking measures in Serbia. In addition, pharmaceutical smoking cessation aids such as NRT are generally prohibitively expensive. In addition, the benefit with such therapies long-term remains modest. In conclusion, there is a great need for further research on effective strategies for smoking reduction/cessation in Serbia.

The current trial aims to determine the acceptability of Swedish snus in a setting without a long cultural tradition of oral tobacco products, as well as to evaluate the efficacy of snus for smoking reduction/cessation. 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 reduction/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.

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 and thus harm reduction.

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 cues 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.

For participants who have managed to quit smoking with snus and who wish to continue with snus after completion of the study, the sponsor intends to make snus available from commercial retailers within the city of Belgrade, unless this is made impossible by regulatory or other circumstances outside of the sponsor's control.

The participants will be given small gifts at the clinical visits involving blood tests as a token of appreciation on the part of the study team. However, the value of these gifts will not exceed 5-10 Euro so there is no reason to believe that these gifts will act as a pressure on the participants to continue in the trial should they wish to terminate their participation.

Against this background, it can be concluded that the scientific value of this study by far outweighs the ethical problems which in general are only of minor significance.

Conduct of the study will be approved by an appropriately constituted institutional review board (IRB) or independent ethics committee (IEC). Approval is required for the study protocol, protocol amendments, informed consent forms, subject information sheets, and advertising materials. No study products will be shipped to a site until written IRB/IEC authorization has been received by the sponsor or its representative. The international coordinating investigator in collaboration with the investigators at each study site will be responsible for obtaining such authorization from the appropriate IRB/IEC.

Informed Consent

For each trial subject, written informed consent will be obtained prior to any protocol-related activities. As part of this procedure, the investigator or one of his or her associates must explain orally and in writing the nature, duration, and purpose of the study, and the action of the study products in such a manner that the subject is aware of the potential risks, inconveniences, or adverse effects that may occur. An English version of the written information to be used is attached to this protocol. This written information remains tentative until approved by the relevant IRB.

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 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 and lung function

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.

As this is a trial only including healthy volunteers there are no clinical records on the participants. Therefore, the CRF will serve as the main source document in this trial, although a variety of documents including laboratory reports, patient diaries, and printouts from medical equipment also will serve as source documents.

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.

Retention of Records

The investigator must arrange for retention of study records at the site for a period of 15 years. The nature of the records and the duration of the retention period thus meet the requirements of regulatory authorities within the European Union. 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 affairs or registration. If necessary, the authorities will be notified of the investigator's name, address, qualifications, and extent of involvement. Reports of the study will be prepared by the international coordinating investigator in collaboration with the sponsor or its representative.

Publications

As a multicenter trial, the sponsor and the investigators intend that the data from all centers participating in the trial will be published in the form of a joint report. A publication committee selected by the international coordinating investigator will submit draft manuscripts to all participating investigators for their comments. In conformity with the uniform requirements for manuscripts submitted to biomedical journals published by the International Committee of Medical Journal Editors (see discussion in Kassirer & Angell, 1991); investigators whose contribution consists solely in the collection of data will not be named individually as authors. Rather, those investigators will be identified and acknowledged in a note.

Individual investigators and/or their associates subsequently may publish additional findings of this study, i.e. results not pertaining to the randomized smoking reduction/cessation comparison, in scientific journals or present them at scientific meetings, provided that the sponsor is given ample opportunity to review any proposed abstract, manuscript, or slide presentation prior to its submission. This review is required to ensure that the sponsor is aware of all written and oral presentations of the data and does not imply any editorial review or restriction of the contents of the presentation or use.

REFERENCES

Bates, C., Fagerström K, Jarvis, M.J., Kunze, M., McNeill, A., and Ramström L. (2003). European Union policy on smokeless tobacco: a statement in favour of evidence based on regulation for public health. *Tobacco Control* 12, 360-367.

Fant, R.V., Owen, L.L., and Henningfield, J.E. (1999). Nicotine replacement therapy. *Prim. Care* 26, 633-652.

Foulds J, Ramström L, Burke M and Fagerström K (2003). The effects of smokeless tobacco (snus) on smoking and public health in Sweden. *Tobacco Control* 12, 349-359.

George T., P., O'Malley, S., S. (2004). Current pharmacological treatments for nicotine dependence. *Trends Pharmacol. Sci.* 25: 42-48.

Henningfield, J., E. and Fagerström, K., O., (2001). Swedish Match company, Swedish snus and public health: a harm reduction experiment in progress? *Tobacco Control* 10, 253-257.

