STATISTICAL ANALYSIS PLAN

Swedish Match AB
SE-118 85
Stockholm
Sweden

Serbian Smoking Reduction/Cessation Trial (2SRT)

Clinical Study Protocol No. SM 07-01: 15 May 2007
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Prepared by:

Kelly Sharp
i3 Statprobe
Star House
20 Grenfell Road
Maidenhead
Berkshire SL6 1EH
United Kingdom

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SIGNATURE PAGE

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Lars-Erik Rutqvist, Project Manager **Swedish Match AB**	**Approval Date**
•	•
Kelly Sharp, Biostatistician, Biostatistics **i3 Statprobe**	**Approval Date**
•	•
Vani Sundaraiyer Ph.D, Principal Biostatistician, Biostatistics **i3 Statprobe**	**Approval Date**
•	•

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event
AM	Arithmetic Mean
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CI	Confidence Interval
CO	Carbon Monoxide
CRF	Case Report Form
CRP	C-Reactive Protein
CSR	Clinical Study Report
DOB	Date of Birth
DVP	Data Validation Plan
GothiaTek®	Industry standard under which snus products are manufactured
g	Grams
EU	European Union
FEV%	FEV_1 / FVC
FEV_1	Force Expiratory Lung Volume during the first second
FVC	Forced Vital Capacity
HDL	High-Density Lipoprotein
ICH	International Conference on Harmonisation
ITT	Intent-To-Treat
kg	Kilograms
L	Litres
LDL	Low-Density Lipoprotein
LSMean	Least Squares Mean
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent-To-Treat
NCS	Not Clinically Signficant
ng	Nanograms
NRT	Nicotine Replacement Therapy
ppm	Parts per million
SAE	Serious Adverse Event
SD	Standard Deviation

SE	Standard Error
TSNA	Tobacco Specific Nitrosamines
WBC	White Blood Cell Count
WHO	World Health Organisation
WHODD	World Health Organisation Drug Dictionary

1. INTRODUCTION

Tobacco-related disease is the most important avoidable cause of premature death among males in developed countries (Europe, North America, Japan, Australia and New Zealand). In these countries, an average of approximately 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. Serbia shares with Croatia the top positions for male all-cause mortality attributable to smoking (Peto et al, 2003). It is therefore of special importance to assess country-specific data for Serbia in comparison with other European countries.

Conversely, Sweden demonstrates a unique pattern in terms of smoking-related disease. Male smoking-related deaths in Sweden are radically fewer than in other European countries, and Sweden is also the only country where the overall risk of smoking-related death is lower in males than females (IARC, 1997). This can be explained by the fact that during recent decades smoking in males has reduced to a considerably larger extent than smoking in females. This reduction is largely due 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 health risks associated with the use of Swedish nitrosamine smokeless tobacco are only a fraction of the health risks caused by smoking (Kozlowski, 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 tobacco-specific nitrosamines (TSNAs) and are often combined with betel and areca nuts, which contain highly carcinogenic non-tobacco substances.

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 TSNAs, 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. This process renders the product virtually sterile, which helps to ensure product stability during storage.

In recent years, public health authorities in Serbia initiated antismoking campaigns and bans on smoking in public places. Funding for such campaigns has been limited due to the difficult financial situation following the Balkan wars, and an alternative nicotine delivery device providing aid in smoking cessation, that is acceptable in terms of efficacy and cost, is lacking.

Reduction of the smoking-related burden of disease is an important public health issue in Serbia. The experience from Sweden and other countries indicates that substantial reduction of risk 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. These approaches are both important, but differ with respect to the short-term versus long-term impact. Most 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 twenty-first century. In contrast, cessation of smoking starts influencing health risk after just 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 nicotine replacement therapy (NRT) products in smoking cessation (George & O'Malley, 2004). However, the low success rates 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 is vastly different to that associated with smoking (Fant et al., 1999). In addition, there is a high cost associated with alternative nicotine sources such as these. More recently, other pharmaceutical smoking cessation aids have been introduced, such as bupropion and vareniclide (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 will likely 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 with 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 packet of cigarettes.

Clinical experience on smoking cessation 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 emphasising 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 abstention. However, for certain 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.

The considerations 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., 1981; IARC, 1985; Idris et al., 1994). Consequently, the European Union (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).

An extensive public health report from the Swedish National Board of Health (2006) emphasised 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 such as 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. Of the 21 participants who tried snus, a total of ten preferred a eucalyptus flavoured brand, seven preferred a liquorice flavoured brand, four preferred a menthol brand, and none liked the taste of a regular unflavoured Swedish snus brand.

One obstacle in conducting the feasibility study was the poor motivation among some male participants, perhaps due to a low awareness of the health risks associated with smoking. However, for the whole group of smokers there was a marked reduction of average carbon monoxide (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 male and female Serbian smokers.

1.1 Study Objectives

1.1.1 Primary Objective

- To assess the efficacy of a traditional Swedish low-nitrosamine smokeless tobacco product ("snus") versus Placebo to help adult cigarette smokers in Serbia to substantially reduce their smoking or completely stop smoking. The level of smoking will be assessed using the average number of cigarettes smoked per day, verified by the concentration of CO in exhaled air.

1.1.2 Secondary Objectives

- To assess the effects of the traditional Swedish low-nitrosamine smokeless tobacco product ("snus") versus Placebo on clinical tests and biomarkers related to lung function, risk of cardiovascular disease, and other health outcomes:
    - Body weight
    - Body Mass Index (BMI)

- Blood Pressure
- CO in exhaled air
- FEV_1
- FVC
- FEV%
- Total White Blood Cell Count measured in serum (Total S-WBC)
- C-Reactive Protein measured in serum (S-CRP)
- Total Cholesterol measured in serum (Total S-Cholesterol)
- High-Density Lipoprotein measured in serum (S-HDL)
- Low-Density Lipoprotein measured in serum (S-LDL)
- Fibrinogen measured in serum (S-Fibrinogen)
- Cotinine measured in serum (S-Cotinine)

1.2 Study Design

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

The study protocol states that the study will be conducted at four centres (sites) in Belgrade, Serbia, and that each of the four sites will enrol approximately 75 evaluable subjects with equal distribution between treatment arms. One of the four sites (Site 03) was never initiated. Site 04 was initiated but was closed following audit recommendation due to lack of compliance with the study protocol. The audit revealed issues at this site including problems with informed consent procedures. Due to the substantial audit findings, the data from this site will not be used in any analysis or summary tables and will not be included in the subject data listings. The study period will be 52 weeks (1 year); 48 weeks of double-blind treatment followed by mail contact 4 weeks after end of study treatment to provide information to subjects regarding test results. The target sample size was reduced from 500 to 300 randomised subjects (see Protocol Amendment 1 and Section 6.1.4 of this SAP for further details).

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

In total, approximately 300 subjects will be randomly allocated in a 1:1 ratio to be treated with snus or placebo. The random allocation will be produced using a computer-based algorithm, and the randomisation will be stratified by study centre to ensure equal allocation of the treatments within each centre. There will be eight 'bins' of study treatment at each site (see the Randomisation Plan for further details regarding how the bins are prepared). Subjects at each site will be sequentially allocated a serial number corresponding to their randomised treatment. The Principal Investigator at each site will have a list to determine which bin products are to be used for each subject based on the serial number and the subject's preference to large or small sachets and liquorice or eucalyptus flavour snus. The Principal Investigator will also have a randomisation envelope for each serial number, containing the treatment information. The randomisation envelope should be opened only if it is deemed necessary to prematurely unblind a subject. As Site 03 was never initiated, a decision was taken by the sponsor that the Investigational Product that was used for Site 03 would be used at Site 02 instead.

It is important to note that at the time of writing of this SAP, the study protocol states that randomisation will be done by telephone. The actual randomisation technique used is described above and in the study Randomisation Plan. A Protocol Amendment will be submitted to reflect the actual randomisation method that was used for the study. The amendment is not expected to have any impact on the statistical analyses and data summaries described in this SAP.

The snus and the placebo products 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 grams and 1 gram) and two different flavours (liquorice and eucalyptus). The rationale for using different sachet sizes is that many individuals feel that the standard 1g 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 flavours were those favoured by most participants in the feasibility study described in Section 1 of this SAP.

The contents of snus and the placebo product are described in detail in an appendix to the protocol for this study. The content of the snus product complies with the industrial standard GothiaTek® for tobacco products. It should be noted that the product used as placebo in this trial is a snus replacement product that does not contain nicotine. The placebo product is similar to a product that is widely marketed in Sweden under the brand name "Onico". At the time of writing of this SAP, the study protocol states that the content of both the snus and placebo products follow the industrial GothiaTek® standard. A Protocol Amendment will be submitted to correct this information. The amendment should not have any impact on the analyses and data summaries described in this SAP.

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 as required. They will be informed that one 1g snus sachet typically can replace one cigarette. There is a possibility of nicotine over-dosage, particularly among those who use both 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 over-dosage is typically self-limiting since it will result in symptoms that are familiar to most habitual smokers, for example nausea, tachycardia or cold sweat. The symptoms are quickly reversible upon cessation of smoking or use of snus.

Potential study subjects will be invited to an information seminar where the goals of the study as well as the means of its achievement are explained. Information will be provided about health risks associated with smoking and possible alternative aids 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. Shortly after the seminar, potential subjects who are interested to participate will be invited to a Baseline visit at one of the study centres.

A Baseline visit will be conducted to obtain written informed consent from the subject and to assess the inclusion and exclusion criteria for the study. Eligible subjects who provide written informed consent will be randomly allocated to one of the two study treatments

(active snus or placebo snus). The Baseline visit will also record 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, intention to participate ["want to quit smoking" versus "want to reduce smoking"], previous use of NRT or other pharmaceutical aids or other smoking cessation aids), blood samples, lung function tests, CO in exhaled air, measurement of blood pressure, height and weight, and the Fagerström test of nicotine dependence.

Each subject will be 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.

