
16. APPENDICES

Table of Contents

16. APPENDICES

16.1 STUDY INFORMATION

- 16.1.1 Protocol and Protocol Amendments
- 16.1.2 Sample Case Report Form (Unique Pages Only)
- 16.1.3 IEC Approval Including List of IEC Members. Representative Written Subject Information and Sample Consent Form
- 16.1.4 List and Description of Investigators and Other Important Participants in the Study, Including Brief (1 page) CVs or Equivalent Summaries of Training and Experience Relevant to the Performance of the Clinical Study
- 16.1.5 Signatures of Sponsor, Statistician and Principal Investigator
- 16.1.6 Listing of Subjects Receiving Investigational Product(s) From Specific Batches, where More than One Batch was used
- 16.1.7 Randomization Scheme and Codes (Subject Identification and Treatment Assigned)
- 16.1.8 Audit Certificates (If Available)
- 16.1.9 Documentation of Statistical Methods
- 16.1.10 Documentation of Inter-Laboratory Standardization Methods and Quality Assurance Procedures if Used
- 16.1.11 Publications Based on the Study
- 16.1.12 Important Publications Referenced in the Report

16.1 STUDY INFORMATION

16.1.1 Protocol and Protocol Amendments

SM17-02 Study Protocol v. 1.0 14Sep2017

Clinical Study Protocol

Investigational Medicinal Product	ZYN®
Study Code	SM 17-02
Protocol Version and Date	Final 1.0, 14 Sep 2017

STUDY TITLE

Open observational study of oral health associated with use of a non-tobacco based nicotine pouch (ZYN®) among current daily snus users.

Design	<p><u>Part 1:</u> Open, randomized, four-way crossover, single administration trial</p> <p><u>Part 2:</u> Open, observational, follow-up study during 6 weeks</p>
Test product and dosage	<p><u>Part 1:</u> 1) ZYN® Smooth 3 mg, 2) ZYN® Peppermint 3 mg, 3) 10% sucrose, 4) 10% xylitol.</p> <p><u>Part 2:</u> Ad libitum use of a ZYN® nicotine pouch, participants can choose from 3 or 6 mg pouches of ZYN® Smooth, ZYN® Peppermint or ZYN® Cinnamon.</p>
Duration of treatment	<p><u>Part 1:</u> Single administration</p> <p><u>Part 2:</u> 6 weeks</p>
Sponsor signatory	<p>(b) (4), (b) (6)</p> <p>Swedish Match SE-Box 17037 104 62 Stockholm Sweden Maria Skolgata 83 SE-118 85 Stockholm Sweden (b) (4), (b) (6)</p>

Principal Investigator

Prof. Peter Lingström, D.D.S., Ph. D.
Department of Cariologi,
Institute of Odontology, Sahlgrenska Academy
University of Gothenburg
SE-405 30 Gothenburg, Sweden

Clinical study management

CTC Clinical Trial Consultants AB
Dag Hammarskjölds väg 13
SE-752 837 Uppsala, Sweden

The following amendments have been made to the Final Clinical Study Protocol version 1.0:

Amendment No.	Date of Amendment	Revised protocol version (if applicable)

2 STUDY SYNOPSIS

Study Title Open observational study of oral health associated with use of a non-tobacco based nicotine pouch (ZYN®) among current daily snus users.	
Study code SM 17-02	
Study period Estimated date of first subject/patient enrolled: Q4 2017 Estimated date of last subject/patient completed: Q1 2018	
Principal Investigator Prof. Peter Lingström, D.D.S., Ph. D. Institute of Odontology, Gothenburg, Sweden	
Study design <u>Part 1:</u> Open, randomized, four-way crossover, single administration trial <u>Part 2:</u> Open, observational, follow-up study for 6 weeks	
Objectives <u>Primary objective(s)</u> Part 1: <ul style="list-style-type: none"> Assessment of dental plaque acidogenicity after short-term exposure (60 mins) to a nicotine pouch. Part 2: <ul style="list-style-type: none"> Assessment of dental plaque acidogenicity after 6 weeks of use of a nicotine pouch. <u>Secondary objective(s)</u> Part 1: <ul style="list-style-type: none"> Adverse events Part 2: <ul style="list-style-type: none"> Adverse events Changes in the oral microflora Occurrence/severity of oral mucosal lesions 	

<p>Number of subjects/patients planned</p> <p><u>Part 1:</u> 20 participants (with available data on all four test articles)</p> <p><u>Part 2:</u> 60 participants</p>
<p>Diagnosis and main eligibility criteria</p> <p>Healthy subjects aged >19 years, who use tobacco-based snus since ≥ 1 year with a weekly consumption of three or more snus cans (brands with nicotine content <1%) or two or more cans (brands with nicotine content >1%), normal stimulated salivary secretion rate (≥ 0.7 ml/min).</p> <p>Pregnant women, subjects who have a history of hypertension or any cardiovascular disease, subjects with allergy toward composite materials, and those with a history of use of antibiotics during or within the last 4 weeks prior to the study are excluded from participation.</p>
<p>Methodology</p> <p>For both parts, potential participants will initially be screened for study eligibility and informed consent procedures. Participants in Part 1 are eligible to later on also participate in Part 2 after a new screening visit.</p> <p>After informed consent, participants will undergo a routine dental and oral examination, assessment of saliva buffer capacity, number of mutans streptococci and lactobacilli.</p> <p>The subjects in both parts of the study will refrain from approximal tooth cleaning during 72 hours prior to visit and toothbrushing during the last 48 hours prior to visit. They will not eat or drink anything during the last 2 hours prior to visit.</p> <p><u>Part 1:</u> Participants will come to the clinic on a total of 4 occasions for testing of the 4 test articles (in randomized order). Each visit is estimated to take 75 min.</p> <p><u>Part 2:</u> Participants will participate in a 6-week observational study during which they are encouraged to substitute as much as possible of their snus with the ZYN® test articles. Participants can choose ad libitum from ZYN® Smooth 3 mg or 6 mg nicotine, ZYN® Peppermint 3mg or 6 mg nicotine, or ZYN® Cinnamon 3 mg or 6 mg nicotine pouches. Use of ZYN® products, snus, or any other nicotine delivery product will be monitored, based on self-reports.</p> <p>Clinical visits are scheduled at screening, after 2 weeks, after 4 weeks, and after 6 weeks. At each visit data will be collected on product use since last visit, AEs, plaque acidogenicity, oral microflora, plaque amount, and oral lesions. Clinical photos will be taken to facilitate comparisons. “Snus lesions” at the site where participants typically place their snus/ ZYN® pouch will be assessed using a 4-degree scale as proposed by Axéll et al (1976). At each visit the subject will report any local and general adverse symptoms.</p>
<p>Investigational products, dosage and mode of administration</p>

<p><u>Part 1:</u> 1) ZYN® Smooth 3 mg, 2) ZYN® Peppermint 3 mg, 3) 10% sucrose, 4) 10% xylitol.</p> <p><u>Part 2:</u> Ad libitum use of a ZYN® nicotine pouch, participants can choose from 3 or 6 mg pouches of ZYN® Smooth, ZYN® Peppermint or ZYN® Cinnamon.</p>
<p>Duration of treatment</p> <p><u>Part 1:</u> Single administration (60 minutes)</p> <p><u>Part 2:</u> 6 weeks</p>
<p>Duration of subjects involvement in the study</p> <p><u>Part 1:</u> Approximately 35 days (single visits)</p> <p><u>Part 2:</u> Approximately Six weeks.</p>
<p>Efficacy assessments</p> <p><u>Part 1:</u> Dental plaque acidogenicity.</p> <p><u>Part 2:</u></p> <ul style="list-style-type: none"> • Adverse Events (AEs) assessed at 2, 4 and 6 weeks • Biofilm acidogenicity at 2, 4 and 6 weeks compared to baseline • Changes compared to screening in the oral microflora at 2, 4 and 6 weeks • Plaque amount at 2, 4 and 6 weeks compared to screening • Appearance and number of oral mucosal lesions (including presence and grade of “snus lesions” at the site where the pouches typically are placed by the consumer), comparisons will be made with screening findings
<p>Safety assessments</p> <p>Adverse Events will be recorded at all visits, with particular focus on local irritation at the site of the oral mucosa where the pouch is placed, and in the throat, hiccups and heartburn.</p>
<p>Statistical methods</p> <p><u>Part 1:</u> Based on previous experience with the described methodology, a total of 20 subjects will be enough to reliably detect a clinically significant increased plaque acidogenicity with the pouched products versus the negative control.</p> <p><u>Part 2:</u> A 6 week observation period is reasonable to assess putative changes in the oral mucosa resulting from use of the nicotine pouches given that “snus lesions” among habitual snus users regress within a few weeks after cessation of exposure. A 6 week observation period is also supported by the fact that the other measures of oral health to be assessed (biofilm acidogenicity, oral microflora, plaque amount) are known to potentially change within a few weeks. With an estimated dropout rate of 25% a total of 45 fully evaluable subjects are expected with a total inclusion of 60 subjects. Descriptive statistics will be used for reporting the results of monitoring of the oral mucosa and for subjective adverse symptoms.</p>

3 TABLE OF CONTENTS

2	STUDY SYNOPSIS	4
3	TABLE OF CONTENTS	7
4	LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS	12
5	IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR	14
5.1	Medical emergencies contacts	14
5.2	Overdose.....	14
6	INVESTIGATOR(S) AND STUDY ADMINISTRATIVE STRUCTURE.....	15
7	INTRODUCTION.....	17
7.1	Project background.....	17
7.2	Investigational medicinal product	18
7.2.1	Product characteristics.....	18
7.3	Risk/benefit assessment	18
7.3.1	Summary of risk management.....	19
8	STUDY OBJECTIVES AND ENDPOINTS.....	20
8.1	Primary objective(s).....	20
8.2	Primary endpoint	20
8.3	Secondary objectives.....	20
8.4	Secondary endpoints	20
9	INVESTIGATIONAL PLAN	21
9.1	Overall study design and schedule of events.....	21
9.2	Rationale for study design and dose groups	22
10	STUDY POPULATION	23
10.1	Recruitment	23
10.2	Screening and enrolment log.....	23
10.3	Number of subjects	23
10.4	Inclusion criteria	23
10.5	Exclusion criteria	24
10.6	Restrictions during the study	24
10.7	Criteria for subject withdrawal	24
10.7.1	General withdrawal criteria	24

10.7.2	Procedures for discontinuation of a subject from the study	24
10.7.1	Subject replacement	24
10.8	Randomization.....	25
10.9	Blinding	25
11	TREATMENTS.....	25
11.1	Identity of investigational products.....	25
11.2	Packaging and labelling.....	25
11.3	Conditions for storage.....	27
11.4	Dispensing and accountability	27
11.5	Treatment administration	28
11.6	Treatment compliance	28
11.7	Return and destruction of investigational products	28
12	STUDY ASSESSMENTS	28
12.1	Part 1	28
12.2	Part 2	29
12.3	Recording of data	30
12.4	Demographics and other baseline characteristics (Part 1 and Part 2).....	30
12.4.1	Informed consent.....	30
12.4.2	Demographic information	31
12.4.3	Medical/surgical history	31
12.4.4	Physical examination.....	31
12.4.5	Prior and concomitant medication.....	31
12.4.6	Pregnancy urine test	31
12.4.7	Baseline symptoms.....	31
12.5	Study Assessments.....	31
12.5.1	Examination of the oral cavity	31
12.5.2	Dental plaque acidogenicity	32
12.5.3	Plaque amount	32
12.5.4	Oral microflora	33
12.5.5	Saliva sampling	33
12.6	Adverse events	33
12.6.1	Event definitions.....	33
12.6.1.1	Adverse event	33