International Agency for Research on Cancer, IARC (1985). *IARC Monographs on the Evaluation of the Carcinogenic Risks to Humans - Tobacco Habits Other Than Smoking: Betel-Qid, and Areca Nut Chewing and Some Related Nitrosamines*. Vol. 37, WHO, Lyon.

International Agency for Research on Cancer, IARC (1997). *GLOBOCAN a database on cancer epidemiology data*. WHO, Lyon, <http://www-dep.iarc.fr/dataava/infodata.htm>

Idris AM, Prokopczyk B, and Hoffmann D. (1994). Toombak: a major risk factor for cancer of the oral cavity in Sudan. *Prev. Med.* 23, 832-839.

Institute of Medicine, *Clearing the Smoke*, IOM (2001). Committee to Assess the Science Base for Tobacco Harm Reduction. (Stratton, K. et al, eds). Board of Health Promotion and Disease Prevention. Institute of Medicine. National Academy Press, Washington, D.C.

Kassirer JP, Angell M. On authorship and acknowledgments. *N Engl J Med* 1991; 325(21): 1510-1512.

Kozlowski L.T. (2002). Harm reduction, public health, and human rights: smokers have a right to be informed of significant harm reduction options. *Nicotine & Tobacco Research*, S55-S60.

Lewin, F., Norell, S.E., Johansson, H., Gustavsson, P., Wennerberg, J., Björklund, A., and Rutqvist, L.E., (1998). Smoking tobacco, oral snuff, and alcohol in the etiology of squamous cell carcinoma of the head and neck. A population based case-referent study in Sweden. *Cancer* 82, 1367-1375.

Levy DT, Mumford EA, Cummings KM, Gilpin EA, Giovino G, Hyland A, Swenor D, Warner KE (2004). The relative risks of a low-nitrosamine smokeless tobacco product compared with smoking cigarettes: estimates of a panel of experts. *Cancer Epidemiol. Biomarkers Prev.* 13, 2035-2042.

Peto, R., Lopez, A.D., Boreham, J., and Thun, M. Mortality From Smoking in Developed Countries 1950-2000 (2nd edition: 2003), Clinical Trial Service Unit, Medical Sciences Division, Oxford University, U.K.

Royal College of Physicians (2002). Protecting Smokers, Saving Lives, Publications Unit of the Royal College of Physicians, London 2002.

Schildt, E.-B., Eriksson, M., Hardell, L., and Magnusson, A. (1998). Oral snuff, smoking habits, and alcohol consumption in relation to oral cancer in a Swedish case-control study. *Int. J. Cancer* 77, 341-346.

Schnoll R. A., Lerman, C. (2006). Current and emerging pharmacotherapies for treating tobacco dependence. *Expert Opin Emerg Drugs* 11:429-444

Swedish National Board of Health and Welfare (2006). Public Health Report 2005. The Health and Social Administration Epidemiological Center.

Winn, D., M., Blot, W., J., Shy, C. M., et al (1981). Snuff dipping and oral cancer among women in the Southern United States. *N Engl J Med*, 304:745-749

APPENDICES

- Detailed description of study products
- Flow chart of scheduled events
- Sample of written informed consent form
- Sample of texts to be used for advertisements and/or posters to recruit participants
- The Fagerström test
- Sample participant diary

Appendix to study protocol

STUDY PRODUCTS

TRADITIONAL SNUS

1. Active substance: Nicotine

1.1 Product name: Snus

1.2 Appearance: Paper sachets

1.3.Content : Snus is made from ground tobacco leaves, water, and food-allowed additives (salt, humidifier, acidity regulator, and flavour substances). The finished product adheres to the industrial standard GothiaTek[®] 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.

1.3.1 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)	
Flavour substances	

1.3.2 Content (small sachets):

Tobacco	0.25 g
Water	0.25 g
Salt (NaCl)	6%
Nicotine	4mg
Propylene glycol (E 1520)	
Sodium carbonate (E 500)	
Flavour substances	

1.3.3 pH 8.1-8.9 (accepted range)

1.4 Administration: The sachets are placed in the mouth between the gingiva and cheek. Usage is *ad libitum*. Typically, the sachets are retained for 20-30 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.

1.5 Nicotine absorption: 10-20% of the nicotine in the sachets is absorbed to the blood through the mucous membranes. The potential nicotine uptake is thus 1-2 mg from the large sachets and 0.5 – 1 mg from the small sachets.

1.6 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

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 slight burning sensation in the mouth at the location of the sachet, particularly among those unaccustomed to the product. However, 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 slight 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.

1.7 Weight variation of study product: Sachet weight may vary between -10% and +20% of the labelled weight, the mean weight is: 1g (large sachets) and 0.5g (small sachets)

1.8 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.