The subjects will be encouraged to substitute as many cigarettes as possible with the study products, although total abstention from cigarettes is not a primary goal during the first 24 weeks of using the study product. Subjects will be 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 may do so (although they should then remove the snus sachet to avoid nicotine over-dosage). 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 subject is provided with a sufficient quantity of the study product to last until the next visit, and is informed that no other source of nicotine than cigarettes or snus should be used, and also that NRT or any other pharmaceutical smoking cessation aid is not allowed.

Subjects will be contacted by telephone one week after the Baseline visit to establish preferences for flavours and sachet size (to direct further distribution of study products), to assess compliance and any adverse events, and to monitor progress.

Further clinical visits will be conducted at site at Week 2 and Week 6 to monitor subjects' progress including self-reported smoking status according to the subject diary, measurement of CO in exhaled air, blood pressure and weight (weight at Week 6 only).

Subjects will be contacted by telephone again at Week 9 to monitor progress, assess compliance and record any adverse events.

At Week 12, a clinical visit is conducted, which includes measurements of the primary and secondary endpoints (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).

Subjects will be informed of their test results via mail between Week 13 and Week 16.

Further clinical visits will be conducted at Week 18 and Week 24. Subjects who are able to achieve a $\geq$ 50% reduction of self-reported cigarette consumption at Week 24 (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 ≥ 50% reduction at Week 24 are defined as treatment failures and will be discontinued from the study. Subjects will be informed of their test results via mail between Week 25 and Week 28.

Continuing subjects will attend clinical visits at Week 30 and Week 36, and will be contacted via mail to be informed of latest test results between Week 37 and Week 40. Further clinical visits will be conducted at Week 42 and Week 48, with test results sent to the subject via mail between Week 49 and Week 52.

Participants who were excluded from the trial at Week 24 due to failure to achieve ≥ 50% smoking reduction will be contacted by telephone at a time corresponding to the Week 48 visit had they continued in the trial (or as soon as possible if more than 48 weeks have elapsed since inclusion in the trial) and asked to provide information on whether they have stopped smoking completely during the 4-week period from Week 44 to Week 48. This process is described in detail in Protocol Amendment 2, which aims to validate the smoking status of those subjects who failed to achieve the primary endpoint at Week 24, and the assumption that these subjects are failures according to the statistical analysis.

Further details of the schedule of assessments recorded on the Case Report Form (CRF) at each visit are provided below.

Baseline – Clinical Visit

- Review of Inclusion and Exclusion Criteria
- Informed consent must be obtained and a subject number assigned prior to any evaluations being performed
- Demography
- Smoking History
- Randomisation to study treatment
    - Blinded active snus or placebo snus
- Medical History
- Prior and Concomitant Medications
- CO in Exhaled Air
- Lung Function Tests
- Vital Signs
- Blood Tests
- Fagerström Test

- Self Reported Smoking Status

Week 1 – Telephone Contact

- Preferred flavour of snus packets (eucalyptus or liquorice)
- Preferred size of snus packets (0.5g or 1g)
- Self Reported Smoking Status (recorded in subject diary)
- Concomitant Medications
- Compliance
- Adverse Events

Week 2 – Clinical Visit

- CO in Exhaled Air
- Concomitant Medications
- Compliance
- Adverse Events

Week 6 – Clinical Visit

- CO in Exhaled Air
- Vital Signs
- Self Reported Smoking Status (weeks 1-6 transcribed from subject diary)
- Concomitant Medications
- Compliance
- Adverse Events

Week 9 – Telephone Contact

- Self Reported Smoking Status (weeks 7-9 transcribed from subject diary)
- Concomitant Medications

- Compliance
- Adverse Events

Week 12 – Clinical Visit

- CO in Exhaled Air
- Lung Function Tests
- Vital Signs
- Blood Tests
- Self Reported Smoking Status (weeks 10-12 transcribed from subject diary)
- Efficacy Assessments
    - Reduced Smoking (Yes/No)
    - Stopped smoking completely (Yes/No)
        - 1-week period
        - 4-week period (weeks 9-12)
- Concomitant Medications
- Compliance
- Adverse Events

Week 18 – Clinical Visit

- CO in Exhaled Air
- Self Reported Smoking Status (weeks 13-18 transcribed from subject diary)
- Concomitant Medications
- Compliance
- Adverse Events

Week 24 – Clinical Visit

- CO in Exhaled Air
- Lung Function Tests
- Vital Signs
- Blood Tests
- Self Reported Smoking Status (weeks 19-24 transcribed from subject diary)
- Efficacy Assessments
    - Reduced Smoking (Yes/No)
    - Stopped smoking completely (Yes/No)
        - 1-week period
        - 4-week period (weeks 21-24)
- Fagerström Test
- Concomitant Medications
- Compliance
- Adverse Events

Week 30 – Clinical Visit

- CO in Exhaled Air
- Self Reported Smoking Status (weeks 25-30 transcribed from subject diary)
- Concomitant Medications
- Compliance
- Adverse Events

Week 36 – Clinical Visit

- CO in Exhaled Air
- Lung Function Tests
- Vital Signs

- Blood Tests
- Self Reported Smoking Status (weeks 31-36 transcribed from subject diary)
- Efficacy Assessments
    - Stopped smoking completely (Yes/No)
        - 1-week period
        - 4-week period (weeks 33-36)
        - 12-week period (weeks 25-36)
        - 24-week period (weeks 13-36)
- Concomitant Medications
- Compliance
- Adverse Events

Week 42 – Clinical Visit

- CO in Exhaled Air
- Self Reported Smoking Status (weeks 37-42 transcribed from subject diary)
- Concomitant Medications
- Adverse Events

Week 48 – Clinical Visit

- CO in Exhaled Air
- Lung Function Tests
- Vital Signs
- Blood Tests
- Self Reported Smoking Status (weeks 43-48 transcribed from subject diary)
- Efficacy Assessments
    - Stopped smoking completely (Yes/No)

  - 1-week period
  - 4-week period (weeks 45-48)
  - 12-week period (weeks 37-48)
  - 24-week period (weeks 25-48)

- Fagerström Test
- Concomitant Medications
- Compliance
- Adverse Events

1.3 Study Timepoints

Patients will participate in this study for up to a maximum of 52 weeks. Patients will attend the study site at Visit 1 (Baseline) for informed consent and confirmation of eligibility.

The primary efficacy endpoint for the study is assessed at Week 24, and the secondary efficacy and safety endpoints are assessed up to Week 48. The study visits are summarised in the table below.

Visit Number	Visit Label for Statistical Output
1	Baseline
2	Week 1
3	Week 2
4	Week 6
5	Week 9
6	Week 12
7	Week 18
8	Week 24
9	Week 30
10	Week 36
11	Week 42
12	Week 48

Should it be necessary to conduct an unscheduled visit for any reason, the date, week and reason for the unscheduled visit will be presented in a data listing only. The study CRF does not record any study-specific measurements on the Unscheduled Visit page.

The procedures to be performed throughout the study are outlined in the Schedule of Events in Table 1.

Table 1: Schedule of Events

Scheduled activity	**Baseline 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**	**x**		
Efficacy Assessments						**x**			**x**			**x**			**x**		
Height, weight[4]	**x**			**x**		**x**			**x**			**x**			**x**		
Blood pressure	**x**			**x**		**x**			**x**			**x**			**x**		
Fagerström test	**x**								**x**						**x**		
Prior / Concomitant Medications	**x**		**x**	**x**		**x**			**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**	**x**		
Information to participants about test results by mail							x			x			x		**x**	x	
Termination case report[5]																	x

1. Telephone contact
2. Including extra 50 ml blood and sampling of buccal cells for exploratory analyses at selected study sites. (These analyses are not part of this SAP).
3. Based on information recorded weekly in the participants' study diaries, transcribed into the CRF. 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

2. STUDY POPULATIONS

A total of three populations will be used for all summaries and analyses. Subjects who have satisfied the population criteria will be classified in the designated population and will only be included in analyses for which they have available data.

Intent-to-Treat (ITT) Population

The ITT population is defined as all randomised subjects, regardless of when they withdrew from the study. All subjects at Site 04 will be excluded from the ITT population. The ITT population will be used to present all the efficacy data (including the primary efficacy endpoint) by randomised treatment group. Subjects will be summarised according to the treatment to which they were randomised, regardless of which treatment they actually received.

Modified Intent-to-Treat (MITT) Population

The MITT population is defined as all subjects (excluding those from Site 04) who achieved smoking reduction at 24 weeks (i.e. the primary efficacy endpoint, defined as a self-reported reduction of ≥ 50% compared to baseline in the average number of cigarettes smoked per day during Weeks 21-24, verified by a reduced concentration of CO in exhaled air of at least 1 ppm). It is a subset of the ITT population. The MITT population will be used to present exploratory analyses of the secondary efficacy data (CO in exhaled air, lung function tests, number of cigarettes smoked per day and the Fagerström test) by randomised treatment group.

Safety Population

The Safety population is defined as all randomised subjects who received at least one dose of study treatment. The Safety population will therefore be identical to the ITT population if all randomised subjects receive at least one dose of study treatment. The Safety population will be used to present the safety summaries by actual treatment received.

3. DEFINITIONS AND DERIVED VARIABLES

3.1 Demography and Baseline Characteristics

Age. Age will be calculated using the Date of Birth (DOB) and the date of the Baseline visit, and presented as age at last birthday as an integer.

$$\text{Age} = \text{Integer part of } [(\text{Date of Baseline visit} - \text{Date of Birth}) / 365.25]$$

Body Mass Index (BMI). BMI is the subject's body weight in kilograms divided by the square of the subject's height in metres.

$$\text{BMI} = \text{Weight in kilograms} / (\text{Height in metres})^2$$

3.2 Smoking Reduction

The achievement of smoking reduction is assessed by means of the subjects' self reported smoking status during the four weeks prior to a visit, verified by the level of CO in exhaled air at that visit.

Smoking Reduction will be a binary variable calculated at the following visits:

- Week 12 (smoking status at weeks 9, 10, 11 and 12)
- Week 24 (smoking status as weeks 21, 22, 23 and 24 – primary efficacy endpoint)

Smoking Reduction = 1 if the subject has reported a decrease of ≥ 50% compared to Baseline in the average number of cigarettes smoked all 4 weeks immediately prior to the visit, and the level of CO in exhaled air at that visit has reduced by at least 1 ppm compared to Baseline (goal achieved).