12.6.1.2	Serious adverse event	34
12.6.2	Adverse Event assessment definitions	34
12.6.2.1	Assessment of severity/intensity	34
12.6.2.2	Assessment of causal relationship	34
12.6.2.3	Assessment of outcome	35
12.6.3	Collecting adverse events	35
12.6.4	Recording adverse events	36
12.6.5	Reporting serious adverse events	36
12.6.6	Treatment and follow-up of adverse events	37
12.6.7	Procedures in case of pregnancy	37
13	PROCEDURES FOR BIOLOGICAL SAMPLES	37
13.1	Sample collection for pharmacokinetic measurements	37
14	ETHICAL AND REGULATORY REQUIREMENTS	37
14.1	Ethical conduct of the study	37
14.2	Ethics and regulatory review	38
14.3	Subject/Patient information and consent	38
14.4	Subject/Patient information card	38
14.5	Subject/Patient data protection	39
14.6	Changes to the approved clinical study protocol	39
14.7	Audits and inspections	39
14.8	Insurance	39
15	STUDY MANAGEMENT	40
15.1	Training of study site personnel	40
15.2	Clinical monitoring	40
15.3	Source data document	41
15.4	Study agreements	41
15.5	Study time table and end of study	41
15.6	Discontinuation of the study	41
15.7	Reporting and publication	41
15.7.1	Clinical study report	41
15.7.2	Annual safety report	42
15.7.3	Confidentiality and ownership of study data	42
15.7.4	Publication	42

15.8 Archiving.....	42
16 DATA MANAGEMENT	42
16.1 Case report form	42
16.2 Database management plan and database design	43
16.3 External data	43
16.4 Medical encoding.....	43
16.5 Database lock.....	43
17 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE	43
17.1 General	44
17.2 Determination of sample size	44
17.3 Analysis data sets.....	44
17.3.1 Full analysis set	44
17.3.2 Per protocol analysis set.....	44
17.4 Description of study population for both parts	45
17.4.1 Demographics and baseline characteristics	45
17.4.2 Medical/surgical history and prior/concomitant medication.....	45
17.4.3 Treatment compliance	45
17.5 Analysis of primary endpoints	45
17.5.1 Dental plaque acidogenicity Part 1.....	45
17.5.2 Dental plaque acidogenicity Part 2.....	45
17.6 Analysis of secondary endpoints	45
17.6.1 Adverse events Part 1 and Part 2.....	45
17.6.2 Biofilm acidogenicity Part 2.....	45
17.6.3 Changes in oral microflora Part 2.....	45
17.6.4 Oral mucosal lesions Part 2	45
17.7 Statistical/analytical issues	46
17.7.1 Adjustments for covariates.....	46
17.7.2 Handling of dropouts or missing data	46
17.7.3 Multi-centre studies	46
17.7.4 Multiple comparison/multiplicity	46
17.7.5 Examination of subgroups.....	46
17.7.6 Interim analyses and data monitoring	46
18 APPENDICES	47

18.1	Signature page	47
18.2	Declaration of Helsinki	48
19	REFERENCES.....	49

List of Tables

Table 1	Schedule of events Part 1	21
Table 2	Schedule of events Part 2.....	22
Table 3	Schedule of events Part 1	29

4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or term	Explanation
ADL	Activities of daily living
AE	Adverse event
ATC	Anatomical therapeutic chemical
AUC	Area under the plasma concentration time curve
BP	Blood pressure
BMI	Body mass index
CRF	Case report form
CSP	Clinical study protocol
CSR	Clinical study report
CTC	Clinical Trial Consultants AB
CTCAE	Common terminology criteria for adverse events
CV	Coefficient of variation
DMP	Data Management Plan
DVP	Data Validation Plan
EEA	European Economic Area
GCP	Good clinical practice
h	hour
ICF	Informed consent form
ICH	International conference on harmonization
IEC	Independent ethics committee
IMP	Investigational medicinal product
MedDRA	Medical dictionary for regulatory activities
min	minute
MPA	Medical products agency
N	number
NCA	Non-compartmental analysis
NIH	National Institute of Health
NOAEL	No observed adverse effect level
NRT	nicotine replacement therapy

OTC	Over the counter
SAR	Serious adverse reaction
PPAS	Per protocol analysis set
PT	Preferred term
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDV	Source data verification
sec	Second
SOC	System organ class
SOP	Standard operating procedures
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment emergent adverse event
WHO	World Health Organisation

5 IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

5.1 Medical emergencies contacts

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. A medical emergency usually constitutes a serious adverse event (SAE) and is to be reported as such. Detailed SAE reporting procedures are included in Section 12.6.5.

In the case of a medical emergency the Investigator may contact the Medical Responsible Person at Swedish Match.

Name	Function in the study	Telephone number and e-mail
(b) (4), (b) (6)		

5.2 Overdose

An overdose is a dose in excess of the dose specified for each cohort in this clinical study protocol (CSP).

Over-dosing is not likely to occur in this study since all subjects are well familiar to Swedish snus. In cases of accidental overdose, standard supportive measures should be adopted as required and reported according to section 5.1.

Overdose should be recorded as follows:

- An overdose with associated adverse event (AE) is recorded as the AE diagnosis/symptoms on the relevant AE modules in the case report form (CRF).
- An overdose without associated symptoms is only reported in the subject's/patient's medical records.

6 INVESTIGATOR(S) AND STUDY ADMINISTRATIVE STRUCTURE

Sponsor

Swedish Match
SE-Box 17037
104 62 Stockholm
Sweden
Maria Skolgata 83
SE-118 85 Stockholm, Sweden

Sponsor's Medical Representative

(b) (4), (b) (6)
[Redacted]
[Redacted]
[Redacted]

Sponsor's Project Manager

(b) (4), (b) (6)
[Redacted]
[Redacted]
[Redacted]
[Redacted]

Principal Investigator

Prof. Peter Lingström, D.D.S., Ph. D.
(b) (4), (b) (6)
[Redacted]
[Redacted]


Clinical conduct and management
CTC Clinical Trial Consultants AB
Dag Hammarskjölds väg 13
SE-752 837 Uppsala, Sweden

(b) (4), (b) (6)
[Redacted]
[Redacted]
[Redacted]

(b) (4), (b) (6)
[Redacted]
[Redacted]
[Redacted]

(b) (4), (b) (6)
[Redacted]
[Redacted]
[Redacted]

(b) (4), (b) (6)

A large black rectangular redaction box covering several lines of text.

6.1.1 Investigational Product manufacturing and packaging

The investigational products will be manufactured and packaged compliant with Swedish law on food production.

6.1.2 Identity of investigational products

For Part 1 the investigational product will be delivered by Swedish Match to the laboratory in identical containers labelled with unique identification numbers in accordance with the randomization list.

For Part 2 the investigational product will be delivered in its original container, packaged in a secondary packaging containing five cans. The container will be labeled in English. The secondary packaging will be labeled in Swedish. Signatures required are provided in Appendix 18.1.

7 INTRODUCTION

7.1 Project background

Clinical experience does not indicate that habitual use of regular, tobacco based snus affects biofilm acidogenicity. Contributing factors may be that snus includes food approved pH regulating substances (such as sodium carbonate) which maintains a relatively high pH in the snus pinch/pouch (c. pH 8-8.5), nicotine itself does not seem to affect biofilm acidogenicity, and that the tobacco does not function as a substrate for the oral microflora. These circumstances may help to explain why caries does not seem to be more prevalent among snus users than among non-tobacco users. The non-tobacco based nicotine pouch (ZYN®) is an alternative form of orally delivered nicotine. The physical properties of ZYN® in terms of pH is the same as with regular, tobacco-based snus and the product is used the same way, that is, it is placed in the upper sulcus for 30-60 minutes. However, the matrix for the nicotine in ZYN® is different from that in regular snus: microcrystals of maltitol and cellulose instead of ground tobacco leaves. In food stuffs, maltitol and cellulose have not been associated with changes in biofilm acidogenicity. However, the prolonged exposure (c. 30-60 minutes) associated with use in a product like ZYN® constitutes a somewhat different type of exposure. Therefore, although there are no priori reasons to believe that use of ZYN® will adversely affect biofilm acidogenicity, it is reasonable to rigorously assess this possibility in the context of a controlled clinical trial. Particularly since ZYN® is marketed as a consumer product and therefore is used ad libitum by consumers.

Smokers frequently exhibit oral mucosal lesions which can be located anywhere in the oral mucosa, such as leukoedema, smoker's palate, smokers's melanosis, lingua villosa/nigra, leukoplakia and erythroplakia^[1]. It is generally assumed that the main reason for these lesions is the smoker's exposure to the combustion products in tobacco smoke, most of which are found in the tar particles in the smoke. Regular snus users may develop mucosal lesions, "snus lesions" (SILs) in the upper sulcus at the site where they typically place the snus pinch/pouch, however, to a significantly lesser extent than among smokers^[2]. The biology of these lesions is clearly different from most of the mucosal lesions associated with smoking: they are strictly localized to the site of exposure in the upper sulcus, they are reversible within weeks after cessation of exposure or if the snus user changes the location of the snus pouch, and they do not appear to be pre-malignant. The exact mechanism behind these lesions remains unclear. It has been suggested that the high pH of snus could result in a localized, chemical irritation of the mucosa. However, the observation that snus lesions are much less prevalent among users of pouched snus compared to loose snus suggests that physical irritation from the tobacco particles in snus may also play a role. The nicotine in snus may be another significant factor. For instance, mucosal lesions have been observed with lozenges of pharmaceutical nicotine replacement therapy. A recent study assessed the oral safety of a sublingual tablet containing 2 mg nicotine with regard to lesions at the site of application^[3]. In a prospective follow-up of smokers using the sublingual nicotine tablet over

a period of 3-6 months 8/30 subjects displayed lesions in the floor of the mouth during the 6-month medication period, all of which appeared in the first 1-6 weeks. By the 6-month visit all such lesions had resolved^[3].

The physical properties of ZYN® in terms of pH is the same as with regular, tobacco-based snus (pH c. 8-8.5) and it is used the same way as snus, that is, it is placed in the upper sulcus for 30-60 minutes. Because of these circumstances it is unclear to what extent use of ZYN® may cause similar mucosal lesions as regular, tobacco based snus. The comparable pH and the nicotine delivery may indicate a similar potential, but the absence of tobacco particles may result in less physical irritation.

The main aim of the present study is to assess the safety and tolerability of the non-tobacco based nicotine pouch (ZYN®), particularly with regard to its potential to adversely affect biofilm acidogenicity. A secondary aim is to investigate to which extent ZYN® has the potential to produce mucosal lesions at the site of application in the oral cavity similar to those occasionally observed among regular snus users and whether pre-existing snus lesions among the included subjects may improve or resolve during a 6 week observation period during which the participants substitute their regular snus with ZYN® products.

Adverse Events will be recorded at all visits, with particular focus on local irritation at the site of the oral mucosa where the pouch is placed, or in the throat, and hiccups and heartburn (which are common side effects with all types of nicotine exposure).