Component¹	Limit²	Content³	Component¹	Limit²	Content³
<u>Nitrite</u> (mg/kg)	3.5	1.1 (<0.5 - 1.9)	<u>Cadmium</u> (mg/kg)	0.5	0.2 (0.1 - 0.3)
<u>TSNA</u> (mg/kg)	5	0.8 (0.4 - 1.1)	<u>Lead</u> (mg/kg)	1.0	0.2 (0.1 - 0.2)
<u>NDMA</u> (µg/kg)	5	0.6 (<0.5 - 1.1)	<u>Arsenic</u> (mg/kg)	0.25	0.08 (<0.03 - 0.13)
<u>BaP</u> (µg/kg)	10	0.9 (<0.5 - 1.8)	<u>Nickel</u> (mg/kg)	2.25	0.8 (0.3 - 1.2)
<u>Pesticides</u>	According to the Swedish Match pesticide policy		<u>Chromium</u> (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%

1.9 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 (6-8 °C) to preserve the water content and freshness of the product.

The product is marked with a best-before date which is c. 20 weeks after production date. It should be noted that the levels of undesired, potentially toxic substances, such as, nitrosoamines, 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

2. Placebo: No active substance

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

2.2.1 Content: Large sachets

Fibres from maize	0.6g
(lignine and cellulose 70%, starch 15%, protein 6%, sugar 2%, fat 2%, water 3%, other 2%)	
Water	0.4 g
Salt	6%
Glycerol (E 422)	
Acidity regulator (E 500)	
Flavour substances (same as in the traditional snus)	

2.2.2 Content: Small sachets

Fibres from maize	0.3g
Water	0.2 g
Salt	6%
Glycerol (E 422)	
Acidity regulator (E 500)	
Flavour substances (same as in the traditional snus)	

2.2.3 pH 8.1-8.9 (accepted range)

2.3 Weight variation of study products: Sachet weight may vary between -20% and +20% of the labelled weight, the mean weight is: 0.9g (large sachets) and 0.45g (small sachets)

2.4 Administration and usage. Same as with traditional snus

2.5 Side effects: None reported. However, because the product is slightly alkaline just as traditional snus, users may initially experience a slight 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.

2.6 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 c. 20 weeks after production date. The product should preferably be stored in a refrigerator (6-8 °C) to preserve the water content and freshness.

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

CONFIDENTIAL

Flow chart of scheduled events (clinical visits highlighted). Visits are to be scheduled within a -1/+1 week “window”.

Scheduled activity	Base-line visit	Weeks after randomization: 1 ¹	2	6	9 ¹	12	13-16	18	24	25-28	30	36	37-40	42	48	49-52	At completion or discontinuation for any reason before week 48
Assessment of eligibility, informed consent, medical & smoking history, randomization, etc.	x																
CO in exhaled air	x		x	x		x		x	x		x	x		x	x		
Lung function test	x					x			x			x			x		
Blood tests, etc ²	x					x			x			x			x		
Self-reported smoking status ³	x	x		x	x	x		x	x		x	x		x	x		
Height, weight ⁴	x			x		x			x			x			x		
Blood pressure	x		x	x		x			x			x			x		
Fagerström test	x								x						x		
Assessment of compliance		x	x	x	x			x	x		x	x		x	x		
Assessment of AE		x	x	x	x			x	x		x	x		x	x		
Information to participants about test results by mail (or telephone)							x			x			x		x	x	
Termination case report ⁵																	x

1. Telephone contact

2. Including extra 30-50 ml blood and sampling of buccal cells for exploratory analyses at selected study sites, see separate protocol.

3. Based on information in the participants' study diaries. At week 1, 2, and 6 self-reported average number of smoked cigarettes per day refers to the situation during the preceding week. At week 12, 24, 36 and 48 the number will be recorded also for the entire preceding 4-week period. At week 36 and 48 the number will be recorded for the preceding 4-week, 12-week, and 24 week period.

4. Height to be measured only at baseline

5. To be filled in for all randomized patients either upon completion of trial at week 48, or at premature discontinuation for any reason

Information about the Serbian Smoking Reduction/Cessation Trial (2SRT)

Would you like to participate in a scientific study aiming to help cigarette smokers to reduce or quit smoking? This document explains the background and rationale for the trial and what it would entail should you decide to participate. The study is an international collaboration with researchers in Sweden and the Medical Faculty of the University of Vienna, Austria. The study is done under strict control by institutions approved in the Republic of Serbia.

Smoking endangers your health!