Smoking Reduction = 0 if the subject has not reported a decrease of ≥ 50% compared to Baseline in the average number of cigarettes smoked all 4 weeks immediately prior to the visit, or the level of CO in exhaled air at that visit has not reduced by at least 1 ppm compared to Baseline (goal not achieved).

The Investigator will tick 'Yes' or 'No' on the CRF to confirm whether smoking reduction has been achieved based on these criteria. The data from these tick boxes will be used for statistical analyses and summaries. Status of smoking reduction will not be re-derived from the data for self-reported smoking status and CO in exhaled air. The study Data Validation Plan (DVP) contains edit checks to verify that if smoking reduction achieved is answered 'Yes', the CO in exhaled air has reduced by at least 1 ppm compared to Baseline, and the average number of cigarettes per week has reduced accordingly. The data from the tick boxes will be cross-checked against the data for self-reported smoking status and CO in exhaled air as part of the statistical review of the study database prior to database freeze, and any discrepancies in the binary smoking reduction variable will be highlighted to the Data Management group.

3.3 Smoking Cessation

The achievement of smoking cessation is assessed by means of the subjects' self reported smoking status during a specified number of weeks prior to a visit, verified by the level of CO in exhaled air at that visit.

Smoking Cessation will be a binary variable calculated at the following visits:

- Week 12 (smoking status 1 week [Week 12] and 4 weeks prior [Weeks 9-12])
- Week 24 (smoking status 1 week [Week 24] and 4 weeks prior [Weeks 21-24])
- Week 36 (smoking status 1 [Week 36], 4 [Weeks 33-36], 12 [Weeks 25-36] and 24 weeks prior [Weeks 13-36])
- Week 48 (smoking status 1 [Week 48], 4 [Weeks 45-48], 12 [Weeks 37-48] and 24 weeks prior [Weeks 25-48])

Smoking Cessation = 1 if the subject has reported no cigarettes smoked in the 1, 4, 12 or 36 weeks (respectively) immediately prior to the visit, and the level of CO in exhaled air at that visit is recorded as < 10 ppm (goal achieved).

Smoking Cessation = 0 if the subject has reported any cigarettes smoked in the 1, 4, 12 or 36 weeks (respectively) immediately prior to the visit, or the level of CO in exhaled air at that visit is recorded as ≥ 10 ppm (goal not achieved).

The Investigator will tick 'Yes' or 'No' on the CRF to confirm whether smoking cessation has been achieved based on these criteria. The data from these tick boxes will be used for statistical analyses and summaries. Status of smoking cessation will not be re-derived from the data for self-reported smoking status and CO in exhaled air. The study DVP contains edit checks to verify that if smoking cessation achieved is answered 'Yes', the CO in exhaled air is recorded as <10 ppm and the subject stopped smoking completely according to the self-reported smoking status. The data from the tick boxes will be cross-checked against the data for self-reported smoking status and CO in exhaled air as part of the statistical review of the study database prior to database freeze, and any discrepancies in the binary smoking cessation variable will be highlighted to the Data Management group.

3.4 Extent of Smoking Reduction

The extent of smoking reduction will be evaluated for each subject at weeks 12, 24, 36 and 48. This is defined at each visit as the reduction in the average number of cigarettes smoked per day during the four-week period immediately prior to the visit, expressed as a percentage. The average number of cigarettes smoked per day during any four-week period will be calculated as the mean of the four recordings of average number of cigarettes smoked for those four weeks. If data are not available for all four weeks prior to a visit, the average number of cigarettes will be estimated by the mean of the values available within those four weeks.

Extent of Smoking Reduction = (Average number of cigarettes smoked in the year prior to Baseline – Average number of cigarettes smoked per day in the four weeks prior to the visit) / Average Number of cigarettes smoked per day in the year prior to Baseline x 100

3.5 Fagerström Test

The Fagerström Test for Nicotine Dependency is conducted at Baseline, Week 24 and Week 48. During the test, the subject answers a series of questions and is allocated a score based on their response. A higher score indicates a stronger nicotine dependency (see Table 2).

Table 2 Fagerström Test Questions, Responses and Scores

Question	Response Choices	Score
1. How soon after you wake up do you smoke your first cigarette?	After 60 minutes 31-60 minutes 6-30 minutes Within 5 minutes	0 1 2 3
2. Do you find it difficult to refrain from smoking in places where it is forbidden?	No Yes	0 1
3. Which cigarette would you hate most to give up?	The first in the morning Any other	1 0

4. How many cigarettes per day do you smoke?	10 or less 11-20 21-30 31 or more	0 1 2 3
5. Do you smoke more frequently during the first hours after awakening than during the rest of the day?	No Yes	0 1
6. Do you smoke even if you are so ill that you are in bed most of the day?	No Yes	0 1

Total Fagerström Test Score: The scores from the individual questions are summed together to give a total score between 0 and 10 for each visit. This total will be used for summaries and statistical analyses. This test is only relevant for individuals who are known to smoke. Subjects who do not have Fagerström Test results at a visit because smoking stopped in the week prior to the visit will be excluded from analyses at that visit. Subjects who do not have Fagerström Test results at a visit due to discontinuation from the study will have an unknown smoking status and will also be excluded from analyses at that visit.

It is possible that the Fagerström Test may be conducted in error for subjects who stopped smoking in the week prior to the visit. In this case, data would be present but not strictly relevant. The study DVP contains edit checks to verify that the test is not performed for subjects who stopped smoking. Any Fagerström Test results that were recorded erroneously for subjects who stopped smoking in the week prior to that visit will not be used in any summary or analysis.

3.6 Self-Reported Smoking Status

Average number of cigarettes per day during the previous week will be transcribed onto the CRF from the subject diary by the Investigator. Whilst CRF data for all weeks will be listed and summarised, only the data for the change from Baseline to Week 24 and Week 48 respectively will be analysed with a statistical model.

Amount of snus consumed per day (g) during the previous week will be calculated for each week (Week 1 to Week 48) for each subject as follows:

Number of Large Sachets Consumed + (0.5 x Number of Small Sachets Consumed)

4. EFFICACY PARAMETERS

4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the achievement of "smoking reduction" at Week 24. Smoking reduction is defined as a self-reported reduction of ≥ 50% compared to Baseline in the average number of cigarettes smoked per day during weeks 21, 22, 23 and 24, verified by a reduced concentration of CO in exhaled air of at least 1 ppm at Week 24 compared to Baseline. The primary efficacy endpoint will be analysed using a binary goal attainment variable (smoking reduction achieved [yes/no]).

4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

4.2.1 Smoking Reduction at Week 12

The achievement of smoking reduction at Week 12, with smoking reduction being defined as a self-reported reduction of ≥ 50% compared to Baseline in the average number of cigarettes smoked per day during weeks 9, 10, 11 and 12, verified by a reduced concentration of CO in exhaled air of at least 1 ppm at Week 12 compared to Baseline. This endpoint will be analysed using a binary goal attainment variable (smoking reduction achieved [yes/no]).

4.2.2 Smoking Cessation at Week 12

The achievement of smoking cessation at Week 12, with smoking cessation being defined at various time points as follows:

- Self-reported total abstention from cigarettes during the preceding week (Week 12), verified by concentration of CO in exhaled air of <10 ppm at Week 12.

- Self-reported total abstention from cigarettes during the preceding 4 weeks (weeks 9, 10, 11 and 12), verified by concentration of CO in exhaled air of <10 ppm at Week 12.

This endpoint will be analysed using a binary goal attainment variable (smoking cessation achieved [yes/no]) for each period.

4.2.3 Smoking Cessation at Week 24

The achievement of smoking cessation at Week 24, with smoking cessation being defined at various time points as follows:

- Self-reported total abstention from cigarettes during the preceding week (Week 24), verified by concentration of CO in exhaled air of <10 ppm at Week 24.

- Self-reported total abstention from cigarettes during the preceding 4 weeks (weeks 21, 22, 23 and 24), verified by concentration of CO in exhaled air of <10 ppm at Week 24.

This endpoint will be analysed using a binary goal attainment variable (smoking cessation achieved [yes/no]) for each period.

4.2.4 Smoking Cessation at Week 36

The achievement of smoking cessation at Week 36, with smoking cessation being defined at various time points as follows:

- Self-reported total abstention from cigarettes during the preceding week (Week 36), verified by concentration of CO in exhaled air of <10 ppm at Week 36.
- Self-reported total abstention from cigarettes during the preceding 4 weeks (weeks 33, 34, 35 and 36), verified by concentration of CO in exhaled air of <10 ppm at Week 36.
- Self-reported total abstention from cigarettes during the preceding 12 weeks (Week 25 to Week 36, inclusive), verified by concentration of CO in exhaled air of <10 ppm at Week 30 and Week 36.
- Self-reported total abstention from cigarettes during the preceding 24 weeks (Week 13 to Week 36, inclusive), verified by concentration of CO in exhaled air of <10 ppm at Week 18, Week 24, Week 30 and Week 36.

This endpoint will be analysed using a binary goal attainment variable (smoking cessation achieved [yes/no]) for each period.

4.2.5 Smoking Cessation at Week 48

The achievement of smoking cessation at Week 48, with smoking cessation being defined at various time points as follows:

- Self-reported total abstention from cigarettes during the preceding week (Week 48), verified by concentration of CO in exhaled air of <10 ppm at Week 48.
- Self-reported total abstention from cigarettes during the preceding 4 weeks (weeks 45, 46, 47 and 48), verified by concentration of CO in exhaled air of <10 ppm at Week 48.
- Self-reported total abstention from cigarettes during the preceding 12 weeks (Week 37 to Week 48, inclusive), verified by concentration of CO in exhaled air of <10 ppm at Week 42 and Week 48.
- Self-reported total abstention from cigarettes during the preceding 24 weeks (Week 25 to Week 48, inclusive), verified by concentration of CO in exhaled air of <10 ppm at Week 30, Week 36, Week 42 and Week 48.

This endpoint will be analysed using a binary goal attainment variable (smoking cessation achieved [yes/no]) for each period.