7.2 Investigational medicinal product

7.2.1 Product characteristics

The Non-tobacco based nicotine pouch (ZYN®) will be delivered in identical glass vials for Part 1 and in its original container for Part 2.

Part: 1) ZYN® Smooth 3 mg, 2) ZYN® Peppermint 3 mg, 3) 10% sucrose solution, 4) 10% xylitol solution.

Part: 2: Ad libitum use of a ZYN® nicotine pouch, participants can choose from 3 or 6 mg pouches of ZYN® Smooth, ZYN® Peppermint and ZYN® Cinnamon.

7.3 Risk/benefit assessment

It may be considered problematic to expose research subjects to a novel nicotine delivery product the properties of which are not yet fully known. The assessments of plaque acidogenicity require participants to refrain from brushing their teeth for 48 hours prior to the examination, and the procedure involves exposure to a positive control substance (sucrose)

that will lower their plaque pH. This may theoretically have adverse effects on the participants' dental health, but previous studies have shown no such clinical adverse effects after refraining from toothbrushing for such a short period of time.

All mentioned potentially adverse effects of study participation are likely to be minor and clinically insignificant. As to the nicotine exposure, all research subjects are required to be daily snus users since at least one year (with an average or above snus consumption) so the participants are well acquainted with and used to the effects of nicotine. Aside from the nicotine, all ingredients used in the test products are food-approved (similar to ingredients in snus).

Pregnant women or individuals with a history of hypertension or any other cardiovascular disease who may be particularly vulnerable to nicotine exposure are excluded from participation. Individuals with a lower than average saliva production are also excluded as adverse effects related to xerostomia may adversely influence outcomes and thus bias the results (it is expected that few if any of the included participants will have problems related to xerostomia as they are all regular snus users since more than one year).

The procedures used to assess oral health, including measurements of plaque acidogenicity, are standard procedures used at odontological research facilities and are not associated with any major discomfort or significant adverse events. The procedures are unlikely to adversely affect the participants' oral health in the long-term because of their limited duration. In fact, theoretically, participation in the studies may help to improve participants' long-term oral health through an increased awareness of the significance of dental hygiene. The studies will not involve invasive procedures.

The theoretical adverse effects of the study procedures, which are likely to be minor and/or insignificant, are from a research ethics perspective counterbalanced by the potential positive health effects of the novel nicotine pouch as a low-toxic alternative to cigarettes or conventional snus among current tobacco users.

7.3.1 Summary of risk management

Subjects will for Part 1 remain in the research clinic during the administration of the Investigational Product and will be closely monitored by medical staff.

8 STUDY OBJECTIVES AND ENDPOINTS

8.1 Primary objective(s)

The primary objective of the present study is to evaluate the amount of dental plaque acidogenicity from the non-tobacco based nicotine pouch.

Part 1: Assessment of dental plaque acidogenicity after short-term exposure (60 mins) to study products (a flavored and an unflavored brand of the nicotine pouch), 10% sucrose (positive control), and 10% xylitol (negative control).

Part 2: Assessment of dental plaque acidogenicity during a total of 6 weeks of ad libitum use of the nicotine pouch.

8.2 Primary endpoint

Part 1:

Assessment of dental plaque acidogenicity after short-term exposure (60 mins) of nicotine pouch.

Part 2:

Assessment of dental plaque acidogenicity after 6 weeks of use of nicotine pouch.

8.3 Secondary objectives

The secondary objective of the present study is to evaluate the clinical tolerability and safety of ZYN® with respect to effects on the oral mucosa

8.4 Secondary endpoints

The secondary endpoints will be

- Adverse events (part 1 and part 2)
- Changes in the oral microflora (part 2)
- Oral mucosal lesions (part 2)

9 INVESTIGATIONAL PLAN

9.1 Overall study design and schedule of events

Part 1 of the study is an open, randomized, four-way crossover, single administration for 60 minutes (measured at 0 minutes and then at 2, 5, 10, 20, 30, 40, 50 and 60 minutes). Subjects will be randomized to one of four treatment sequences using a flavored and an unflavored brand of the nicotine pouch), 10% sucrose (positive control), and 10% xylitol (negative control) with one-week washout. The number of healthy subjects aged over 19 needed to be evaluate should complete the four-period cross over is estimated to be 20. Each visit lasts for about 75 min.

Table 1 Schedule of events Part 1

EVENT	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Follow-Up
	Screening Day -10 - -3	Day 0	Day 7(+2)	Day 14(+2)	Day 21(+2)	Day 28(+/-2)
ELIGIBILITY CHECK	✓					
HEALTH CHECK (Physical exam)	✓					
MEDICAL HISTORY	✓					
CONCOMITANT MEDICATION	✓	✓	✓	✓	✓	✓
INFORMED CONSENT	✓					
URINE PREGNANCY TEST	✓					
DOSAGE OF STUDYPRODUCT		✓	✓	✓	✓	
AE INTERVIEW	✓	✓	✓	✓	✓	✓
DENTAL PLAQUE ACIDOGENICITY		✓	✓	✓	✓	

Part 2 of the study is an open, observational, safety and tolerability study during 6 weeks. The subjects will use the non-tobacco based nicotine pouch (ZYN®) *ad libitum*. At each visit the subject will report any local and general adverse symptoms.

All subjects are seen on an individual basis and each visit lasts for about 90 min.

Healthy subjects aged >19 years, who use tobacco-based snus since ≥ 1 year with a weekly consumption of three or more snus cans (brands with nicotine content <1%) or two or more cans (brands with nicotine content >1%), normal stimulated salivary secretion rate (≥ 0.7 ml/min).

Table 2 Schedule of events Part 2

EVENT	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Follow-up
	Screening Day -2	Day 0	Day 14 (+/-2)	Day 28 (+/-3)	Day 42 (+/-4)	Day 49 (+/-2)
ELIGIBILITY CHECK	✓					
HEALTH CHECK (Physical exam)	✓					
MEDICAL HISTORY	✓					
CONCOMITANT MEDICATION	✓	✓	✓	✓	✓	✓
INFORMED CONSENT	✓					
URINE PREGNANCY TEST	✓					
AE INTERVIEW	✓	✓	✓	✓	✓	✓
PHOTO	✓		✓	✓	✓	
INSPECTION OF THE ORAL CAVITY (MUCOSAL LEISIONS)	✓		✓	✓	✓	
DENTAL PLAQUE ACIDOGENICITY	✓		✓	✓	✓	
ORAL MICROFLORA	✓		✓	✓	✓	
PLAQUE AMOUNT	✓		✓	✓	✓	
DIARY FOR COMPLICANCE			✓	✓	✓	
SUPPLY OF STUDY PRODUCT	✓	✓	✓	✓		

9.2 Rationale for study design and dose groups

The rationale for the choice of the study design is from a recent study that assessed the oral safety of a sublingual tablet containing 2 mg nicotine with regard to lesions at the site of application^[3] and from a prospective follow-up of smokers using the sublingual nicotine tablet over a period of 3-6 months 8/30 subjects displayed lesions in the floor of the mouth during the 6-month medication period, all of which appeared in the first 1-6 weeks. By the 6-month visit all such lesions had resolved^[3].

10 STUDY POPULATION

10.1 Recruitment

Healthy adult males and females will be recruited using an advertisement in the local newspaper. Following a telephone interview to evaluate eligibility, potential participants are invited to a screening visit. The potential participants will then submit a Health Declaration that will be checked by the responsible Investigator.

10.2 Screening and enrolment log

A screening number will be allocated to each subject undergoing screening. Investigators must keep a record of all screened subjects even if they were not subsequently included in the study. This information is necessary to verify that subjects were selected without bias. The reason for screen failure should be stated for all subjects screened but not included. The reason for withdrawal should be stated for all subjects included but not completed.

All subjects who have signed the Informed Consent Form (ICF) will be assigned a screening number (S0001, S0002 and S0003 etc.). Subjects included and randomised will be assigned a subject number (101, 102 and 103 etc.).

If a subject cannot receive the planned dose of investigational product within 28 days after screening (*i.e.*, the time interval between signing informed consent until dose administration) the subject should be rescreened before proceeding in the trial.

10.3 Number of subjects

Part 1: 20 participants (with available data on all four test articles)

Part 2: 60 participants

10.4 Inclusion criteria

For inclusion in the study, subjects must fulfill the following criteria:

1. Snus user, with a minimum weekly consumption of three or more snus cans (brands with nicotine content $\leq 1\%$) or two or more cans (brands with nicotine content $> 1\%$) since ≥ 1 year.
2. Consent to participate voluntarily and sign Informed Consent Form prior to any study procedure.
3. Healthy male/female, age ≥ 19 . Female subjects should have a negative pregnancy test.
4. Willing and able to comply with study procedures.
5. Normal stimulated salivary secretion rate (≥ 0.7 ml/min).

10.5 Exclusion criteria

Subjects must not enter the study if any of the following exclusion criteria are fulfilled:

1. A history or presence of diagnosed hypertension or any cardiovascular disease.
2. Surgery within 6 months of the screening visit that, in the opinion of the investigator, could negatively impact on the subject's participation in the clinical study.
3. Any surgical or medical condition, which, in the judgment of the clinical investigator, might interfere with the absorption, distribution, metabolism or excretion of nicotine.
4. Subjects who are pregnant.
5. Allergy towards composite materials.
6. Antibiotic use during or within the last 4 weeks prior to the study period.

10.6 Restrictions during the study

The subjects in both parts of the study will refrain from approximal tooth cleaning during the 72 hours prior to visit and toothbrushing during the last 48 hours prior to visit. They will not eat or drink anything during the last 2 hours prior to visit.

Other therapy considered necessary for the subject's welfare may be given at the discretion of the Investigator. All such therapy must be recorded in the Case Report Form.

Study subjects are not allowed to participate in any other clinical study during the study period.

10.7 Criteria for subject withdrawal

10.7.1 General withdrawal criteria

A subject should be withdrawn from the study treatment if, in the opinion of the Investigator, it is medically necessary, or if it is the wish of the subject. The reason for withdrawal should be clearly described and the subject should, whenever possible, irrespective of the reason for withdrawal, as soon as possible be medically examined. Relevant samples should be obtained and all relevant assessments should be completed, preferably according to the schedule for the final assessment. The Case Report Form should be completed as far as possible and collected by the staff.

10.7.2 Procedures for discontinuation of a subject from the study

A subject who prematurely discontinues participation in the study will be asked about the reason(s) for discontinuation and the presence of any AEs. If possible, they will be seen by the Investigator and assessed according to the procedures scheduled for the follow-up visit. Any ongoing AEs will be followed as described in Section [12.6.6](#).

10.7.1 Subject replacement

Subjects who are prematurely withdrawn from the study for any reason except the occurrence of TEAEs assessed as possibly or probably related to study treatment will not be replaced during the course of the study.

10.8 Randomization

For Part 1 the subjects will be assigned to the treatments using a computer-generated randomization list.

10.9 Blinding

The present study will be an open randomized study. Subjects will be administered each dose by the personnel according to the randomization list.

11 TREATMENTS

11.1 Identity of investigational products

Part 1: 1) ZYN® Smooth 3 mg, 2) ZYN® Peppermint 3 mg, 3) 10% sucrose solution, 4) 10% xylitol solution.

Part 2: Ad libitum use of a ZYN® nicotine pouch, participants can choose from 3 or 6 mg pouches of ZYN® Smooth, ZYN® Peppermint or ZYN® Cinnamon.