Smoking has been classified by the World Health Organisation (WHO) as one of the world's most significant health problems. In Serbia c. 15,000 people die prematurely each year because of diseases caused by smoking: various types of cancer (e.g. in the lung, oral cavity, larynx, esophagus, urinary bladder, and pancreas), cardiovascular disease (e.g. myocardial infarction), and chronic lung diseases. If you stop smoking these risks are significantly diminished.

Have you tried to stop smoking?

Many smokers have tried to stop smoking – or decrease their cigarette consumption – but have failed. The problem is that smoking is addictive because tobacco contains nicotine which is a highly addictive substance. In low doses nicotine acts like a stimulant, like caffeine. But long-term use is detrimental to your health.

There is help!

Most smokers who quit are able to do so on their own. For those who fail, there are pharmaceutical products that may help, for example, nicotine chewing gum or nicotine patches. The problem with these products is that their delivery of nicotine is much slower than with cigarettes. In Sweden, a traditional oral, smokeless tobacco product called “snus” has been an effective alternative for smokers who want to quit cigarettes.

What is “snus”?

Snus is a traditional Swedish smokeless tobacco product that comes in small sachets (or pouches) that are placed in the mouth between the upper gingiva and cheek. The sachet is typically retained in the mouth up to 30-60 minutes. One sachet of traditional snus delivers about the same amount of nicotine as one cigarette. Some brands are flavored with e.g. liquorice or eucalyptus. One reason that snus has been used successfully by many smokers who want to quit is that the delivery of nicotine from snus resembles that with smoking. In Sweden snus has to a large part replaced smoking, particularly among males. As a consequence, Swedish males now have record low risks of smoking related disease. Many Swedish women now also switch from cigarettes to snus. The proportion of female snus users today in Sweden is about 5%. A preliminary study in Belgrade in 2005 indicated that both Serbian female and male smokers found the use of snus quite acceptable.

What does it entail to participate?

If you decide to participate you will receive snus products free of charge for the duration of the study period. The aim trial is to assess the efficacy of snus to help you reduce – or ideally completely quit – smoking. The study extends over a period of 24 to 48 weeks. Here is a description of what the study entails:

At your first visit to the clinic it will be determined if you are eligible to participate. You should be aged between 20 and 65 years, have smoked daily for more than 1 year and smoke on average more than 10 cigarettes per day. You should be motivated to reduce your smoking, with the ultimate aim of eventually quitting altogether. You should be in good general health. You will be asked about your smoking habits and medical history. Your height and weight will be noted and your blood pressure and lung function will be tested. Blood tests will be made of blood lipids and other markers of risk of smoking-related disease (total amount of blood drawn will be small, less

than 80-100 ml). We will also measure the amount of carbon monoxide (CO) in exhaled air. Smokers have invariably increased levels of CO compared to non-smokers so it is a good marker of your smoking habits. At selected centers, participants will also be asked to provide samples of buccal cells. These will be obtained by gently brushing the inside of your cheek with a tooth brush. All these tests are done to determine the presence of findings related to your smoking, and how quickly any such smoking-related findings will normalize should you be able to substantially reduce or quit smoking. All samples and test results will be treated confidentially. Once the study is completed, all remaining samples will be destroyed.

You will be given snus products of two different sizes (1.0 g and 0.5 g sachets) and two different flavors (liquorice and eucalyptus) that you can test to determine which you prefer. Two substantially different types of snus will be used in the study: traditional tobacco-based snus and a more modern type of snus that does not contain tobacco or nicotine. Half of the participants will receive the traditional product and half the modern type. Which type of product you will receive will be determined by the study secretariat using a special statistical technique called randomization. Neither you nor any of the staff responsible for the study (including the responsible physician) will know which type of product you are selected for. This technique is necessary to allow an unbiased scientific evaluation of the efficacy of the two types of products. The physical appearance of the snus sachets, the flavoring etc. is the same irrespective of the type of product. **It is therefore vitally important that you only use products delivered specifically to you that are labeled with your individual identifiers.**

When the trial is finished, you will have the possibility to receive information about which type of product you were allocated to.

Over the next 24-48 weeks you will be asked to return for follow-up visits at the clinic on a total of 9 occasions, at first with short intervals (the first return visit is scheduled after 2 weeks) but later on with longer intervals. These visits will include blood tests at four occasions, measurements of carbon monoxide in exhaled air and a simple lung function test. We will also contact you by mail or telephone to monitor your progress and to inform you about test results.