4.2.6 CO in Exhaled Air

The level of CO in exhaled air (ppm) will be assessed at the Baseline visit and at weeks 2, 6, 12, 18, 24, 30, 36 and 48. This endpoint will be analysed as a continuous variable.

4.2.7 Lung Function Tests

The following lung function tests will be assessed at the Baseline visit and at weeks 12, 24, 36 and 48:

- Forced vital capacity (FVC) in litres
- Forced expiratory volume during the first second (FEV_1) in litres (L)
- $FEV_{\%}$ (defined as FEV_1 / FVC)

Each of these tests will be analysed as continuous variables.

4.2.8 Fagerström Test

The Fagerström Test for Nicotine Dependency will be conducted at the Baseline visit, and at weeks 24 and 48 (if the subject has not stopped smoking during the preceding week for Week 24 and Week 48, respectively). This endpoint will be summarised as a non-parametric continuous variable. If the test was not conducted at Week 24 or Week 48 due to either smoking cessation or discontinuation from the study, subjects will be excluded from all summaries and analyses at that visit. The Fagerström Test is relevant only for subjects who are known to smoke. If the Fagerström Test was conducted in error at any visit for subjects who stopped smoking in the week prior to the visit, the results are considered irrelevant and will not be used in any summary or analysis.

4.2.9 Self-Reported Smoking Status

The average number of cigarettes smoked per day during the past year will be recorded at the Baseline visit. The subject will then record in the diary on a weekly basis the average number of cigarettes smoked and the average number of large and small snus sachets consumed per day during the previous week. This information will be transcribed onto the CRF by the Investigator. The raw diary data will not be captured on the database. The transcribed data from the CRF will be used for summary and analysis. The average number of cigarettes smoked and the average number of snus sachets consumed per day will be summarised as continuous variables.

The amount of snus consumed per day (g) during the previous week will be summarised as continuous variables for Week 1 to Week 48.

4.2.10 Vital Signs

Systolic and diastolic blood pressure (mmHg) and body weight (kg) are recorded at the Baseline Visit and at weeks 6, 12, 24, 36 and 48. Height (cm) is recorded at the Baseline visit only. These measurements will be summarised as continuous variables.

4.2.11 Blood Tests

Haematology (Total S-WBC) and Chemistry (S-CRP, Total S-Cholesterol, S-HDL, S-LDL, S-Fibrinogen and S-Cotinine) parameters are recorded at the Baseline visit and at weeks 12, 24, 36 and 48. Each of these tests will be summarised as continuous variables.

5. SAFETY PARAMETERS

The safety data will be summarised for all subjects in the Safety population.

Safety will be assessed through summary of adverse events and compliance with study treatment.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 10.1. Events will be summarised by system organ class and preferred term for active snus and placebo for the following:

- All adverse events
- All serious adverse events
- Events judged to be related to study treatment
- Events leading to discontinuation of study treatment

Other safety parameters include:

- Compliance with study treatment

These parameters will be summarised appropriately by treatment group and visit.

6. STATISTICAL METHODOLOGY

6.1 Statistical and Analytical Issues

6.1.1 Statistical Methods

All statistical methods will be based on the International Conference on Harmonisation (ICH) E9 document "Statistical Principles for Clinical Trials".

All data will be summarised by treatment group. For baseline characteristics and safety outputs a total overall column will be included to summarise all subjects. Where appropriate, data will be summarised by visit in addition to treatment group.

For all baseline, demographic and efficacy outputs, data will be summarised by randomised treatment. Safety outputs will be summarised by actual treatment received.

In summary tables of continuous variables, the minimum and maximum statistics will be presented to the same number of decimal places as the original data. The arithmetic mean (AM), median, 95% confidence interval (CI), standard deviation (SD) and standard error (SE) will be presented to one more decimal place than the original data.

In non-parametric summaries and analyses the minimum and maximum will be presented to the same number of decimal places as the original data. The mean, median, lower and upper quartiles will be presented to one more decimal place than the original data. The median difference, Wilcoxon rank sum test and 95% CI will only be presented in statistical analysis outputs.

In summary tables of categorical variables, counts and percentages will be used. The denominator for each percentage will be the number of subjects within the population treatment group unless otherwise specified.

For categorical efficacy parameters, comparison of treatment groups will be performed using Generalised Linear Models. The odds ratio estimate, 95% CI and p-values of all covariates included in the model will only be presented in statistical analysis outputs.

All hypothesis testing will be carried out at the 5% (2-sided) significance level unless otherwise specified.

P-values will be rounded to three decimal places. P-values less than 0.001 will be reported as <0.001 in tables. P-values greater than 0.999 will be reported as >0.999.

All CRF data collected (excluding Site 04) will be presented within data listings. The data listings will be sorted by treatment group, site number, subject number and visit.

The treatment label for all Tables, Listings and Figures will be:

Treatment	Treatment Label for TLF
Traditional, low-nitrosamine Swedish snus in 0.5 or 1.0 g sachets ad libitum	Active snus
Placebo snus (without tobacco or nicotine)	Placebo snus
All Treatments	Total (Tables only)

Should any of the statistical methods proposed prove unsuitable during the final analysis, more appropriate methods will be used, and any changes documented in the clinical study report (CSR), including the rationale for use. These include the transformation of the data (for example to a logarithmic scale) in order to satisfy the model assumptions such as normally distributed residuals with constant variance; or the application of non-parametric techniques.

Additional ad-hoc analyses may be conducted as deemed appropriate.

All statistical analysis will be performed using SAS® v9.2 or higher for Windows.

6.1.2 Handling of Dropouts and Missing Data

Subjects will be allocated a 4-digit subject number and their inclusion/exclusion criteria eligibility will be determined at the Baseline visit. Subjects who do not meet all criteria will be discontinued from the study without randomisation. Subjects who are not randomised are considered as screening failures. Data for screening failures will not be captured.

If a subject is discontinued at any time after entering the study, the Investigator will make every effort to see the subject and complete the Final Visit procedures. The reasons for withdrawal will be recorded on the CRF and, for randomised subjects, will be included in the final report.

The Fagerström Test is only relevant for subjects who are known to smoke, and as such it is not conducted at Week 24 or Week 48 if the subject stopped smoking during the previous week. If the test was not conducted at Week 24 or Week 48 due to either smoking cessation or discontinuation from the study, subjects will be excluded from all summaries and analyses at that visit. Any Fagerström Test results that were recorded erroneously for subjects who stopped smoking in the week prior to that visit will not be used in any summary or analysis.

Randomised subjects who withdraw from the study for any reason will still be included in logistic regression models for smoking reduction and smoking cessation at all time points modelled, and will be considered as not achieving the endpoint under analysis.

Subjects who withdraw from the study at Week 24 due to not achieving smoking reduction will be contacted by telephone at a time corresponding to the Week 48 visit had they continued in the trial (or as soon as possible afterwards if more than 48 weeks have passed since the Baseline visit; see Protocol Amendment 2 for full details). Smoking cessation in these subjects will be assessed for exploratory purposes for the 4 weeks (Week 45, Week 46, Week 47 and Week 48) and the 12 weeks (Week 37 to Week 48) leading up to what would

have been the Week 48 visit. Subjects who answer 'Yes' to achievement of smoking cessation are invited to attend a clinical visit to verify their smoking status with the measurement of CO in exhaled air, where <10 ppm represents evidence of smoking cessation. The exploratory data collected for smoking cessation and CO in exhaled air at Week 48 will be not used as observed case data for statistical analyses and summaries of these parameters. Subjects who do not have the relevant data for a time point will be assumed to have not achieved smoking reduction/cessation at that time point for the logistic regression analyses. The exploratory data collected at Week 48 will be summarised separately to assess the assumption that subjects who had not achieved smoking reduction at Week 24 would not have achieved smoking cessation by Week 48.

All subjects with at least one post-dosing assessment will be incorporated within the relevant mixed model repeated measures analysis, whether they completed or discontinued the study. Missing assessments will not be imputed for any analysis using the mixed model repeated measures technique.

All data summaries of the results will be produced on an observed case basis. Safety data will not be subjected to any imputation and will be summarised on an observed case basis.

6.1.3 Pooling of Investigator Sites and Countries

Pooling of sites is defined as grouping the subjects from one or more sites together and considering these subjects as representing a single site for the purpose of summary and analysis. The purpose of pooling is to ensure that each site contains a sufficient number of subjects for statistical analyses that consider site as a factor.

This study is conducted in two sites in Belgrade, Serbia. No pooling of sites will be used in this study as each of the two sites contains enough subjects for the use of site as a factor in statistical models to be appropriate.

The study protocol states that four sites will be used, but Site 03 was not initiated and Site 04 was discontinued due to substantial audit findings. The data for subjects from Site 04 will not be listed and will not be included in any summary or analysis.

6.1.4 Determination of Sample Size

In order 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 was originally estimated at 250 per treatment group for a total size of 500 study participants.

The first publication of results of a randomised smoking cessation trial with a Danish chewing tobacco product (Tönnesen et al., 2008) reported that 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. Point prevalence of smoking cessation at Week 7 was 36% in the smokeless tobacco group versus 21% in the control group (corresponding to an odds ratio of 2.1, $p<0.001$). The

continued abstinence rates from Week 4 to Week 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).

There are several important design features of the Serbian SM 07-01 trial which suggest that efficacy in terms of achieving the primary endpoint will probably be higher than that illustrated by the odds ratios in the Danish trial (see Protocol Amendment 1 for full details and considerations). The circumstances and considerations make it reasonable to expect that the treatment effect in the Serbian trial in terms of the primary endpoint will be greater than the Week 4 to Week 7 continued abstinence rate in the Danish trial (odds ratio 1.9).

The target sample size in study SM 07-01 was originally estimated at a total of 500 subjects based on assumptions of a 25% success rate in the active snus group compared to 15% in the placebo group, corresponding to an odds ratio of 1.9.

If the success rate among those allocated to active 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 or 274, respectively. Based on these considerations, it was reasonable to lower the target total sample size from 500 to 300 evaluable subjects.

6.2 Subject Characteristics

6.2.1 Subject Disposition

The subject disposition table will summarise the following and will be presented for all subjects by treatment group and overall.