11.2 Packaging and labelling

Part1:

The Non-tobacco based nicotine pouch (ZYN®) will be delivered by Swedish Match to the laboratory in identical containers labelled with unique identification numbers in accordance with the randomization list.

The positive- and negative control will be prepared by the laboratory and labelled with unique identification numbers by the laboratory in accordance with the randomization list.

The container will be labelled with unique identification numbers (in Swedish):

Trial code: SM 17-02

Subject No.: 1 (20)

Visit:

Dose:

Storage conditions: Refrigerated storage

Part2:

The Non-tobacco based nicotine pouch (ZYN®) will be delivered in its original container. Labeling of the secondary packaging will be in Swedish.

The secondary packaging will be labelled by the laboratory (in Swedish):

Non-tobacco based nicotine pouch (ZYN® Smooth 3 mg).

For clinical trial.

Trial code: SM 17-02

Subject No.: 1 (60)

Batch No.:

Expiry date:

Dosage: Ad libitum

Responsible investigator: Prof. Peter Lingström, D.D.S., Ph. D.

Keep out of reach of children.

Non-tobacco based nicotine pouch (ZYN® Smooth 6 mg).

For clinical trial.

Trial code: SM 17-02

Subject No.: 1 (60)

Batch No.:

Expiry date:

Dosage: Ad libitum

Responsible investigator: Prof. Peter Lingström, D.D.S., Ph. D.

Keep out of reach of children.

Non-tobacco based nicotine pouch (ZYN® Peppermint 3 mg).

For clinical trial.

Trial code: SM 17-02

Subject No.: 1 (60)

Batch No.:

Expiry date:

Dosage: Ad libitum

Responsible investigator: Prof. Peter Lingström, D.D.S., Ph. D.

Keep out of reach of children.

Non-tobacco based nicotine pouch (ZYN® Peppermint 6 mg).

For clinical trial.

Trial code: SM 17-02

Subject No.: 1 (60)

Batch No.:

Expiry date:

Dosage: Ad libitum

Responsible investigator: Prof. Peter Lingström, D.D.S., Ph. D.

Keep out of reach of children.

Non-tobacco based nicotine pouch (ZYN® Cinnamon 3 mg).

For clinical trial.

Trial code: SM 17-02

Subject No.: 1 (60)

Batch No.:

Expiry date:

Dosage: Ad libitum

Responsible investigator: Prof. Peter Lingström, D.D.S., Ph. D.

Keep out of reach of children.

Non-tobacco based nicotine pouch (ZYN® Cinnamon 6 mg).

For clinical trial.

Trial code: SM 17-02

Subject No.: 1 (60)

Batch No.:

Expiry date:

Dosage: Ad libitum

Responsible investigator: Prof. Peter Lingström, D.D.S., Ph. D.

Keep out of reach of children.

11.3 Conditions for storage

The Investigational Product will be stored in the access-controlled cold (ca 7°C) storage area at the investigational site, as per storage conditions specified by the Sponsor.

11.4 Dispensing and accountability

Part 1:

The study product will be dispensed as per randomisation schedule by site personnel.

Part 2:

The subject will try out the appropriate product during two days and after that collect 14 days supply of the selected product on the visits to the clinic. Subjects are allowed to switch between all of the study products ad libitum.

The Investigator will maintain a *Product Dispensing Log* based on the amount of cans detailing the dates and quantities of study product received, dispensed to and used by each subject/patient and study product returned or destroyed at the end of the study. Any discrepancies between dispensed and returned investigational products must be explained and documented. Products deliberately and/or accidentally destroyed by the site personnel or the subject must be accounted for.

11.5 Treatment administration

Part 1:

A single dose will be given on each study day.

Part 2:

The subjects will be recommended to replace as many as possible of their regular snus products (ideally all) with ZYN® products during the 6 week period and to use as much ZYN® as they need.

The duration of the treatment period is 6 weeks. It is entirely at the discretion of the subject when he/she will use the pouch during the day and how many pouches per day that are used.

11.6 Treatment compliance

Part 1:

All Investigational Products will be administered at the research clinic under supervision to ensure compliance.

Part 2:

In part 2 of the study the subjects will receive enough study products for 14 days period.

The amount of study product for part 2 will be recorded in a paper diary.

11.7 Return and destruction of investigational products

Any unused study product will be collected and kept at site until returned to the Sponsor. Empty containers will be destroyed at the study site. The Monitor will perform final investigational product accountability reconciliation at the study end to verify that all unused investigational product is adequately destroyed and documented.

12 STUDY ASSESSMENTS

The study assessments are described in the sections below and the timing of these assessments are detailed in the schedule of events (Overall study design and schedule of events).

12.1 Part 1

Screening

Subjects will be seen in a screening visit (day -10 to -3), during which informed consent will be obtained prior to any study procedures. The past medical /surgical history will be reviewed. Information will be obtained regarding any current medications. Health check and saliva secretion assessment will be completed. Urine sample for pregnancy test (female only) will be collected.

Visit 2, 3, 4 and 5:

Eligible subjects will return for their first dosing visit on visit 2, 3, 4 and 5. They will be interviewed regarding concomitant medication and AEs (Basal events) since the screening visit. After that assessment of dental plaque acidogenicity and plaque amount will be performed. After the initial assessments the subject will be given the study product, positive or negative control. Study products will be kept in the vestibule during the 60 minutes of acidogenicity assessment while positive and negative control will be rinsed in the mouth for 60 seconds. After that dental plaque acidogenicity will be assessed 8 more times during 60 minutes followed by an assessment of plaque amount.

Table 3 Detailed schedule of events Part 1

TIME POINT	PRE-DOSE	0 MIN	1 MIN	2 MIN	5 MIN	10 MIN	20 MIN	30 MIN	40 MIN	50 MIN	60 MIN	65 MIN
<i>Con. Med</i>	X											
<i>AE interview</i>	X											X
<i>Plaque Acidogenicity</i>		X		X	X	X	X	X	X	X	X	
<i>Dosage of pouch</i>		X										
<i>Removal of pouch</i>											X	
<i>Pos/Neg control in</i>		X										
<i>Pos/neg control out</i>			X									

Follow-up:

A phone call will be made by the study researcher to the subjects 5-10 days after end of visit 5. AEs and concomitant medication will be checked.

12.2 Part 2**Screening:**

Subjects will be seen in a screening visit (day -2), during which informed consent will be obtained prior to any study procedures. The past medical/surgical history will be reviewed. Information will be obtained regarding any current medications. Health check and saliva secretion assessment will be completed. Urine sample for pregnancy test (female only) will be collected.

Assessment of the following parameters will be performed:

- Inspection of the oral cavity
- Photo
- Biofilm acidogenicity
- Oral microflora
- Plaque amount

At the end of the screening visit the subject will receive samples of the study products, 3 or 6 mg pouches of ZYN® Smooth, ZYN® Peppermint or ZYN® Cinnamon to be able to choose based on their preferences.

Visit 2

Two days after the screening visit the subject will return to the clinic and pick up a supply for the first two weeks. Subsequent, the study product will be supplied on the forthcoming clinic visits.

Visit 3, 4 and 5:

Eligible subjects will return for their visit 3, 4 and 5. They will be interviewed regarding concomitant medication and AEs (Adverse Events) since the last visit.

The following assessments will be performed:

- Inspection of the oral cavity
- Photo
- Biofilm acidogenicity
- Oral microflora
- Plaque amount

Follow-up:

A phone call will be made by the study researcher to the subjects 5-10 days after end of visit 4. AEs and concomitant medication will be checked.

12.3 Recording of data

The Principal Investigator will provide the Sponsor with all data produced during the study from the scheduled study assessments. He/she ensures the accuracy, completeness, legibility, and timeliness of the data reported to Sponsor in the CRF and in all required reports.

12.4 Demographics and other baseline characteristics (Part 1 and Part 2)

12.4.1 Informed consent

Signed informed consent must be obtained before any screening procedures are initiated. The informed consent procedure is further described in Section [14.3](#).

12.4.2 Demographic information

The following demographic data will be recorded: gender, age, and ethnic origin.

12.4.3 Medical/surgical history

Medical/surgical history will be obtained by interview to verify that the eligibility criteria are met.

12.4.4 Physical examination

Physical examination will be obtained by interview to verify that the eligibility criteria are met.

12.4.5 Prior and concomitant medication

Prior medication will be obtained by interview in order to verify that the eligibility criteria are met (see also Section 10.6).

Medications are classified as prior if the stop date was before or on the day of the first dose administration and as concomitant if ongoing at, and stopped after the first dose administration or started after the first dose administration.

Any use of concomitant medication from screening until the last Follow-up Visit must be documented appropriately in the subject's CRF. Relevant information (*i.e.* name of medication, total daily dose, unit, start and stop dates, reason for use if consistent with the definition of an AE) must be recorded. All changes in medication should be noted in the CRF.

12.4.6 Pregnancy urine test

Pregnancy urine test will be performed at screening visit (females only) at the research clinic using dip sticks.

12.4.7 Baseline symptoms

A *baseline symptom* is an event in a clinical study subject that occurs after he/she signed the informed consent form (ICF) up until the first administration of study product (*i.e.* during the screening period). These events are not regarded as AEs and should not be recorded in the AE log in the CRF.

12.5 Study Assessments

12.5.1 Examination of the oral cavity

Clinical examination of the oral cavity will be performed at screening and visit 3, 4 and 5.

The oral mucosa will be inspected and any pathological changes will be recorded and classified. *Lesions* in the mucosa at the placement of the pouch, particularly "snus lesions" (SILs), will be registered according to four grade clinical scale suggested by Axéll et al^[1]. In addition gingival retractions will be recorded

Clinical examination of the oral cavity will be performed according to Axéll et al (1976)^[1]:

- **Degree 1.** A superficial lesion with a color similar to the surrounding mucosa and with slight wrinkling. No obvious mucosal thickening.
- **Degree 2.** A superficial, whitish or yellowish lesion with wrinkling. No obvious thickening.
- **Degree 3.** A whitish-yellowish to brown, wrinkled lesion with intervening furrows of normal mucosal colors, obvious thickening.
- **Degree 4.** A marked yellowish to brown and heavily wrinkled lesion with intervening deep reddened furrows and/or heavy thickening.

By the 6-week visit (study termination) it will be summarized to which extent such lesions have changed (according to the above scale or have resolved completely).

Oral *leukoplakias* and *erythroplakias* will be followed up according to standard clinical routines.

Local symptoms reported by the subject, are recorded at each visit, elicited using open-ended general questions. Other adverse events reported spontaneously are also recorded and duration thereof.

The oral cavity will be documented by photography.

12.5.2 Dental plaque acidogenicity

Plaque acidogenicity will be measured using the microtouch method. An iridium microelectrode (Beetrode MEPH-1, WPI Instruments, New Haven, Conn., USA) will be inserted into the plaque on two buccal surfaces in the upper jaw and two approximal surfaces in the upper and lower jaw. The electrode will be connected to an Orion SA720 pH/ISE Meter (Orion Research, Boston, Mass., USA) to which also a reference electrode is connected. The reference electrode is placed into a solution of 3 M KCl to which also a finger of the volunteer is placed in order to create a salt bridge. Prior to and during each test session, the electrode is calibrated against a standard buffer at pH 7.00. After baseline registration (0 min), the subjects will rinse with the sucrose or xylitol solution or use the study products for 1 min after which pH was measured at 8 different time points up to 60 min.