During the first 24 weeks of the study the aim is for you to reduce the number of cigarettes smoked per day as much as possible with the help of the snus products. If you feel an urge to smoke you should instead try a snus sachet for at least 20-30 minutes to relieve the urge. If you still want to smoke after 30 minutes you can do so (but then remove the snus sachet to avoid nicotine overdosage). You will be asked to record in a simple diary each week the average number of cigarettes smoked per day and number snus sachets consumed. Those participants who cannot substantially reduce their smoking will not be followed beyond 24 weeks. Those that have succeeded in substantially reducing their smoking at the 24 week follow-up visit will be encouraged to quit smoking completely, and will be followed for the entire 48-week study period.

Study participation is entirely voluntary and you can decide to withdraw your consent to participate at any time without giving any specific reason. You may also decide at any time to withdraw your consent to have your blood, other tissue samples, and test results

Are there any benefits or risks to participate in the study?

If you can substantially reduce your smoking, or preferably quit smoking completely, as a result of this study, this will have a substantial beneficial impact on your health and will significantly diminish your future risks of smoking-related disease. Participation also entails tests of your general health which may be beneficial.

The nicotine in traditional snus can result in a temporary slight increase in pulse rate and blood pressure, just as cigarettes. However, use of snus during a limited period for the purpose of smoking reduction/cessation is not associated with adverse health effects. Several large, epidemiological studies from Sweden have shown that the health risk profile of long-term snus

use (many decades) is close to that of no tobacco use, and it is generally agreed that snus is associated with vastly less health risks than cigarettes.

All data collected on the participants in this trial will be treated confidentially. Results will only be published on a group level which means that data that are specific to you will not be revealed.

All participants in the study are covered by insurance in the unlikely event that you are harmed in any way by the study procedures.

Will I be compensated for participating in the study?

You will not receive any financial compensation for participating in the trial.

Where will the study take place?

The study will be carried out at four centres in the Belgrade area. Your center is

The study has been approved by theResearch Ethics Committee. The trial is funded by Swedish Match AB, Stockholm, Sweden.

Sincerely yours,

Responsible clinician at study center
Address, other contact details

INFORMED CONSENT

I hereby declare that I have received written and oral information about the 2SRT-trial, and what it entails. I consent to be a participant in the trial. I am aware that my participation is voluntary and that I can, at any time, cancel my participation without having to specify any reason.

All data collected on me will be treated confidentially by the staff involved in the trial. Results from the trial are intended to be published in scientific journals but always on a group level which means that data specific to me will not be disclosed.

I consent to donate my blood samples as a gift to the research team to be used for research related to monitoring of effects of smoking and smoking reduction/cessation. Some of that research may be carried out in countries within the European Union. All samples will be handled confidentially and results that are specific to me will not be disclosed. These provisions also concerns samples of buccal cells that participants at selected center will be asked to donate.

I give my consent to having my trial data reviewed by relevant authorities, such as, the research ethics committee, national or international regulatory authorities or other relevant bodies, should such review be considered necessary. At such reviews my identity will not be revealed to any external individuals.

Date

Participant signature

Date

Investigator signature

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)

Sample participant diary:

At the end of each week (1-24, 25-48) each participant will record the following:

During the past week:

1. I have smoked on average cigarettes per day (brand name:)
2. I have not smoked any cigarette at all during the past week: correct/incorrect
3. I have consumed on average snus sachets per day (sachet size: small/large)
4. I have experienced the following adverse events:(free text).....
5. I think the adverse event is related to the snus product: correct/incorrect/don't know/I have not experienced an adverse event

Amendment of target sample size in the clinical study protocol SM 07-01: Serbian Smoking Reduction/Cessation Trial (2SRT)

Summary: This memorandum describes an amendment of the clinical study protocol SM 07-01 which is a randomized trial of the efficacy of Swedish snus to help smokers aged 20-65 years to reduce or quit smoking. The amendment consists of a decreased target sample size from 500 to 300 eligible participants. The decrease is motivated by recently published data from a Danish randomized clinical trial on the efficacy of a smokeless tobacco product for smoking cessation purposes. No such data were available when the original sample size was decided. With a sample size of 300 participants the trial will have reasonable statistical power ($>80\%$, $p<0.05$) to detect an effect on the primary end-point (smoking reduction at 24 weeks verified by a decrease in CO in exhaled air) and key secondary end-points (smoking cessation) corresponding to an odds ratio (active snus group versus placebo snus group) of 2.2-2.3. The original target size of 500 participants was selected to permit detection of a treatment effect corresponding to an odds ratio 1.9.