- The number (%) of subjects randomised at the Baseline visit
- The number (%) of subjects withdrawn before Week 24
- The number (%) of subjects withdrawn before Week 48
- The number (%) of subjects that attended the Week 24 visit
- The number (%) of subjects who completed the study
- The number (%) of subjects in the ITT population
- The number (%) of subjects in the MITT population
- The number (%) of subjects in the Safety population

The number (%) of subjects who complete and withdraw from the study and the primary reason for withdrawal will be summarised by treatment group and overall for all subjects.

6.2.2 Protocol Violations

Protocol violations are defined as deviations from the procedures outlined in the protocol. There is no Per Protocol population defined for this study. All statistical analyses and summaries will be conducted on an intent-to-treat basis.

6.2.3 Background and Demographic Characteristics

Demographic data presented will be age and gender. Body measurements collected at the Baseline visit are weight and height, from which a BMI is calculated. Weight, height and BMI at Baseline will be presented as demographic data.

Smoking history is collected at the Baseline visit.

Demographic and background data will be summarised using summary statistics for continuous variables (number of subjects [n], mean, standard deviation [SD], median, minimum and maximum) or by way of group frequencies and percentages for categorical variables, as appropriate.

The ITT population will be used to present these data. Demographic data will also be presented for the MITT population. The Safety population is identical to the ITT population if all randomised subjects receive study treatment, and therefore demographic data will be presented for the Safety population only if subjects receive study treatment that is different to their randomised treatment, or if any randomised subjects do not receive treatment.

6.2.4 Treatment Exposure and Compliance

Compliance with study treatment will be determined at each study visit. Subjects will be asked at Weeks 1, 2, 6, 9, 12, 18, 24, 30, 36 and 48 whether or not they:

- Tried the study products as instructed at least once every day (i.e. tried the product instead of immediately lighting up a cigarette when they felt the urge to smoke).

- Used any source of nicotine other than cigarettes or snus, e.g. cigars, NRT or other pharmaceutical smoking cessation aid.

The number and percentage of subjects answering Yes/No to each of these questions respectively will be summarised by treatment and visit for the Safety population. This summary will also be presented for each centre individually for comparison of treatment compliance between centres.

The log numbers for the study treatment dispensed to each subject are recorded on the CRF. The study packaging company, Orifice Medical AB, maintains a list to link each individual log number to its corresponding content. This list will be provided to i3 Biostatistics as part of the unblinding process after database freeze. Each subject will receive a number of treatment logs throughout the study. In order to check that subjects received only logs corresponding to their randomised treatment, a listing will be produced to compare the randomised treatment with the actual treatment logs received. Only subjects who received at

least one log that did not contain their randomised treatment will be included in this listing, so an empty listing implies that all subjects received the correct treatment in all cases. It should be noted that if logs are dispensed incorrectly, it is possible that they may not correspond to the sachet size or snus flavour of the subject but still contain the correct study treatment. In this case, the subject would not be included in the treatment listing as long as the correct treatment was dispensed at all visits.

6.2.5 Prior and Concomitant Medication

Prior and concomitant medications taken by or administered to a subject will be recorded in the CRF. If a subject confirms during the recording of Medical History that they are currently taking prescription drugs on a regular basis, these must be documented on the CRF. After the Baseline visit, 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. If the medication is taken for the treatment of an adverse event (AE), the event should be recorded in the appropriate page of the CRF.

All medications will be classified using the World Health Organisation Drug Dictionary (WHODD) July 2006 Q3 coding dictionary. The Anatomical Therapeutic Chemical (ATC) Classification and Preferred Term will be used to list and summarise the data.

Prior medications are defined as the medication that started and stopped before Baseline. Only medications where the stop date is prior to the date of the Baseline visit exclusive will be considered *prior*. If the stop date is unknown or incomplete and the medications cannot definitely be considered as stopped prior to Baseline then the medications will be considered as *concomitant medications*.

Concomitant medications are defined as the medications that started before Baseline and continued into the study (i.e. medication is ongoing or the stop date is on or after the date of the Baseline visit).

Changes in concomitant medications are defined as the medications that started during the study (i.e. the start date is on or after the date of the Baseline visit).

The number (%) of subjects reporting the use of any prior medications, and the number of reported prior medications by ATC Classification Level 4 and Preferred Term will be summarised for the ITT population. This table will be repeated for concomitant medications and changes in concomitant medications.

6.2.6 Medical Histories

Investigators should document all significant medical conditions that the subject has experienced in the past. Any medical condition present at the time informed consent is given is to be regarded as concomitant. A condition first occurring or detected on or after the day of the Baseline visit and/or worsening of a concomitant condition on or after the day of the baseline visit is to be documented as an AE on the CRF.

All conditions will be coded using MedDRA version 10.1.

- The number of subjects reporting one or more conditions for past medical history will be summarised using counts and percentages.
- The number of past history events will be tabulated.
- Past histories will be summarised by MedDRA System Organ Class and Preferred Term. The number (%) of subjects reporting each condition, and the number of reports will be presented by treatment group and overall.

This table will be repeated for all concomitant medical conditions. Both prior and concomitant medical conditions summaries will use the ITT population.

6.3 Efficacy Analysis

6.3.1 Primary Efficacy Variable

The primary efficacy variable is the achievement of smoking reduction at Week 24, defined as a self-reported smoking reduction of ≥50% compared to Baseline in the average number of cigarettes smoked per day during weeks 21-24, verified by a reduced concentration of CO in exhaled air of ≥1 ppm at Week 24 compared to Baseline.

The comparison of the proportion of subjects achieving smoking reduction at Week 24 in the two treatment arms will be conducted using logistic regression techniques allowing for treatment, centre, age at Baseline, gender and the interaction between treatment and centre.

Response (Yes/No) for this endpoint as defined in Section 3 will be analysed using a model of the form:

Response = Treatment + Centre + Age + Gender + Treatment x Centre Interaction

Covariates will be checked for colinearity. Where colinearity occurs between two variables, only one of these variables will be included in the final model.

An assessment of goodness of fit of the model will be performed using the Pearson Chi-Squared Goodness of Fit test, deviance test and visual inspection of index plots.

The odds ratio of achieving smoking reduction at Week 24 on Active snus versus Placebo snus will be reported along with the 95% confidence interval and 2-sided p-value.

The number and proportion of subjects who achieved smoking reduction at Week 24 will be summarised by treatment group.

If the interaction term is not significant at the 10% level, it will be excluded from the final model. If the interaction term is significant, the number and proportion of subjects who achieved smoking reduction at Week 24 along with the odds ratio will also be summarised by treatment group for each centre individually. If the centre term is significant at the 5% level, the number and proportion of subjects who achieved smoking reduction at Week 24 will be summarised by treatment group for each centre individually.

Summaries and analyses will be presented for the ITT population, with subjects who discontinued in the study for any reason prior to Week 24 considered to have NOT achieved smoking reduction at Week 24. The MITT population will not be used for the primary endpoint analysis, as by definition all subjects in this population will have achieved smoking reduction at Week 24.

6.3.2 Secondary Efficacy Variables

All secondary efficacy analyses will be performed using the ITT population, unless otherwise specified. In addition, the MITT population will be used for exploratory analyses of CO in exhaled air, lung function tests, number of cigarettes smoked per day and the Fagerström test.

- **Proportion of Subjects who Achieved Smoking Reduction/Cessation**

The number and percentage of subjects achieving each smoking reduction or cessation endpoint specified below will be presented by treatment group. The odds ratio of achieving each endpoint respectively on Active snus versus Placebo snus will be reported along with the 95% confidence interval and 2-sided p-value for each outcome. If the interaction term is not significant at the 10% level for an endpoint, it will be excluded from the final model for that endpoint. If the interaction term is significant, the number and proportion of subjects who achieved the endpoint along with the odds ratio will also be summarised by treatment group for each centre individually. If the centre term is significant at the 5% level, the number and proportion of subjects who achieved the endpoint will be summarised by treatment group for each centre individually.

This analysis will be conducted on the following endpoints:

- Proportion of subjects who achieved smoking reduction at Week 12, defined as a self-reported smoking reduction of ≥50% compared to Baseline in the average number of cigarettes smoked per day during weeks 9-12, verified by a reduced concentration of CO in exhaled air of ≥1 ppm at Week 12 compared to Baseline.

- Proportion of subjects who achieved smoking cessation for one week prior to Week 12, defined as a self-reported total abstention from cigarettes during the preceding week (Week 12), verified by a concentration of CO in exhaled air of <10 ppm at Week 12.

- Proportion of subjects who achieved smoking cessation for four weeks prior to Week 12, defined as a self-reported total abstention from cigarettes during the preceding 4 weeks (weeks 9-12), verified by a concentration of CO in exhaled air of <10 ppm at Week 12.

- Proportion of subjects who achieved smoking cessation for one week prior to Week 24, defined as a self-reported total abstention from cigarettes during the preceding week (Week 24), verified by a concentration of CO in exhaled air of <10 ppm at Week 24.

- Proportion of subjects who achieved smoking cessation for four weeks prior to Week 24, defined as a self-reported total abstention from cigarettes during the preceding 4 weeks (weeks 21-24), verified by a concentration of CO in exhaled air of <10 ppm at Week 24.

- Proportion of subjects who achieved smoking cessation for one week prior to Week 36, defined as a self-reported total abstention from cigarettes during the preceding week (Week 36), verified by a concentration of CO in exhaled air of <10 ppm at Week 36.

- Proportion of subjects who achieved smoking cessation for four weeks prior to Week 36, defined as a self-reported total abstention from cigarettes during the preceding 4 weeks (weeks 33-36), verified by a concentration of CO in exhaled air of <10 ppm at Week 36.

- Proportion of subjects who achieved smoking cessation for 12 weeks prior to Week 36, defined as a self-reported total abstention from cigarettes during the preceding 12 weeks (weeks 25-36), verified by a concentration of CO in exhaled air of <10 ppm at Week 30 and Week 36.

- Proportion of subjects who achieved smoking cessation for 24 weeks prior to Week 36, defined as a self-reported total abstention from cigarettes during the preceding 24 weeks (weeks 13-36), verified by a concentration of CO in exhaled air of <10 ppm at Week 18, Week 24, Week 30 and Week 36.