12.5.3 Plaque amount

The plaque amount will be assessed with a plaque score calculated by the index described by Silness and Løe (1964)^[6]. The amount of plaque will be measured on all surfaces. For each tooth six sites (mesio-buccal, buccal, disto-buccal, disto-lingual, lingual and mesio-lingual) from score 0-3.

12.5.4 Oral microflora

Pooled plaque samples will be collected by a sterile toothpick according to Kristoffersson and Bratthall (1982)^[7] from the buccal areas of respective quadrants.

12.5.5 Saliva sampling

The salivary factors pH and flow rate (unstimulated and stimulated) will be measured. Saliva will be collected into a beaker and the secretion rate calculated in ml/min. The buffer capacity will be determined using a chairside kit (CRT Buffer®, Vivadent, Germany)

12.6 Adverse events

The Principal Investigator is responsible for ensuring that all medical staff involved in the study is familiar with the content of this section and the content of the CTC standard operating procedures (SOPs).

12.6.1 Event definitions

12.6.1.1 Adverse event

An Adverse Event (AE) is any untoward medical occurrence in a subject or trial subject to whom a drug is administered or in whom a medical device is used: The event does not necessarily have a causal relationship with that treatment or usage.

Adverse Events include the following:

- a) All suspected adverse reactions to the study products (such as excess salivation, nausea, vomiting, hiccups, head ache, palpitations, dyspepsia).
- b) Apparently unrelated illnesses, including the worsening of a pre-existing illness (see 'Pre-existing Conditions' below).
- c) Injury or accidents.
- d) Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test) unless they are associated with a clinical event already reported. Laboratory abnormalities associated with a clinical event (e.g. elevated liver enzymes in a subject with jaundice) should be described under 'Comments' on the report of the clinical event rather than be listed as a separate adverse event.

Baseline symptom

In this trial, a baseline symptom (i.e. a disorder present before the AE reporting period started and will be noted on the pre-treatment medical history/physical examination form) should not be reported as an AE unless the condition worsens or episodes increase in frequency during the AE reporting period.

Procedures

Diagnostic and therapeutic invasive and non-invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that

begins during the AE reporting period should be reported as the AE and the resulting appendectomy be noted under 'Comments'.

12.6.1.2 Serious adverse event

An AE that meets one or more of the following criteria is classified as serious:

- Death
- Life-threatening (i.e. immediate risk of death)
- In-subject hospitalization or prolongation of existing hospitalization
- Permanent or significant impairment of function or permanent damage to a body structure or intervention is required to prevent permanent impairment or damage
- Cancer
- Any other AE that the investigator or company judges to be serious, or which is defined as serious by the regulatory agency in the country in which the adverse event occurred.

12.6.2 Adverse Event assessment definitions

12.6.2.1 Assessment of severity/intensity

The grading of the severity/intensity of AEs will follow the CTCAE v4.03. Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline.

The Investigator must assess the *severity/intensity* of an AE using the following definitions, and record it on the *Adverse Event Form* in the CRF:

<i>Grade 1</i>	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
<i>Grade 2</i>	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
<i>Grade 3</i>	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self- care ADL**.
<i>Grade 4</i>	Life-threatening consequences; urgent intervention indicated.
<i>Grade 5</i>	Death related to AE.

**Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.*

***Self- care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.*

12.6.2.2 Assessment of causal relationship

The Investigator must assess the *causal relationship* between an AE and the Investigational Product using the definitions below and record it on the *Adverse Event Form* in the CRF as well as on the *Serious Adverse Event Report Form*, if applicable:

- *Probable* – the AE has a strong temporal relationship to the Investigational Product or recurs on re-challenge, and another etiology is unlikely or significantly less likely
- *Possible* – the AE has a suggestive temporal relationship to the Investigational Product, and an alternative etiology is equally or less likely
- *Not related* – the AE has no temporal relationship to the IMP or is due to underlying/concurrent illness or effect of another drug (that is, there is no causal relationship between the Investigational Product and the AE).

An AE is considered causally related to the use of the Investigational Product when the causality assessment is *probable* or *possible*.

For a baseline symptom, a causality assessment is not relevant.

12.6.2.3 Assessment of outcome

The Investigator must assess the *outcome* of an AE using the definitions below and record it on the *Adverse Event Form* in the CRF:

- *Recovered* – the subject has recovered completely, and no symptoms remain.
- *Recovering* – the subject's condition is improving, but symptoms still remain.
- *Recovered with sequelae* – the subject has recovered, but some symptoms remain (for example, the subject had a stroke and is functioning normally, but has some motor impairment).
- *Not recovered* – the subject's condition has not improved and the symptoms are unchanged (for example, an atrial fibrillation has become chronic).
- *Death*

12.6.3 Collecting adverse events

AEs (including baseline events) identified using any of the following methods will be recorded:

- AEs spontaneously reported by the subject
- AEs observed by the Investigator or medical personnel
- AEs elicited based on non-leading questions from the Investigator or medical personnel

Collection of baseline events starts after the subject signs the ICF and continues until the first administration of Investigational Product.

AE collection starts with administration of the Investigational Product (*i.e.* only TEAEs will be collected and recorded in the CRF) and continues until the last follow-up assessment. Any AE with start date on the day of first Investigational Product administration must be recorded with start time.

At the Follow-up Visit, information on new AEs or SAEs, if any, and stop dates for AEs recorded and on-going during the dosing period must be recorded.

12.6.4 Recording adverse events

AEs (including baseline events) must be recorded on an *Adverse Event Form* in the CRF. The investigator must provide information on the AE, preferably with a diagnosis or at least with signs and symptoms; start and stop dates, start and stop time; intensity; causal relationship to IMP; action taken, and outcome.

If the AE is serious, this must be indicated in the CRF. Furthermore, the Investigator must fill out the *Serious Adverse Event Report Form* and report the SAE to the Sponsor as described in Section 12.6.5.

AEs, including out-of-range clinically significant clinical safety laboratory values, must be recorded individually, except when considered manifestations of the same medical condition or disease state; in such cases, they must be recorded under a single diagnosis.

If the severity/intensity of an AE increases a new *Adverse Event Form* must be completed in the CRF.

12.6.5 Reporting serious adverse events

All AEs should be followed until they are resolved, or the subject's participation in the trial ends. Instructions for reporting changes in an ongoing AE during a subject's participation in the trial are provided in the instructions that accompany the CRF AE forms.

In addition, all serious AEs and those non-serious events assessed by the investigator as possibly related to the investigational medication/product should continue to be followed even after the subject's participation in the trial is over. Such events should be followed until they are resolved or until the Investigator assesses them as "chronic" or "stable". Resolution of such events is to be documented on the appropriate CRF.

The Investigator must report SAEs to the Sponsor immediately (within 24 hours) after becoming aware of them, by contacting:

(b) (4), (b) (6)

Swedish Match

(b) (4), (b) (6)

The same information must also be sent to the CTC SAE email inbox: (b) (4)

To report SAEs, the *Serious Adverse Event Report Form* for clinical studies provided must be used. The first report should contain as much information as possible. The initial report is to be followed by submission of more detailed and additional AE information within 5 working days of the event using the same form. If unexpected, SAEs are also to be reported immediately to the responsible Independent Ethics Committee.

The Sponsor or a delegate will assume responsibility for reporting SAEs in accordance with local regulations.

The Sponsor is responsible for informing the Investigators concerned of relevant information about SUSARs that could adversely affect the safety of subjects.

12.6.6 Treatment and follow-up of adverse events

Subjects with AEs that occur during the study must be treated according to daily clinical practice at the discretion of the Investigator.

AEs must be followed up until resolution or the follow-up assessment, whichever comes first. At the Follow-up Visit, information on new AEs, if any, and stop dates for previously reported AEs must be recorded. AEs assessed as stable by the Investigator at the last Follow-up visit will not have to be followed up until resolution.

It is the responsibility of the Investigator to follow up on all SAEs until the subject has recovered, stabilized, or recovered with sequelae, and to report to the Sponsor all relevant new information using the same procedures and timelines as those for the initial report. Relevant information includes discharge summaries, autopsy reports, and medical consultation.

SAEs spontaneously reported by a subject to the Investigator within 30 days after the last follow-up assessment must be handled in the same manner as SAEs occurring during the study. These SAEs will be reported to the Sponsor.

12.6.7 Procedures in case of pregnancy

In case of pregnancy or suspicion of possible pregnancy, the study treatment must be stopped immediately, and the subject discontinued from participation in the study. Pregnancy itself is not regarded as an AE unless there is a suspicion that any of the Investigational Products may have interfered with the effectiveness of the contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even after the subject was discontinued from the study.

All events of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as AEs. All outcomes of pregnancy must be reported to the Sponsor and the Principal Investigator on the pregnancy outcomes report form.

13 PROCEDURES FOR BIOLOGICAL SAMPLES

13.1 Sample collection for pharmacokinetic measurements

No blood samples will be collected in this study.

14 ETHICAL AND REGULATORY REQUIREMENTS

14.1 Ethical conduct of the study

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and later revisions. The trial will be consistent with Good Clinical Practice (GCP) and applicable regulatory requirements.

A link to the Declaration of Helsinki is included in Appendix 18.2.

14.2 Ethics and regulatory review

The Principal Investigator is responsible for submission of the CSP, the patient information and ICF, any other written information to be provided to the subjects/patients and any advertisements used for recruitment of subjects/patients to applicable Independent Ethics Committee (IEC) for approval.

Approval must be obtained in writing from IEC before the first subject/patient can be recruited.

The Sponsor will provide IEC and Principal Investigators with safety updates/reports according to local requirements. Progress reports and notifications of SUSARs will be provided to the IEC according to local regulations and guidelines.

It is the responsibility of the investigator to obtain approval of the trial protocol/amendments from EC. The investigator should file all correspondence with the EC. Copies of EC approvals should be forwarded to CTC AB.

14.3 Subject/Patient information and consent

It is the responsibility of the Investigator or an authorised associate to give each potential study subject/patient (or the subject's/patient's legally acceptable representative and/or witness, as applicable) adequate verbal and written information before any study specific assessments are performed.

The information will include the objectives and the procedures of the study as well as any risks or inconvenience involved. It will be emphasised that participation in the study is voluntary and that the subject/patient may withdraw from participation at any time and for any reason, without any prejudice. All subjects/patients will be given the opportunity to ask questions about the study and will be given sufficient time to consider participation before signing the ICF.

Before performing any study-related procedures the ICF must be signed and personally dated by the subject/ patient (or their legally acceptable representative and/or witness, as applicable) and by the Investigator. A copy of the subject/patient information including the signed ICF will be provided to the subject/patient.

Documentation of the discussion and the date of informed consent must be recorded in the source documentation and in the CRF. The subject/patient information sheet and the signed ICF should be filed by the Investigator for possible future audits and/or inspections.

The final approved version of the subject/patient information and ICF must not be changed without approval from the Sponsor and the applicable IEC.

14.4 Subject/Patient information card

The subject/patient will be provided with a Subject/Patient information card including the following information:

- That he/she is participating in a clinical study
- Subject study ID
- That he/she is treated with the IMP
- The name and phone number of the Investigator

- Name and address of the Sponsor

14.5 Subject/Patient data protection

The ICF includes information that data will be recorded, collected and processed and may be transferred to European Economic Area (EEA) or non-EEA countries. In accordance with the European Union Data Protection Directive (95/46/EC), the data will not identify any persons taking part in the study.