Background: The 2SRT is a randomized, placebo-controlled, double-blind clinical trial that examines the ability of snus, a traditional Swedish low-nitrosamine smokeless tobacco product, to help cigarette smokers reduce and eventually quit smoking. The primary end-point in the trial is smoking reduction at week 24 defined as a self-reported reduction in the number of cigarettes smoked daily during the preceding 4-week period of $>50\%$, verified by a decrease in CO in exhaled air of at least 1 ppm. Participants who fulfill the criteria for the primary end-point continue in the trial up to 48 weeks with the aim of complete smoking cessation (defined as self-reported total abstinence from cigarettes verified by a CO concentration in exhaled air of <10 ppm). Secondary trial end-points include point prevalence estimates of smoking cessation as well as continued abstinence rates.

To reliably detect ($p<0.05$, statistical power $>80\%$) a two-fold increase in the odds of smoking reduction at 24 weeks among the active versus placebo groups, and assuming a smoking reduction rate of 15% in the placebo group versus 25% (corresponding to an odds ratio of 1.9) the target sample size was originally estimated at 250 participants per group for a total sample size of 500 participants. This was motivated by the results of previous randomized trials of nicotine replacement therapies versus placebo showing increases in the proportion of participants achieving short- to medium term smoking cessation with odds ratios in the order of 1.5-2.5. Also, epidemiological, cross-sectional surveys in Sweden had suggested that Swedish snus might be more effective as an aid in smoking cessation than conventional nicotine replacement therapies. At the time when the protocol was developed, there were no data available from controlled clinical trials on the efficacy of Swedish snus or any other smokeless tobacco product for smoking reduction or smoking cessation purposes.

Rationale for the protocol amendment: The first results of a randomized smoking cessation trial with a Danish chewing tobacco product were recently published (1). The study tested the efficacy of smokeless tobacco pellets together with group support for smoking cessation in an open, randomized study. The control subjects received group support alone. The study enrolled 263 smokers of whom 143 were allocated to the smokeless tobacco group and 120 to the group support alone group.

Smokeless tobacco was provided for 7-12 weeks combined with 8 nurse-led group support sessions. The control group received group support alone. The participants were followed up to 6 months. Self-reported smoking cessation verified by a CO concentration in exhaled air of <8 ppm was statistically significantly better in the smokeless tobacco group than in the control group during the first 7 weeks, that is, during the period of

active intervention. Point prevalence of smoking cessation at week 7, for instance, were 36% versus 21% ($p < 0.001$), in the two groups respectively. This difference corresponds to an odds ratio of 2.5. The continued abstinence rates from week 4 through 7 were 32% versus 19% (odds ratio 1.9, $p = 0.023$), respectively. However, the 6-month point prevalence estimates of smoking cessation were not significantly different in the two groups, 23% and 21% (odds ratio 1.3). Only a small proportion of those allocated to the smokeless tobacco product continued to use such products after 6 months (18%).

Some aspects on the trial design merit consideration when judging the results this study:

- The nicotine delivery from the product tested in the trial was relatively low and protracted (c. 2 mg during 60-90 minutes) compared to Swedish snus. In addition, the recommended dose was only 5-6 pellets per day and the maximum 10-15 pellets per day.
- The intervention period was short (7-12 weeks) and the participants were instructed to try to gradually reduce their usage already after 4 weeks.
- Compliance with the tobacco pellets was low. Only 62% of those allocated to pellets used them after one week, and this proportion decreased to 20% at week 12.
- The study was not double-blind and the authors admit that the nurses responsible for the protocol interventions including delivery of the tobacco pellets probably had a negative view of the efficacy and relevance of using a smokeless tobacco product for smoking cessation purposes.
- C. 50% of the participants had made previous quit attempts and failed using nicotine replacement therapies.

There are several important design features of the Serbian trial that suggest that efficacy in terms of achieving the primary end-point probably will be higher than that illustrated by the mentioned odds ratios in the Danish trial.

- The nicotine delivery from Swedish snus is better than from the product tested in the Danish trial.
- Usage is ad libitum to avoid nicotine craving which might result in increased smoking or smoking relapse
- The study design allows for a much longer transition period from a smoking to a non-smoking behavior as the primary end-point is defined as a continued smoking reduction during the last 4 weeks of the initial 6-month intervention period, that is, during a period when the participants are still using their allocated study product.
- Primary end-point is smoking reduction, not cessation. Smoking reduction is probably easier to achieve than total abstention from smoking.
- Smoking cessation as a secondary end-point might be easier to achieve after an initial period of smoking reduction and the study design allows for a relatively long transition period.
- Study design is double-blind
- Few participants are likely to have made previous quit attempts using nicotine replacement therapies as usage of such products is still relatively limited in Serbia.

Because of these circumstances and considerations, it is reasonable to expect that the treatment effect in the Serbian trial in terms of the primary end-point will be greater than the week 4 through week 7 continued abstinence rate in the Danish trial (odds ratio 1.9).