- Proportion of subjects who achieved smoking cessation for one week prior to Week 48, defined as a self-reported total abstention from cigarettes during the preceding week (Week 48), verified by a concentration of CO in exhaled air of <10 ppm at Week 48.

- Proportion of subjects who achieved smoking cessation for four weeks prior to Week 48, defined as a self-reported total abstention from cigarettes during the preceding 4 weeks (weeks 45-48), verified by a concentration of CO in exhaled air of <10 ppm at Week 48.

- Proportion of subjects who achieved smoking cessation for 12 weeks prior to Week 48, defined as a self-reported total abstention from cigarettes during the preceding 12 weeks (weeks 37-48), verified by a concentration of CO in exhaled air of <10 ppm at Week 42 and Week 48.

- Proportion of subjects who achieved smoking cessation for 24 weeks prior to Week 48, defined as a self-reported total abstention from cigarettes during the preceding 24 weeks (weeks 25-48), verified by a concentration of CO in exhaled air of <10 ppm at Week 30, Week 36, Week 42 and Week 48.

Subjects who withdrew from the study prior to the visit under analysis will be considered as having not achieved that endpoint. If no subjects achieved smoking reduction (or cessation, as appropriate) in the time period specific to a particular table, then that summary and analysis will not be produced. For example, if no subjects achieved smoking cessation for four weeks prior to Week 12 in the ITT population, the table containing summary and

analysis of the proportion of subjects who achieved smoking cessation for four weeks prior to Week 12 will not be produced for the ITT population.

As an additional exploratory analysis, separate logistic regression models will be fitted on the ITT population to examine the effect of other baseline factors on the following endpoints:

- Proportion of subjects who achieved smoking reduction at Week 24
- Proportion of subjects who achieved smoking cessation for one week prior to Week 48.

Response (Yes/No) for each endpoint will be analysed using a model of the form:

Response = Treatment + Centre + Age + Gender + Baseline Fagerström Total Score + Previously Attempted to Quit (Yes/No) + Intention to Participate (Quit Smoking/Reduce Smoking) + Any Previous Medical Conditions (Yes/No) + BMI + Age at Initiation of Smoking

Subjects will be considered as having previously attempted to quit if the total number of quit attempts recorded is greater than zero, otherwise they will be considered as not having previously attempted to quit.

Subjects will be considered as having previous medical conditions if they have one or more previous conditions recorded in the Medical History section of the CRF, otherwise they will be considered as not having any previous medical conditions.

Each of the factors considered in the exploratory model will be examined for their interaction with the study treatment, with the exception of centre as this interaction is examined in the previous analysis described above. Due to the large number of potential parameters in these models, a stepwise selection procedure will be used to identify the most significant model parameters. Only those parameters included by the stepwise selection option in SAS PROC LOGISTIC will be included in the final model.

Subjects who withdraw from the study at Week 24 due to not achieving smoking reduction (i.e. subjects in the ITT population but not in the MITT population) will be contacted by telephone at a time corresponding to the Week 48 visit had they continued in the trial (or as soon as possible afterwards if more than 48 weeks have passed since the Baseline visit). The exploratory data collected will be summarised for these subjects only, to assess the validity of the assumption that subjects who did not achieve smoking reduction at Week 24 would not have stopped smoking by Week 48.

- **Extent of Smoking Reduction**

Efficacy measurements relating to smoking reduction and cessation are recorded at weeks 12, 24, 36 and 48. The extent of smoking reduction at a visit is defined as the reduction in the average number of cigarettes smoked per day during the preceding four-week period compared to the Baseline visit, expressed as a percentage. The extent of smoking reduction will be evaluated for each subject (using the definition in Section 3.4) at weeks 12, 24, 36 and 48 and categorised into one of the following groups: 0 – <25%, 25 – <50%, 50 – <75%, 75 – <100% and 100%. The number and percentage of subjects in each category will be summarised at weeks 12, 24, 36 and 48 for the ITT population.

- **Carbon Monoxide (CO) in Exhaled Air**

The level of CO in exhaled air, measured in parts per million (ppm), will be summarised using statistics for continuous variables by treatment and visit. The change from Baseline value will also be summarised for all post-Baseline visits. Summaries will be presented for the ITT population. These summaries will also be presented separately for each category of smoking reduction as defined in the previous bullet point (Extent of Smoking Reduction). The extent of smoking reduction at Week 24 will be used for this summary. Subjects for whom it is not possible to derive the smoking reduction category due to lack of data will be categorised as Missing.

The level of CO in exhaled air from Baseline to each post-Baseline measurement (up to and including Week 48) will be analysed using a mixed effects repeated measures model. The model will include treatment, week number, centre, treatment x week number interaction, and treatment x centre interaction as fixed effects, and will use an unstructured (general) residual covariance matrix for repeated records within subjects. The adjusted mean level of CO in exhaled air will be presented for each treatment by week and overall, along with the corresponding standard error. The difference in adjusted means (Active snus versus Placebo snus) will also be presented with 95% confidence interval and p-value for each week and overall. P-values will also be presented for the model parameters of week number, centre, treatment x week number interaction, and treatment x centre interaction. If the treatment x centre interaction term is not significant at the 10% level, it will be excluded from the final model. If the treatment x centre interaction term is significant, the LS means, SE, LS Mean difference, 95% CI and p-values will also be shown for each centre individually. Analysis will be conducted on the ITT and MITT populations. In addition, an exploratory analysis will be conducted on the MITT population using only the data from Week 24 to Week 48 inclusive. Subjects with both Baseline and at least one post-Baseline measurement will be included in the model. The repeated measures analysis will also be presented separately on the ITT population for each category of smoking reduction. It is recognised that due to the number of subjects in the study, not all categories will contain a sufficient number of subjects for a repeated measures analysis to be possible. Therefore only those categories containing enough subjects to fit the model will be presented.

- **Lung Function Tests**

The summaries and analyses described below will be conducted for the following lung function tests respectively:

- FEV_1 (litres)
- FVC (litres)
- $FEV_{\%} = FEV_1 / FVC$

Lung function tests will be summarised using statistics for continuous variables by treatment and visit for the ITT population. The change from Baseline value will also be summarised for all post-Baseline visits. These summaries will also be presented separately for each category of smoking reduction as defined in the bullet point for Extent of Smoking Reduction, earlier in this section. The extent of smoking reduction at Week 24 will be used for this summary. Subjects for whom it is not possible to derive the smoking reduction category due to lack of data will be categorised as Missing.

The results for each lung function test from Baseline to each post-Baseline measurement (up to and including Week 48) will be analysed using a mixed effects repeated measures model. The model will include treatment, week number, centre, treatment x week number interaction, and treatment x centre interaction as fixed effects, and will use an unstructured residual covariance matrix for repeated records within subjects. The adjusted mean result of the lung function test will be presented for each treatment by week and overall, along with the corresponding standard error. The difference in adjusted means (Active snus versus Placebo snus) will also be presented with 95% confidence interval and p-value for each week and overall. P-values will also be presented for the model parameters of week number, centre, treatment x week number interaction, and treatment x centre interaction. If the treatment x centre interaction term is not significant at the 10% level, it will be excluded from the final model. If the treatment x centre interaction term is significant, the LS means, SE, LS Mean difference, 95% CI and p-values will also be shown for each centre individually. Subjects with both Baseline and at least one post-Baseline measurement will be included in the model. The ITT and MITT populations will be used. In addition, an exploratory analysis will be conducted on the MITT population using only the data from Week 24 to Week 48 inclusive. The repeated measures analysis will also be presented separately on the ITT population for each category of smoking reduction. It is recognised that due to the number of subjects in the study, not all categories will contain a sufficient number of subjects for a repeated measures analysis to be possible. Therefore only those categories containing enough subjects to fit the model will be presented.

- **Fagerström Test**

The Fagerström Test is used to assess the nicotine dependency of the subject at Baseline, Week 24 and Week 48. The subject is asked a series of 6 questions and a total score is calculated based on their responses to each question. The total score ranges from 0 to 10 inclusive, with a higher score denoting a stronger nicotine dependency.

The total scores will be summarised using statistics for non-parametric continuous variables by treatment and visit for the ITT population. The change from Baseline total score will also be summarised for post-Baseline visits.

The total scores will be compared between Active snus and Placebo snus using the Wilcoxon Rank Sum test at Baseline, Week 24 and Week 48 respectively. The median difference for Active snus versus Placebo snus will be reported along with the 95% confidence interval and 2 sided p-value for each visit. The ITT and MITT populations will be used.

The Fagerström Test is only relevant for subjects who are known to smoke. If the test is not conducted at Week 24 or Week 48 either because the subject stopped smoking during the previous week or because the subject discontinued from the study, the subject will be excluded from summary and analysis at that visit. Any test results that were recorded in error for subjects who stopped smoking in the week prior to that visit will not be used in any summary or analysis.

- **Self-Reported Smoking Status**

The average number of cigarettes smoked per day during the previous week will be summarised using statistics for continuous variables by treatment and week (Baseline and

weeks 1 to 48) for the ITT population. The change from Baseline average number of cigarettes will also be summarised for each week post-Baseline.

The average number of large (1g) and the average number of small (0.5g) snus sachets respectively consumed per day during the previous week will be summarised using statistics for continuous variables by treatment and week (Weeks 1 to 48) for the ITT population. In addition, the amount of snus consumed per day (g) during the previous week will be summarised using statistics for continuous variables by treatment and week. The statistics for continuous variables will only be presented for those subjects in the ITT population who reported some usage of snus each week. For the purpose of this summary, "some usage" will be defined as having used at least one large or at least one small snus sachet per day during that week. The number of subjects with no usage reported will also be displayed.