The potential study subject/patient (or the subject's/patient's legally acceptable representative and/or witness, as applicable) should be informed that by signing the ICF he/she approves that authorized representatives from Sponsor and CTC, the concerned IEC and CA have direct access to his/her medical records for verification of clinical study procedures. This agreement is to be substantiated in a separate document, according to local requirements.

The subject/patient has the right to request access to his/her personal data and the right to request rectification of any data that is not correct and/or complete.

The Investigator must file a *Subject/Patient Identification List* which includes sufficient information to link records, i.e. the CRF and clinical records. This list should be preserved for possible future inspections/audits but should not be made available to the Sponsor except for monitoring or auditing purposes.

14.6 Changes to the approved clinical study protocol

Any proposed change to the approved Final CSP (including appendices) will be documented in a written and numbered clinical protocol amendment. All amendments including substantial changes to the protocol must be approved by the appropriate IEC and/or CA before implementation according to applicable regulations.

14.7 Audits and inspections

Authorised representatives of Sponsor or an IEC may perform audits or inspections at the research clinic, including source data verification (SDV). The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, ICH-GCP guidelines and any applicable regulatory requirements.

14.8 Insurance

Subjects will be covered under the Sponsors liability insurance policy through If. The certificate of insurance and an information leaflet containing essential information about the insurance coverage can be provided upon request. The participating subjects/patients are also protected in accordance with national regulations, as applicable. Göteborgs university has a company insurance covering services performed at the laboratory.

15 STUDY MANAGEMENT

15.1 Training of study site personnel

Before enrolment of the first study subject a Sponsor representative or delegate will perform a study initiation visit at the research clinic. The requirements of the CSP and related documents will be reviewed and discussed and the investigational staff will be trained in any study specific procedures and system(s) utilised.

It is the responsibility of the Investigator to ensure that all personnel involved in the study are fully informed of all relevant aspects of the study, and have a detailed knowledge of and training in the procedures that are to be executed by them. Any new information of relevance to the performance of this study must be forwarded to the staff involved in a timely manner.

The Investigator will keep a list of all personnel involved in the study together with their function and study related duties delegated. A *Curriculum Vitae* will be available for all staff delegated study-specific duties.

15.2 Clinical monitoring

The study site will be periodically visited by a Monitor from an independent group at times agreed on by the Investigator and the Monitor. At the time of each monitoring visit, the function of the Monitor is to:

- provide information and support to the investigational team.
- confirm that facilities and resources remain acceptable.
- confirm that the investigational team is adhering to the CSP, applicable standard operating procedure (SOPs), guidelines, manuals and regulatory requirements.
- verify that data are being accurately and timely recorded in the CRFs and that IMP accountability checks are being performed.
- verify that data in the CRF are consistent with the clinical records (SDV) in accordance with the Monitoring Plan.
- verify that the correct informed consent procedure has been adhered to for participating subjects/patients.
- ensure that withdrawal of informed consent to the use of the subject's/patient's biological samples will be reported and biological samples are identified and disposed of/destroyed accordingly, and that this action is documented and reported to the subject/patient.
- verify that AEs are recorded and reported in a timely manner and according to the CSP.

When the study has been completed and all queries have been resolved and the database has been locked, the Monitor will perform a close-out visit.

Monitoring visits to the trial site will be made periodically during the trial, to ensure that all aspects of the protocol are followed. The report will be reviewed for verification of agreement with data on Case Report Forms. The investigator/institution guarantee access to CRFs and report and all relevant documents by CTC AB and appropriate regulatory agencies.

The trial site may also be subject to quality assurance audit by CTC AB as well as inspection by appropriate regulatory agencies.

It is important that the investigator and their relevant personnel are available during the monitoring visits and possible audits and that sufficient time is devoted to the process.

15.3 Source data document

A separate *Source Data Verification List* will be generated for each site before start of enrolment, specifying the location of the source of derived information appearing in the CRF. This document must be signed by the Principal Investigator and the Monitor to confirm agreement before start of recruitment.

The Investigator should guarantee access to source documents to the Monitor, CAs and the IECs, if required.

15.4 Study agreements

The Principal Investigator must comply with all the terms, conditions, and obligations of the Clinical Study Agreement for this study.

Agreements between Sponsor and CTC must be in place before any study-related procedures can take place, or subjects/patients be enrolled.

15.5 Study time table and end of study

The end of the clinical part of the study is defined as the last visit of the last subject/patient participating in the study.

The study is expected to start in Quarter 4, 2017 and to be completed by Quarter 2, 2018.

15.6 Discontinuation of the study

The Sponsor reserves the right to discontinue the study at any time, but intends only to exercise this right for valid scientific or administrative reasons.

After such a decision, the Investigator must inform all participating subjects/patients and perform relevant assessments, preferably according to the scheme for the final assessments. All delivered and unused study products and other study materials must be returned and all CRFs completed as far as possible.

15.7 Reporting and publication

15.7.1 Clinical study report

A summarising report must be submitted to the applicable IEC within 12 months after completion of the study (in accordance with LVFS 2011:19, Chapter 9).

A clinical study report (CSR), in compliance with ICH E3; *Structure and content of clinical study reports*, describing the conduct of the study and the results obtained, will be prepared by CTC. The report will be reviewed and approved by, as a minimum, the Principal Investigator,

the Statistician and the Sponsor. The study results will be reported in the EudraCT database per applicable regulations within 12 months after completion of the study.

15.7.2 Annual safety report

If the study duration exceeds one year, the Sponsor must submit an annual safety report to the CA and to the IEC. The report shall summarize all SAEs and contain an update of the risk-benefit evaluation if there has been any change since the approval of the clinical study.

15.7.3 Confidentiality and ownership of study data

Any confidential information relating to the investigational product or the study, including any data and results from the study, will be the exclusive property of the Sponsor. The Investigator and any other persons involved in the study will protect the confidentiality of this proprietary information belonging to the Sponsor.

15.7.4 Publication

The results from this study may be submitted for publication at the discretion of the Sponsor.

15.8 Archiving

The Principal Investigator is responsible for maintaining essential documents, (as defined in ICH E6 GCP, Section 8) for 10 years after finalization of the CSR. This includes any original source documents related to the study, the Patient/Subject Identification List (providing the sole link between named subject/patient source records and anonymous CRF data), the original signed ICFs and detailed records of disposition of IMP.

It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

The Sponsor will archive the Trial Master File in accordance with ICH E6 GCP, Section 8 and applicable regulatory requirements.

16 DATA MANAGEMENT

16.1 Case report form

Data will be collected in paper CRFs specifically designed for this study. The Investigator or an authorised person will record subject data in the CRF in a precise and accurate manner. Abbreviations should not be used. The Investigator is responsible for the data entered and sign off the CRF at each visit and at the end of the study. The data should be recorded as soon as they are generated. CRF entries must be made with an archive resistant pen. Any correction should be marked with a single bar through the error and the correct information should be written next to it. All corrections must be initialled and dated. Correction fluid must not be used. Only persons authorised by the Investigator are allowed to make entries to the CRF.

A Case Report Form (CRF) is required and should be completed for each included subject. The completed original CRFs forms as templates are the sole property of CTC AB and should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from CTC AB.

16.2 Database management plan and database design

Detailed information on data management will be described in a study-specific Data Management Plan (DMP). The person entering data into the database is not allowed to attempt any personal interpretation or to make any decisions on the data other than self-evident corrections as listed in the study-specific Data Entry Instructions or Data Handling Report. Single data entry type will be applied.

Data validation/data cleaning procedures are designed to assure validity and accuracy of clinical data. These procedures consist of manual reviewing during data entry and computerised edit checks and queries for identifying data values that are outside the allowed range, protocol violations, incomplete or inconsistent. The Data Validation Plan specifies the checks that are to be performed on subject data for the study. All study-specific and standard data validation programming will be tested in a separate testing environment prior to use on production data.

16.3 External data

External data consists of data that is not recorded in CRFs. Data may be received in electronic format or paper printout. Key variables are defined in order to uniquely identify each sample record. File and data formats are agreed with the external data provider. Any electronically transferred data must contain origin, date created, date sent and number of records at minimum.

16.4 Medical encoding

Medical encoding will be performed by trained personnel at CTC. AEs and medical history verbatim terms are encoded using the Medical Dictionary of Regulatory Activities (MedDRA), latest version available when approving the DMP. Prior and concomitant medications will be coded according to the World Health Organisation (WHO) Anatomic Therapeutic Chemical (ATC) classification system.

All coding will be approved by Sponsor.

16.5 Database lock

When all data have been entered and discrepancies solved, the database will be locked and the data will be analysed. The data cleaning process will be performed in close collaboration between the Sponsor and CTC.

17 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The following is an outline of the statistical methodology that will be used to analyze this study. A more detailed description will be provided in a separate statistical analysis plan (SAP) which may also include additional exploratory analyses not explicitly mentioned in the following sections. The SAP will be finalized before closure of the study database and deviations from the SAP will be reported and justified in the clinical study report.

17.1 General

Data will be presented in terms of number (N), arithmetic mean, standard deviation (SD), median, minimum and maximum value.

Categorical data will be presented as counts and percentages. When applicable, summary data will be presented by treatment, and by assessment time. Individual subject data will be listed by subject number, treatment, and, where applicable, by assessment time.

Descriptive statistics will be used for the reporting of the results.

17.2 Determination of sample size

Part 1: Based on previous experience with the described methodology, a total of 20 subjects will be enough to reliably detect a clinically significant increased plaque acidogenicity with the pouched products versus the negative control.

Part 2: A 6 week observation period is reasonable to assess putative changes in the oral mucosa resulting from use of the nicotine pouches given that “snus lesions” among habitual snus users regress within a few weeks after cessation of exposure (Wallström et al, [1999]^[3]). A 6-week observation period is also supported by the fact that the other measures of oral health to be assessed (biofilm acidogenicity, oral microflora, plaque amount) are known to potentially change within a few weeks. With an estimated dropout rate of 25% a total of 45 fully evaluable subjects are expected with a total inclusion of 60 subjects. Descriptive statistics will be used for reporting the results of monitoring of the oral mucosa and for subjective adverse symptoms. Each subject receives six weeks’ treatment.

17.3 Analysis data sets

17.3.1 Full analysis set

Part 1:

The Full Analysis Set (FAS) will consist of all subjects who have been randomised and received at least one dose of the product. This population will be used as Safety analysis set.

Part 2:

The Full Analysis Set (FAS) will consist of all enrolled subjects. This population will be used as Safety analysis set.

17.3.2 Per protocol analysis set

Part 1:

The Per Protocol Analysis Set (PPAS) will consist of all subjects who have been randomised and completed the study period without any major protocol deviations. All protocol violations will be judged as major or minor at the clean file meeting.

Part 2:

The Per Protocol Analysis Set (PPAS) will consist of all subjects who have been enrolled and completed the study period without any major protocol deviations. All protocol violations will be judged as major or minor at the clean file meeting.

17.4 Description of study population for both parts

17.4.1 Demographics and baseline characteristics

Descriptive statistics for demographics, weight and height will be presented by product.

17.4.2 Medical/surgical history and prior/concomitant medication

Medical/surgical history and prior/concomitant medications will be presented by product using descriptive statistics and listings.