As mentioned, the target sample size in 2SRT was originally estimated at 250 participants per group for a total sample size of 500 participants. These numbers were based on assumptions of a success rate of 25% in the active snus group and 15% in the placebo group which corresponds to an odds ratio of 1.9.

If the success rate among those allocated to snus is assumed to be slightly higher, for instance 28% or 29% (corresponding to odds ratios of 2.2 and 2.3, respectively), the required total sample size ($p < 0.05$, statistical power $> 80\%$) would be 312 and 274, respectively.

Against this background it is reasonable to lower the target total sample size from 500 to 300 eligible participants.

Reference

1. Tønnesen P, Mikkelsen K, Bremann L. Smoking cessation with smokeless tobacco and group therapy: an open, randomized, controlled trial. *Nicotine & Tobacco Research* 10; 1365-1372, 2008

ler, 2008-11-06

Amendment of the clinical study protocol SM 07-01: Serbian Smoking Reduction/Cessation Trial (2SRT): collection of data on smoking status among participants excluded from the trial at week 24

Summary: This memorandum describes an amendment of the clinical study protocol SM 07-01 which is a randomized trial of the efficacy of Swedish snus to help smokers aged 20-65 years to reduce or quit smoking. The amendment consists of collection of data on self-reported smoking status at week 48 among participants who were excluded from the trial at week 24 because they failed to achieve the trial's primary end-point ("smoking reduction" as defined in the protocol). The amendment is motivated by the fact that some of these participants may have stopped smoking during week 24-48 as they were included in the trial because they wished to decrease or completely stop smoking. Availability of data on smoking status also from these participants would enhance the validity of the statistical analyses of differences in quit rates at week 48 based on the entire ITT (Intention To Treat) population.

Background & rationale: The 2SRT is a randomized, placebo-controlled, double-blind clinical trial that examines the ability of snus, a traditional Swedish low-nitrosamine smokeless tobacco product, to help cigarette smokers reduce and eventually quit smoking. The primary end-point in the trial is "smoking reduction" at week 24 defined as a self-reported reduction in the number of cigarettes smoked daily during the preceding 4-week period of >50%, verified by a decrease in CO in exhaled air of at least 1 ppm. Participants who fulfill the criteria for the primary end-point continue in the trial up to 48 weeks with the aim of complete smoking cessation (defined as self-reported total abstinence from cigarettes verified by a CO concentration in exhaled air of <10 ppm). Secondary trial end-points include point prevalence estimates of smoking cessation as well as continued abstinence rates.

According to the protocol all participants who terminate the study prematurely for any reason are to be considered failures in analyses of both the primary and secondary efficacy analyses. This approach represents the standard in most smoking cessation trials. However, in the current study some participants are actively excluded from the trial at week 24 because of failure to achieve the primary end-point, which is, "smoking reduction" as defined above. The rationale for considering these participants as failures is that it is unlikely that they would quit smoking during week 24-48 had they continued in the study. However, although unlikely, it remains a possibility that some of them may stop smoking after week 24 as they were included in the trial because they were "motivated to substantially reduce or quit smoking" (inclusion criteria #4).

Against this background the validity of analyses of the secondary end-point "smoking cessation at week 48" as defined in the protocol would be enhanced if data were collected on self-reported smoking status from these participants.

Protocol amendment: Participants who were excluded from the trial at week 24 because they failed to achieve "smoking reduction" will be contacted by telephone at a time corresponding to the week 48 visit had they continued in the trial. If more than 48 weeks has elapsed since inclusion in the trial, the participant will be contacted as soon as possible. They will be asked to provide information on smoking status according to the following format:

1. "Have you stopped smoking completely since the week 24 visit?": yes/no (To "stop smoking completely" means not to have a single puff on any occasion during the mentioned time period)

2. "Did you stop smoking completely during the past 12 weeks?": yes/no
3. "Have you stopped smoking completely during the past 4 weeks?": yes/no

For participants who are interviewed after their theoretical week 48 "visit window" (-/+ 1 week) the questions will be rephrased so that they relate to the week 24-48 period:

1. "Did you stop smoking completely for at least 16 weeks after the week 24 visit, that is, since you were excluded from the trial?: yes/no
2. "Did you stop smoking completely during the following period:
(week 36 through 48)?": yes/no
3. "Did you stop smoking completely during the following period:
.....(week 44 through 48)?": yes/no

Participants who answer yes to any of these questions will be offered to verify their smoking status at a clinical visit through test of CO in exhaled air (where CO < 10 ppm will be taken as evidence of non-smoking status).