The average number of cigarettes smoked per day during the previous week from Baseline to each week post Baseline (up to and including Week 48) will be analysed using a mixed effects repeated measures model. The model will include treatment, week number, centre, treatment x week number interaction, and treatment x centre interaction as fixed effects. The number of subjects and adjusted mean of the average number of cigarettes smoked will be presented for each treatment by week and overall, along with the corresponding standard error. The difference in adjusted means (Active snus versus Placebo snus) will also be presented with 95% confidence interval and p-value for each week and overall. P-values will also be presented for the model parameters of week number, centre, treatment x week number interaction, and treatment x centre interaction. If the treatment x centre interaction term is not significant at the 10% level, it will be excluded from the final model. If the treatment x centre interaction term is significant, the LS means, SE, LS Mean difference, 95% CI and p-values will also be shown for each centre individually. Subjects with both Baseline and at least one post-Baseline measurement will be included in the model. The ITT and MITT populations will be used. In addition, an exploratory analysis will be conducted on the MITT population using only the data from Week 24 to Week 48 inclusive.

Note that the average number of cigarettes smoked per day during the previous week is recorded on a weekly basis throughout the 48 weeks on study treatment. All 48 weeks will be included in the descriptive statistics summaries and will be analysed via the repeated measures model described above.

- **Vital Signs**

Vital signs performed at the Baseline visit and at weeks 6, 12, 24, 36 and 48 are systolic and diastolic blood pressure (mmHg) and weight (kg). Supine recordings will be made after the subject has been recumbent for 3 minutes. Height (cm) is recorded only at the Baseline visit, and will be summarised as demographic data (see Section 6.2.3). The BMI at each visit will be calculated using the weight at that visit and the Baseline height.

The absolute values of systolic blood pressure, diastolic blood pressure, weight and BMI will be summarised at each visit by treatment group and overall using summary statistics for continuous variables. Change from Baseline values will also be summarised for post-Baseline visits. The ITT population will be used. These summaries will also be presented separately for each category of smoking reduction as defined in the bullet point for Extent of Smoking Reduction, earlier in this section. The extent of smoking reduction at Week 24 will

be used for this summary. Subjects for whom it is not possible to derive the smoking reduction category due to lack of data will be categorised as Missing.

The analyses described below will be conducted for the following vital signs measurements respectively:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Weight (kg)
- BMI (kg/m^2)

The results for each vital signs examination from Baseline to each post-Baseline measurement (up to and including Week 48) will be analysed using a mixed effects repeated measures model. The model will include treatment, week number, centre, treatment x week number interaction, and treatment x centre interaction as fixed effects, and will use an unstructured residual covariance matrix for repeated records within subjects. The adjusted mean test result will be presented for each treatment by week and overall, along with the corresponding standard error. The difference in adjusted means (Active snus versus Placebo snus) will also be presented with 95% confidence interval and p-value for each week and overall. P-values will also be presented for the model parameters of week number, centre, treatment x week number interaction, and treatment x centre interaction. If the treatment x centre interaction term is not significant at the 10% level, it will be excluded from the final model. If the treatment x centre interaction term is significant, the LS means, SE, LS Mean difference, 95% CI and p-values will also be shown for each centre individually. Subjects with both Baseline and at least one post-Baseline measurement will be included in the model. The ITT population will be used. The repeated measures analysis will also be presented separately on the ITT population for each category of smoking reduction. It is recognised that due to the number of subjects in the study, not all categories will contain a sufficient number of subjects for a repeated measures analysis to be possible. Therefore only those categories containing enough subjects to fit the model will be presented.

- **Laboratory Parameters**

The following laboratory tests are to be performed at the Baseline visit and at weeks 12, 24, 36 and 48:

- Hematology: Total S-WBC (10^9/L)
- Chemistry: S-CRP (mg/L), Total S-Cholesterol (mmol/L), S-HDL (mmol/L), S-LDL (mmol/L), S-Fibrinogen (g/L) and S-Cotinine (ng/mL)

The results of each of these tests respectively will be summarised at each visit by treatment group and overall using summary statistics for continuous variables. Change from Baseline values will also be summarised for post-Baseline visits. The results of each test will be converted to the units specified above before the summaries are calculated. The ITT population will be used. These summaries will also be presented separately for each category of smoking reduction, as defined in the bullet point for Extent of Smoking Reduction, earlier in this section. The extent of smoking reduction at Week 24 will be used for this summary. Subjects for whom it is not possible to derive the smoking reduction category due to lack of data will be categorised as Missing.

The expected ranges for each laboratory parameter are given below:

- Total S-WBC: 4–10 10^9/L
- S-CRP: 0–5 mg/L
- Total S-Cholesterol: 0–5 mmol/L
- S-HDL: ≥1.55 mmol/L
- S-LDL: 0–2.5 mmol/L
- S-Fibrinogen: 2–3.3 g/L
- S-Cotinine: >25 ng/mL

It will be indicated in the laboratory data listing whether each parameter is lower than, within or higher than these ranges for each subject and visit.

The analyses described below will be conducted for each of the 7 laboratory parameter respectively.

The results for each laboratory parameter from Baseline to each post-Baseline measurement (up to and including Week 48) will be analysed using a mixed effects repeated measures model. The model will include treatment, week number, centre, treatment x week number interaction, and treatment x centre interaction as fixed effects, and will use an unstructured residual covariance matrix for repeated records within subjects. The adjusted mean test result will be presented for each treatment by week and overall, along with the corresponding standard error. The difference in adjusted means (Active snus versus Placebo snus) will also be presented with 95% confidence interval and p-value for each week and overall. P-values will also be presented for the model parameters of week number, centre, treatment x week number interaction, and treatment x centre interaction. If the treatment x centre interaction term is not significant at the 10% level, it will be excluded from the final model. If the treatment x centre interaction term is significant, the LS means, SE, LS Mean difference, 95% CI and p-values will also be shown for each centre individually. Subjects with both Baseline and at least one post-Baseline measurement will be included in the model. The ITT population will be used. The repeated measures analysis will also be presented separately on the ITT population for each category of smoking reduction. It is recognised that due to the number of subjects in the study, not all categories will contain a sufficient number of subjects for a repeated measures analysis to be possible. Therefore only those categories containing enough subjects to fit the model will be presented.

6.4 Safety Analysis

Safety analysis will be performed using the Safety population. All outputs will be summarised by actual treatment received. Missing data will not be imputed.

6.4.1 Adverse Events

Adverse events may be volunteered spontaneously by the subject or discovered as a result of general questioning by the Investigator. The subject records in the diary on a weekly basis whether or not any adverse events were experienced. For all events, the Investigator must pursue and obtain information adequate to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE, requiring immediate notification.

All adverse events (AE) for a subject are recorded as separate events within the CRF (and hence the database). All AEs will be classified using the MedDRA coding dictionary version 10.1.

The following presentations will be produced by treatment group:

All adverse events:

- The number of subjects having at least one AE will be tabulated using counts and percentages. The number of AEs will be tabulated.

- AEs will be summarised by system organ class and preferred term. The number (%) of subjects having each event, and the number of events will be presented. Note: If a subject records multiple AEs with the same preferred term (i.e. with distinct start and stop dates), these shall be summarised once within the count for N (%) of subjects, yet each event will be counted within the number of reports n of each AE. Events that are ongoing will be only counted once.

- AEs will be summarised by system organ class, preferred term and severity. The number (%) of subjects having each severity for each event and the number of events will be presented. Any missing severity will be queried for completion by Data Management, and any events that still have missing severity in the final data will be assumed to be severe. If a subject has events with different severity for the same preferred term, each event will be summarised under its corresponding severity. This means that a subject may be counted across multiple severities for the same preferred term, which may result in the total number of subjects across all severities in the table appearing higher than the total number of subjects in the Safety population.

Similar tables will be presented for:

Serious adverse events:
An AE indicated as serious. Any missing serious criteria will be queried and must be completed.

Treatment-related adverse events:
Any AE where the relationship to study drug is recorded as “Possibly”, “Probably” or “Definitely” related to the study treatment. Any missing responses will be queried for completion by Data Management, and any events that still have missing relationship in the final data will be assumed to be definitely related to study drug.

Adverse events leading to discontinuation of study treatment:
Any AE where the action taken regarding study treatment is recorded as “Discontinued”. Any missing responses will be queried for completion by Data Management, and any events that still have missing action taken in the final data will be assumed to have an action taken of discontinued, if the subject did not complete the study.

In addition, a general summary table reporting the number (%) of subjects and the number of events within each of the above categories will be presented by treatment group.

Four general adverse event listings will be produced:

- All adverse event details will be presented for all adverse events.
- All serious adverse events will be listed separately.
- Adverse events leading to discontinuation of study treatment will be listed
- All adverse events leading to death will be listed

6.5 PK/PD Analysis

There is no planned PK/PD analysis for this study.

6.6 Interim Analysis

There is no planned interim analysis for this study.

6.7 Data Monitoring Committee Charter

There is no planned Data Monitoring Committee for this study.

6.8 Analysis of Other Assessments

There will be no analysis of other assessments.

6.9 Analyses Performed

Should any of the planned statistical methods proposed prove unsuitable during the final analysis, more appropriate methods will be used, and any changes, including the rationale for use, will be documented in the CSR.

7. TABLES, LISTINGS, AND FIGURES

The default tables, listings and figures (TLF) layout will be as follows.

Orientation	Landscape
Paper Size	A4
Margins	Top: 3.2 cm Bottom: 2.5 cm Left: 2.5 cm Right: 2.5 cm
Font	Courier New 9pt
Headers (Centre)	Sponsor name and Protocol number; Page X of Y (Right) TLF Number and Title
Footers (Left)	SAS program path and file name Date TLF generated Listing no. data source for tables and figures CRF page number data source for listings

The font size may be reduced as necessary to allow additional columns to be presented, but not at the expense of clarity. Also the orientation may be changed to portrait if appropriate.

The date format for all presentations will be 'DDMMMYYYY'.

All TLF outputs will be generated using SAS® v9.2 or higher for Windows.

CRF data collected will be present within data listings. The data listings will be sorted by treatment group, centre number, subject number and visit.

7.1 Preparation of Tables

The intended layouts for unique summary tables are presented in Appendix I. However, it may be necessary to change the table layouts, as appropriate, in the light of the data available.