17.4.3 Treatment compliance

The number of subjects treated in each treatment period and their product will be tabulated. In Part 2 it will also be tabulated to which extent participants replaced their habitual snus with study products.

17.5 Analysis of primary endpoints

17.5.1 Dental plaque acidogenicity Part 1

Assessment of dental plaque acidogenicity for 60 minutes of use of nicotine pouch will be described using AUC and changes from 0 minutes to 60 minutes and presented using summary statistics.

17.5.2 Dental plaque acidogenicity Part 2

Assessment of dental plaque acidogenicity for 6 weeks of use of nicotine pouch will be described using change from baseline to 6 weeks and presented using summary statistics.

17.6 Analysis of secondary endpoints

17.6.1 Adverse events Part 1 and Part 2

All AE data will be fully listed by Investigator terms and MedDRA Preferred Term (PT). AE data will be summarised by System Organ Class (SOC) and PT.

17.6.2 Biofilm acidogenicity Part 2

Changes compared to baseline in the oral microflora at 2, 4 and 6 weeks

17.6.3 Changes in oral microflora Part 2

Biofilm acidogenicity at 2, 4 and 6 weeks compared to baseline

17.6.4 Oral mucosal lesions Part 2

Appearance and number of oral mucosal lesions (including presence and grade of “snus lesions” at the site where the pouches typically are placed by the consumer), comparisons will be made with baseline findings

17.7 Statistical/analytical issues

17.7.1 Adjustments for covariates

Not applicable

17.7.2 Handling of dropouts or missing data

No imputations for missing values will be used

17.7.3 Multi-centre studies

Not applicable

17.7.4 Multiple comparison/multiplicity

Not applicable

17.7.5 Examination of subgroups

Not applicable

17.7.6 Interim analyses and data monitoring

Not applicable

18 APPENDICES

18.1 Signature page

We, the undersigned, have read and understood the protocol specified above, and agree on the contents. The Study Protocol and the Clinical Trial Agreement will serve as a basis for co-operation in the study.

Sponsor signatory

(b) (4), (b) (6)

Principal Investigator

(b) (4), (b) (6)

18.2 Declaration of Helsinki

http://www.up.ac.za/media/shared/Legacy/sitefiles/file/45/2875/declarationofhelsinki_fortaleza_brazil_2013.pdf

19 REFERENCES

1. Axéll T, Mörnstad H, Sundström B. The relation of the clinical picture to the histopathology of snuff dipper's lesions in a Swedish population. *J Oral Pathol* 1976;5:229-36.
2. Andersson G, Axéll T. Clinical appearance of lesions associated with the use of loose and portion-bag packed Swedish moist snuff: a comparative study. *J Oral Pathol Med* 1989;18:2-7.
3. Wallström M, Sand L, Nilsson F, Hirsch JM. The long-term effect of nicotine on the oral mucosa. *Addiction* 1999;94(3):417-23.
4. Lingström P, Imfeld T, Birkhed D. Comparison of three different methods for measurement of plaque - phin humans after consumption of soft bread and potato chips. *J Dent Res* 1993;72:865- 870.
5. Persson A, Lingström P, van Dijken JW. Effect of a hydroxyl ion - releasing composite resin on plaque acidogenicity. *Caries Res* 2005;39:201-206.
6. Silness J, Loe H. Periodontal disease in pregnancy. II. Correlation between oral hygiene and periodontal condition. *Acta Odontol Scand* 1964;22:121-135.
7. Kristoffersson K, Bratthall D. Transient reduction of *Streptococcus mutans* interdentally by chlorhexidine gel. *Scand J Dent Res* 1982;90:417-422.

16.1.2 Sample Case Report Form (Unique Pages Only)

Swedish Match 17-02 eCRF specification v. 1.0

SM 17-02

Open observational study of oral health associated with use of a non-tobacco based nicotine pouch (ZYN®) among current daily snus users.

(b) (4)



SM 17-02

(b) (4)



SM 17-02 / study start

Start

Event description

Informed Consent

Informed Consent

4

Start / Informed Consent

Informed Consent

Informed consent #1

No

Yes

Date of signing the informed
consent form

Study Part #2

Part A

Part B

Randomization Number

Informed Consent - Code Lists

#1 Informed consent

NO INFORMED CONSENT OBTAINED	No
INFORMED CONSENT OBTAINED	Yes

#2 Study Part

A	Part A
B	Part B

(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



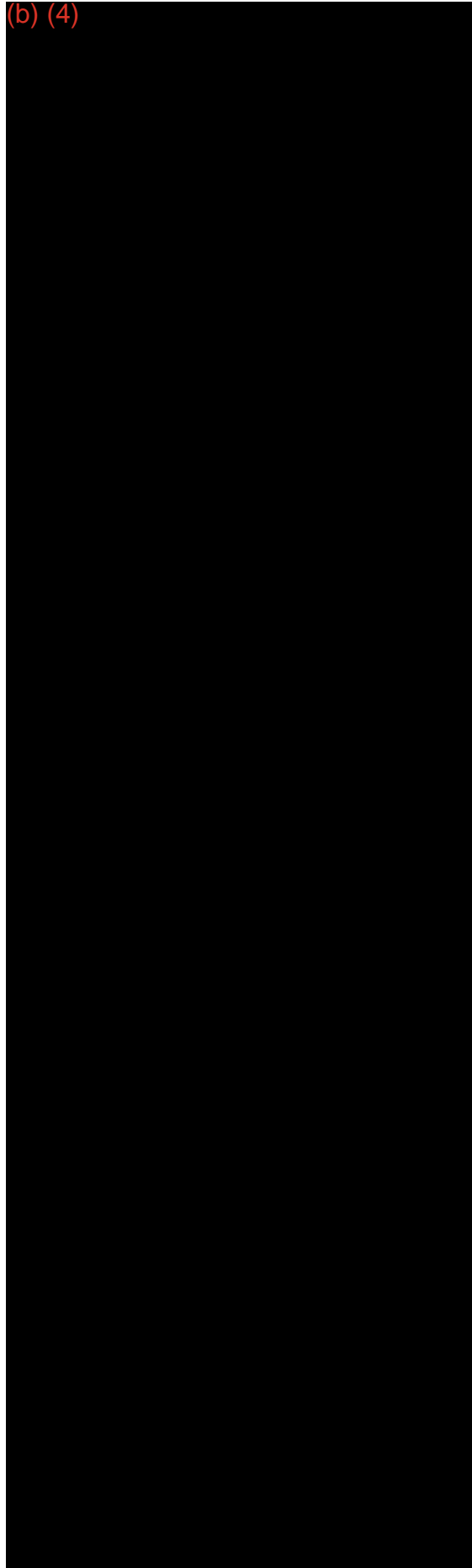
(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



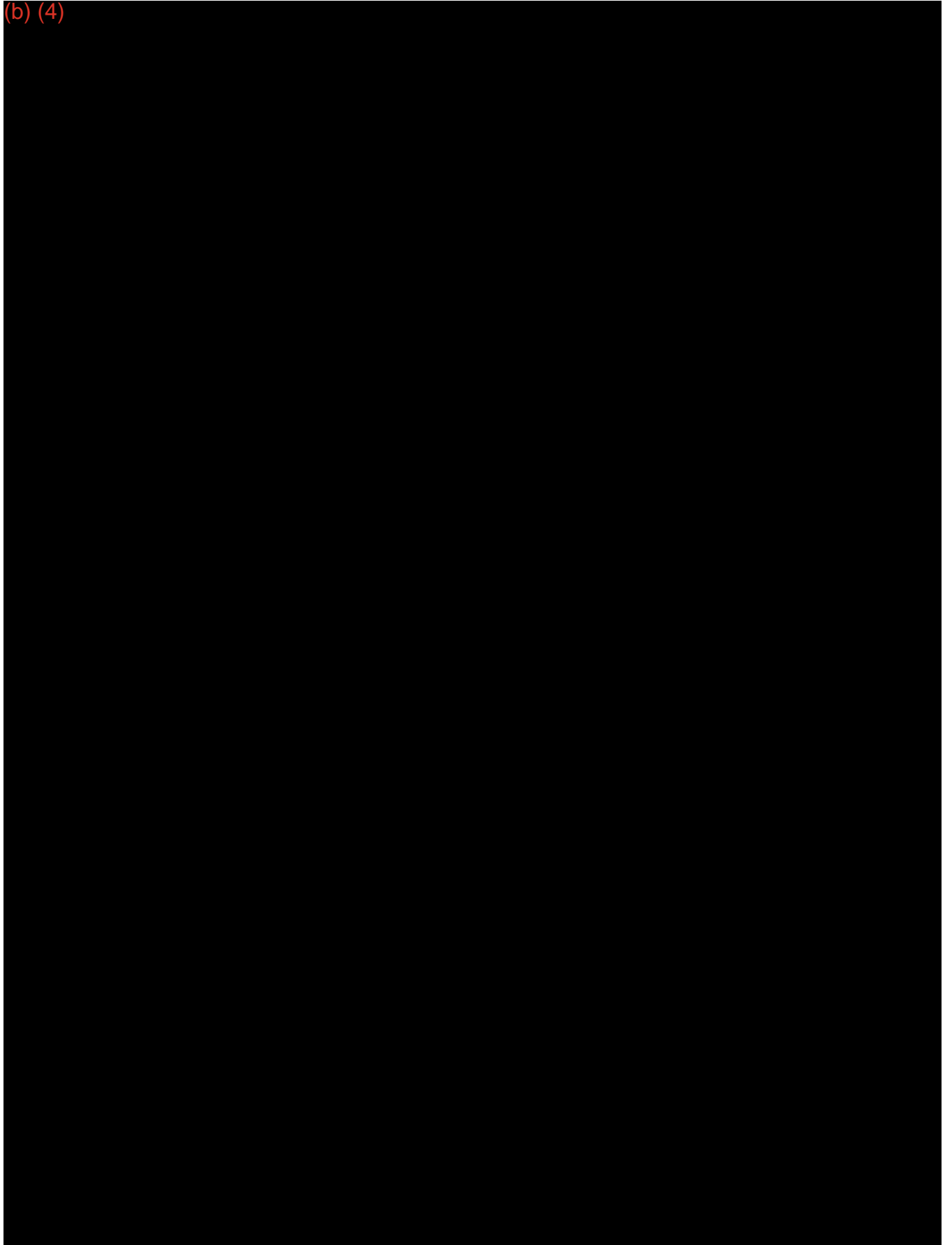
(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



16.1.3 IEC Approval Including List of IEC Members. Representative Written Subject Information and Sample Consent Form

Approval IEC: Regional Ethics Committee in Göteborg, chair Göran Bodin

SM 17-02 Part 1 Subject Information and Informed Consent Form v. 2.0 13OKT2017

SM 17-02 Part 2 Subject Information and Informed Consent Form v. 2.0 13OKT2017

Information for research subjects in part 1, Crossover stage with multiple treatments

Study number: SM17-02

Study title: A study examining the oral health of daily snus users when using tobacco-free nicotine pods (ZYN®).

Request for participation

You are hereby invited to participate in a study to investigate the status of dental health following the use of tobacco-free nicotine-containing snus and tobacco-based snuff, which will be conducted by the company Swedish Match AB, Sweden (sponsor), in collaboration with Professor Peter Lingström at Gothenburg University.

The study sponsor has developed a product that, similar to regular snus, contains nicotine but does not contain tobacco, and wishes to evaluate the product with regard to its impact on dental health.