In addition to these questions the date for the interview will be recorded, and how this date relates to the theoretical week 48 visit had the participant not been excluded from the trial (-/+ 1 week, +1/+4 weeks, +4/+8 weeks, +8/+16 weeks, >+16 weeks)

Re: Amendment no. 3 of the protocol for the study "Serbian Smoking Reduction/Cessation Trial" (2SRT)

During the development of the Statistical Analysis Plan for the mentioned study, some inconsistencies, errors, or omissions have been detected in the protocol text. The purpose of this amendment is to correct these so that the protocol accurately reflects the study procedures and/or the intended purposes of the trial.

1. Randomization technique

p. 13, 3.3.3 Treatment assignment

Original protocol text:

"After providing informed consent at the baseline visit, the subjects will be randomly allocated to either active snus or placebo snus. Stratification will be made according to treatment centre. Randomization will be done by telephone to a central office where participant's identifiers are recorded. The random allocation will be done according to a computer-based algorithm"

Proposed amendment:

"After providing informed consent at the baseline visit, the subjects will be randomly allocated to either active snus or placebo snus. Stratification will be made according to treatment centre. *Randomization will be done by consecutively associating each included participant's identifiers with a unique, sequential number. A computer-based algorithm will generate these numbers in blocks of six for the two parallel treatment groups with equal probability: three to receive active snus and three to receive placebo snus. Lists at the study sites link the numbers to specific study products, that is, either active or placebo snus (in two sachet sizes and two flavours). At the sites all study products are identified solely by numbers to ensure the double-blinded study design. The procedures are described in more detail in the Randomisation Plan*".

2. Study products

p. 10, 3.1 Description of Overall Study Design and Plan, 3rd and 4th paragraph.

Original protocol text:

"The contents of snus and the placebo product are described in detail in an appendix to this protocol. The content of both products complies with the industrial standard GothiaTek.

It should be noted that the product used as the placebo in this trial is a snus replacement product that does not contain nicotine, but is widely marketed in Sweden under the brand name "Onico"

Proposed amendment: "

"The contents of snus and the placebo product are described in details in an appendix to this protocol. *The content of the snus products complies with the industrial standard GothiaTek which has been developed for smokefree tobacco products. As the placebo product does not contain tobacco, the GothiaTek standard is not applicable.*

However, the production of both snus and the placebo product accords with the Swedish Food Act.

It should be noted that the placebo product does not contain *tobacco or nicotine*. An *almost identical product* is widely marketed as a *snus replacement product* in Sweden under the brand name “Onico””

3. Secondary outcome variables

p. 17, 2nd paragraph “Secondary Efficacy Assessment”

Original protocol text:

“Secondary efficacy assessments will be made at 12, 24, 36 and 48 weeks. Secondary end-points include

- “Smoking reduction” at 12 weeks
- Smoking cessation at 12 and 24 weeks defined as self-reported total abstinence from cigarettes during the preceding 4-week period verified by a concentration of CO in exhaled air of <10 ppm
- Smoking cessation at 36 and 48 weeks among those who achieved smoking reduction at 24 weeks (cessation here defined as self-reported total abstinence from cigarettes during the preceding 4, 12, or 24-week period, verified by a CO-concentration in exhaled air of <10 ppm at all measurements during the specified time period
- Clinical tests and biomarkers at 12 and 24 weeks among all participants, and at 36 and 48 weeks among those who achieved smoking reduction at 24 weeks including body weight, BMI, blood pressure, CO in exhaled air, measures of lung function (FEV1.0, FVC, FEV%), total S-WBC, S-CRP, total S-cholesterol, S-HDL, S-LDL, S-fibrinogen, S-cotinine”

Proposed amendment:

Secondary efficacy assessments will be made at 12, 24, 36 and 48 weeks. Secondary end-points include

- “Smoking reduction” at 12 weeks
- Smoking cessation at 12 and 24 weeks defined as self-reported total abstinence from cigarettes during the preceding 4-week period verified by a concentration of CO in exhaled air of <10 ppm
- Smoking cessation at 36 and 48 weeks among those who achieved smoking reduction at 24 weeks (cessation here defined as self-reported total abstinence from cigarettes during the preceding 4, 12, or 24-week period, verified by a CO-concentration in exhaled air of <10 ppm at all measurements during the specified time period
- Clinical tests and biomarkers at 12 and 24 weeks among all participants, and at 36 and 48 weeks among those who achieved smoking reduction at 24 weeks including body weight, BMI, blood pressure, CO in exhaled air, measures of lung function (FEV1.0, FVC,

FEV%), total S-WBC, S-CRP, total S-cholesterol, S-HDL, S-LDL, S-fibrinogen, S-cotinine

- *Vital signs, body weight, and BMI at all clinical visits*