7.2 Table of Contents for Tables

7.2.1 Demographic and Background Data

Table 14.1.1	Summary of Subject Disposition, by Treatment and Overall (All Subjects)
Table 14.1.2	Summary of Final Status and Reason for Withdrawal, by Treatment and Overall (All Subjects)
Table 14.1.3.1	Summary of Subject Demographics, by Treatment, and Overall (ITT Population)
Table 14.1.3.2	Summary of Subject Demographics, by Treatment, and Overall

	(MITT Population)
Table 14.1.3.3	Summary of Subject Demographics, by Treatment, and Overall (Safety Population) *Presented only if one or more subjects receive treatment other than the randomised treatment or if one or more subjects was randomised but not treated*
Table 14.1.4	Summary of Smoking History by Treatment and Overall (ITT Population)
Table 14.1.5.1	Summary of Compliance by Treatment, Visit and Overall (Safety Population)
Table 14.1.5.2	Summary of Compliance by Treatment, Visit, Centre and Overall (Safety Population)
Table 14.1.6	Summary of Past Medical History by Treatment and Overall, System Organ Class and Preferred Term (ITT Population)
Table 14.1.7	Summary of Concomitant Medical Conditions by Treatment and Overall, System Organ Class and Preferred Term (ITT Population)
Table 14.1.8	Summary of Prior Medications by Treatment and Overall, ATC and Preferred Term (ITT Population)
Table 14.1.9	Summary of Concomitant Medications at Randomisation by Treatment and Overall, ATC and Preferred Term (ITT Population)

7.2.2 Efficacy Data

Table 14.2.1.1	Summary and Analysis of Proportion of Subjects who Achieved Smoking Reduction at Week 24 (ITT Population)
Table 14.2.1.2	Summary and Analysis of Proportion of Subjects who Achieved Smoking Reduction at Week 12 (ITT Population)
Table 14.2.1.3	Summary and Analysis of Proportion of Subjects who Achieved Smoking Cessation for One Week prior to Week 12 (ITT Population)
Table 14.2.1.4	Summary and Analysis of Proportion of Subjects who Achieved Smoking Cessation for Four Weeks prior to Week 12 (ITT Population)
Table 14.2.1.5	Summary and Analysis of Proportion of Subjects who Achieved Smoking Cessation for One Week prior to Week 24 (ITT Population)
Table 14.2.1.6	Summary and Analysis of Proportion of Subjects who Achieved Smoking Cessation for Four Weeks prior to Week 24 (ITT Population)
Table 14.2.1.7	Summary and Analysis of Proportion of Subjects who Achieved Smoking

	Cessation for One Week prior to Week 36 (ITT Population)
Table 14.2.1.8	Summary and Analysis of Proportion of Subjects who Achieved Smoking Cessation for Four Weeks prior to Week 36 (ITT Population)
Table 14.2.1.9	Summary and Analysis of Proportion of Subjects who Achieved Smoking Cessation for 12 Weeks prior to Week 36 (ITT Population)
Table 14.2.1.10	Summary and Analysis of Proportion of Subjects who Achieved Smoking Cessation for 24 Weeks prior to Week 36 (ITT Population)
Table 14.2.1.11	Summary and Analysis of Proportion of Subjects who Achieved Smoking Cessation for One Week prior to Week 48 (ITT Population)
Table 14.2.1.12	Summary and Analysis of Proportion of Subjects who Achieved Smoking Cessation for Four Weeks prior to Week 48 (ITT Population)
Table 14.2.1.13	Summary and Analysis of Proportion of Subjects who Achieved Smoking Cessation for 12 Weeks prior to Week 48 (ITT Population)
Table 14.2.1.14	Summary and Analysis of Proportion of Subjects who Achieved Smoking Cessation for 24 Weeks prior to Week 48 (ITT Population)
Table 14.2.1.15	Summary of Extent of Smoking Reduction Compared to Baseline by Treatment and Visit (ITT Population)
Table 14.2.1.16	Summary of Smoking Status at Week 48 for Subjects who Discontinued at Week 24 (ITT Population minus MITT Population)
Table 14.2.1.17	Exploratory Analysis of Proportion of Subjects who Achieved Smoking Reduction at Week 24 (ITT Population)
Table 14.2.1.18	Exploratory Analysis of Proportion of Subjects who Achieved Smoking Cessation for One Week prior to Week 48 (ITT Population)
Table 14.2.2.1.1	Statistical Analysis of Carbon Monoxide (CO) in Exhaled Air (ppm) (ITT Population)
Table 14.2.2.1.2	Statistical Analysis of Carbon Monoxide (CO) in Exhaled Air (ppm) by Extent of Smoking Reduction Category (ITT Population)
Table 14.2.2.2.1	Statistical Analysis of Carbon Monoxide (CO) in Exhaled Air (ppm) (MITT Population)
Table 14.2.2.2.2	Exploratory Analysis of Carbon Monoxide (CO) in Exhaled Air (ppm) from Week 24 to Week 48 (MITT Population)

Table 14.2.6.5.1	Summary of Vital Signs, by Treatment, Visit and Overall (ITT Population)
Table 14.2.6.5.2	Summary of Vital Signs, by Treatment, Visit and Overall, by Extent of Smoking Reduction Category (ITT Population)
Table 14.2.7.1.1	Statistical Analysis of Total S-WBC (10^9/L) (ITT Population)
Table 14.2.7.1.2	Statistical Analysis of Total S-WBC (10^9/L) by Extent of Smoking Reduction Category (ITT Population)
Table 14.2.7.2.1	Statistical Analysis of S-CRP (mg/L) (ITT Population)
Table 14.2.7.2.2	Statistical Analysis of S-CRP (mg/L) by Extent of Smoking Reduction Category (ITT Population)
Table 14.2.7.3.1	Statistical Analysis of Total S-Cholesterol (mmol/L) (ITT Population)
Table 14.2.7.3.2	Statistical Analysis of Total S-Cholesterol (mmol/L) by Extent of Smoking Reduction Category (ITT Population)
Table 14.2.7.4.1	Statistical Analysis of S-HDL (mmol/L) (ITT Population)
Table 14.2.7.4.2	Statistical Analysis of S-HDL (mmol/L) by Extent of Smoking Reduction Category (ITT Population)
Table 14.2.7.5.1	Statistical Analysis of S-LDL (mmol/L) (ITT Population)
Table 14.2.7.5.2	Statistical Analysis of S-LDL (mmol/L) by Extent of Smoking Reduction Category (ITT Population)
Table 14.2.7.6.1	Statistical Analysis of S-Fibrinogen (g/L) (ITT Population)
Table 14.2.7.6.2	Statistical Analysis of S-Fibrinogen (g/L) by Extent of Smoking Reduction Category (ITT Population)
Table 14.2.7.7.1	Statistical Analysis of S-Cotinine (ng/mL) (ITT Population)
Table 14.2.7.7.2	Statistical Analysis of S-Cotinine (ng/mL) by Extent of Smoking Reduction Category (ITT Population)
Table 14.2.7.8.1	Summary of Laboratory Parameters by Treatment, Visit and Overall (ITT Population)
Table 14.2.7.8.2	Summary of Laboratory Parameters by Treatment, Visit and Overall, by

Extent of Smoking Reduction Category
(ITT Population)

7.2.3 Safety Data

Table 14.3.1.1	Summary of Adverse Events by Treatment and Overall (Safety Population)
Table 14.3.1.2.1	Summary of Adverse Events by System Organ Class, Preferred Term, Treatment and Overall (Safety Population)
Table 14.3.1.2.2	Summary of Serious Adverse Events by System Organ Class, Preferred Term, Treatment and Overall (Safety Population)
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Table 14.3.1.3.4	Summary of Adverse Events Leading to Discontinuation of Study Treatment Severity by Treatment, System Organ Class and Preferred Term (Safety Population)
Table 14.3.2.1	Listing of Adverse Events Leading to Death (Safety Population)
Table 14.3.2.2	Listing of Serious Adverse Events (Safety Population)
Table 14.3.2.3	Listing of Adverse Events Leading to Discontinuation of Study Treatment (Safety Population)
Table 14.3.3	Summary of Changes in Concomitant Medication by Treatment and Overall (ITT Population)

7.3 Preparation of Data Listings

A table of contents, including the listing order and content of the data listing appendices, is presented in Section 7.4.

The intended layouts for listings are presented in Appendix III. However, it may be necessary to change the listing layouts, as appropriate, upon review of the data available.

Data will be presented within the data listings according to the following order:

- Treatment group
- Site number
- Subject number
- Visits: Baseline, Week 1, Week 2, Week 6, Week 9, Week 12, Week 18, Week 24, Week 30, Week 36 and Week 48

All subjects with relevant data will be included in data listings. Subjects from Site 04 will not be included in any data listings.

7.4 Table of Contents for Data Listings

7.4.1 Subject Data Listings

Listing 16.2.1	Discontinued Subjects
Listing 16.2.2	Informed Consent
Listing 16.2.3	Subjects Included in Analysis Populations
Listing 16.2.4.1	Demographic Data
Listing 16.2.4.2	Smoking History
Listing 16.2.5	Compliance
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7.4.2 Efficacy Data

Listing 16.2.6.1	Efficacy Assessments
Listing 16.2.6.2	Carbon Monoxide (CO) in Exhaled Air
Listing 16.2.6.3	Lung Function Tests
Listing 16.2.6.4	Fagerström Test
Listing 16.2.6.5	Self-Reported Smoking Status

7.4.3 Adverse Events

Listing 16.2.7	Adverse Events

7.4.4 Laboratory Parameters

Listing 16.2.8	Laboratory Parameters

7.4.5 Archive Subject Data Listings

Listing 16.4.1	Final Status
Listing 16.4.2	Inclusion Criteria
Listing 16.4.3	Exclusion Criteria
Listing 16.4.4	Medical History and Current Medical Conditions
Listing 16.4.5	Vital Signs
Listing 16.4.6	Prior Medications
Listing 16.4.7.1	Concomitant Medications
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Listing 16.4.8	Preferences to Flavour and Size of Study Product at Week 1
Listing 16.4.9	Comments
Listing 16.4.10	Unscheduled Visits
Listing 16.4.11	Smoking Status at Week 48 for Subjects Discontinued Due to Not Achieving Smoking Reduction at Week 24

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9. APPENDICES

Appendix I: Table Shells for Unique Summary Tables
Appendix II: Layout for Data Listings.