The study will be carried out in two parts and your participation is requested in the first part, the crossover stage with multiple treatments.

This information describes the reasons why the study is being carried out, how it will be conducted and the potential risks and symptoms that may result from participation in the study. It also describes how data that will be collected is processed.

Please take the time to review this information thoroughly. If anything is unclear, it is important that you inquire with the researcher. If you decide to participate in the study, you will receive a copy of this information to keep along with a copy of the signed consent form.

Background and purpose

There are approximately 1 million snus users in Sweden. Snus, which is a tobacco-based product, can contain small amounts of carcinogenic substances. Therefore, a tobacco-free snus product would be a good substitute for snus that contains tobacco. The purpose of the study is to investigate the impact of non-tobacco portion snus on dental health, which will be done in the crossover stage by measuring acidity (pH) in dental plaque. Two types of tobacco-free pods will be tested, ZYN Smooth 3 mg and ZYN Peppermint 3 mg, which have nicotine concentrations that are somewhat lower than that in the most commonly used portion snus. In addition to the two pods, there will also be a positive control, a treatment that will result in a higher degree of plaque acidity, and a negative control, a treatment that is known to have no effect on plaque acidity. The positive control in the study will be a sugar solution, while the negative control will be a xylitol solution.

The Regional Ethical Review Board in Gothenburg has approved the implementation of the study.

Participation in the study

Participation in the study is fully voluntary. You have the right to discontinue your participation in the study at any time without providing an explanation. The researcher in charge may decide to discontinue your participation in the study if it is deemed necessary for you or if you fail to comply with the restrictions participation in the study requires. The study's sponsor can decide to discontinue the study. If your participation in the study is discontinued for any reason, it is important that you come in for the follow-up visits the researcher considers necessary for your safety.

The study will be carried out in two parts and your participation is requested in the first part, what is known as the crossover stage. In this part of the study, you will be given one treatment, i.e. one of the study products or a positive or negative control, at each visit for about four weeks.

You will be continuously informed of new and important study data that may have an impact on your decision to continue participation.

What is involved in the crossover stage of the study?

The study will be conducted at the research laboratory at the Department of Cariology, Institute of Odontology, at Gothenburg University. 20 healthy volunteer men or women over the age of 19 will participate

in the crossover stage of the study.

The study product will be given as a "portion snus" that will be placed inside the upper lip, while the negative and positive control will be a solution that will be swilled in the mouth.

Your participation in the crossover stage of the study will consist of a total of up to 5 visits to the laboratory and a phone follow-up. The first visit is a screening, where you will be examined to determine your suitability as a study participant, while visits two through five are treatment visits which are described below.

A final follow-up call will be made 5-10 days after the final treatment visit. Your participation in this study will last about five weeks. More detailed information about each visit is given below.

Visit 1 (approximately 1 hour) screening visit

During this visit, you will be provided with information about the study and have the opportunity to ask questions individually. If you decide to participate in the study, you will be required to sign a consent form. You will then be asked to fill out a questionnaire with questions about your past and present illnesses and use of medications and homeopathic remedies. You will be asked to provide urine samples for a pregnancy test (female participants). If you are found to be a suitable study participant, you will be called in for visit 2 and so on.

Visit 2 through 5 (approximately 1.5 hours) treatment visit

The study consists of a total of 4 test days of approximately 1.5 hours each, with a minimum one week break in between each test day. You will book your test date with the staff at the laboratory.

At each treatment visit, the staff will ask you how you have been feeling since the last visit and if you have used any medications. You will then be given one of the following doses:

1. One portion pouch of a tobacco-free pod ZYN® Smooth 3 mg for 60 minutes.
2. One portion pouch of a tobacco-free pod ZYN® Peppermint 3 mg for 60 minutes.
3. Negative control, 10% xylitol solution, which is swilled in the mouth for 60 seconds.
4. Positive control, 10% sugar solution, which is swilled in the mouth for 60 seconds.

The exact order in which you receive the different preparations will be pre-determined according to an established schedule. Since all subjects participating in the study will receive all treatments, it can be said that the treatments are crossed, which means that this part of the study is called crossover with multiple treatments.

You will be instructed to keep the portion pouch under your upper lip for 60 minutes while measurements of acidity (pH) are taken in the mouth. During the laboratory visits, you will receive a negative or positive control. You will be asked to swill the respective solution in your mouth for 60 seconds then spit out the solution. Acidity (pH) measurements are then taken in the mouth for 60 minutes.

A follow-up call will be made 5-10 days after the final treatment visit

You will be called in to the laboratory five to ten days after your final visit and we will follow up on your general health and any medications you may be taking.

What do I need to consider during the study period?

- In order for the results of the study to be as reliable as possible, certain restrictions must be observed.
- You may not participate in any other medical study during the time you participate in this study.
- You must not use dental floss in the 72 hours before your visit to the laboratory.
- You must not brush your teeth in the 48 hours before your visit to the laboratory.
- You must not eat or drink in the two hours before your visit until you receive your dose.
- You may not use any drugs. If you need to take any medications during the study period, you must notify the lead researcher before the test day or when you arrive at the laboratory.
- Women must not become pregnant during the study period.
- You must not take antibiotics in the four-week period before the study and during the study period.



Side effects, risks and symptoms

As with normal snus products, the test product can cause a stinging sensation under the lip. However, this is not likely for habitual snus users. The test product is expected to provide the same approximate nicotine dose as a portion pouch of regular tobacco-based snus, therefore providing the same “nicotine buzz”. In the event that the dose you receive is higher than what you are used to, common symptoms include increased saliva production, mild nausea, hiccups, dizziness or heart palpitations.



In general, nicotine has an effect on blood circulation, increases heart rate and constricts blood vessels. Individuals with a history of heart problems, such as irregular heartbeat or angina, should therefore avoid nicotine. The study will be interrupted if serious symptoms arise.

If, during the course of the study, you feel any discomfort or other symptoms, you should immediately talk with one of the study staff members.

Benefits of participation in the study

You will not receive any direct benefit for participating in the study nor will you benefit directly from the results of the study other than the fact that you will receive a thorough dental examination.

Insurance

The study sponsor has taken out insurance that covers the cost of potential injury that may be attributed to the use of its product. Gothenburg University also holds liability insurance that covers any injury that may arise when you are present at the laboratory. If you believe your participation in the study has resulted in an injury, you must contact the researcher in charge.

Processing of personal data (Personal Data Act SFS 1998:204)

We will collect your personal data during the study (this is collectively called "Study data"). Study data includes your date of birth, sex, health information (such as previous illnesses) and results from examinations during the study. Your consent to the processing of study data will remain applicable unless you decide to withdraw your consent. All information in the study is handled in accordance with applicable confidentiality regulations.

All study data will be encoded, i.e., your name and personal identity number will not be collected but will be replaced with a code. Only the researcher in charge and his or her and staff members will be able to access the code key that allows the personal data to be directly linked to you. The collected study data will be processed, (i.e. stored, processed and compiled) both manually and using computerised technology. The study data will be processed for research purposes. Once a year, you have the right to submit a written request to learn what personal data has been recorded, from where this data was obtained and to which categories of recipients this data may have been disclosed. Gothenburg University is the data controller for your personal data. You are welcome to contact the university office if you would like to receive an extract of the personal data that has been stored and for any assistance with data rectification (University Lawyer Kristina Ullgren, Universitetsledningens kansli, Box 100, 405 30 Gothenburg, telephone 031- 7861092). The application must be signed and contain the study name. You also have the right to have inaccurate personal data corrected. If you would like to exercise this right, you should contact the researcher in charge.

Collected study data will be transferred to the company in charge, the sponsor and companies working on behalf of the sponsor. The sponsor and Gothenburg University are each responsible for following the Personal Data Act. Your study data may be transferred to recipients in countries outside Sweden and the European Union (EU). These countries may have laws that do not require the same high level of protection with regard to the processing of personal data.

Results may be published in a medical journal, however, this will be done in a way that does not disclose your identity. If you have any questions about this, you are welcome to contact the researcher in charge.

If you decide to withdraw your consent, the researcher in charge will not collect or process any new study data. However, the study data collected before you withdrew your consent will be used and processed by the study sponsor.

Financial remuneration

For your participation in the crossover stage of the study, you will receive taxable remuneration amounting to SEK 2,900.

No remuneration is provided for lost income or travel expenses. If you only participated in the initial study visit, the health check, no remuneration will be paid.

Your participation may be discontinued before the end of the study for a number of reasons



- if you decide to discontinue your participation
- if continuation of the study would be harmful for you
- if you need to take a medication that is not permitted during the study
- if you fail to follow established restrictions
- if all of the treatments cannot be carried out due to results from the previous groups.

If the researcher/study sponsor in charge decides to discontinue your participation before the end of the study, you will receive remuneration in proportion to your actual participation.

If you have any further questions or need to contact us, you are welcome to call:

	Name	Telephone
Researcher in charge:	Professor Peter Lingström	(b) (4), (b) (6)
Research assistant in charge:	(b) (4), (b) (6) - [REDACTED] [REDACTED]	(b) (6), (b) (4)



Screening number: _____

CONSENT OF RESEARCH SUBJECTS

I have been verbally informed of the study described above and reviewed the attached printed information containing the details of the study.

I have been provided with the opportunity to submit questions and have any questions answered.

I hereby consent:

- To participate in the study
- For my study data (personal data) to be processed as described and that my data may be transferred to countries outside Sweden and the European Union (EU).
- For a person designated by the study sponsor or a person working for a supervisory authority, under a duty of professional secrecy, to compare collected study data with relevant information in my medical record.
- For my samples to be used as described.

I am aware that my participation in the study is fully voluntary. I am aware that I can discontinue my participation at any time without providing further explanation and without this affecting my future dental care.

Signature of research subject:

.....
Signature

.....
date (research subject signature date)

.....
Printed name

Signature of the researcher who has provided the information and received this signed form:

.....
Signature

.....
Date

.....
Printed name



Screening number: _____

Information for research subjects in part 2, 6-week follow-up stage

Study number: SM17-02

Study title: An open observational study examining the changes in oral health in daily snus users when using tobacco-free nicotine pods (ZYN®).

Request for participation

You are hereby invited to participate in a study to investigate the status of dental health following the use of tobacco-free nicotine-containing snus portions, which will be conducted by the company Swedish Match AB, Sweden (sponsor), in collaboration with Professor Peter Lingström at Gothenburg University.

The study sponsor has developed a product that, similar to regular snus, contains nicotine but does not contain tobacco, and wishes to evaluate the product with regard to its impact on dental health.

The study will be carried out in two parts and your participation is requested in the second part, the 6-week follow-up stage.

This information describes the reasons why the study is being carried out, how it will be conducted and the potential risks and symptoms that may result from participation in the study. It also describes how data that will be collected is processed.

Please take the time to review this information thoroughly. If anything is unclear, it is important that you inquire with the researcher. If you decide to participate in the study, you will receive a copy of this information to keep along with a copy of the signed consent form.

Background and purpose

There are approximately 1 million snus users in Sweden. Snus, which is a tobacco-based product, can contain small amounts of carcinogenic substances. Therefore, a tobacco-free snus product would be a good substitute for snus that contains tobacco. The purpose of the study is to investigate the effect on dental health of using non-tobacco-based portion snus in different strengths and flavours. During the study, you will be given the choice of using ZYN® Smooth, ZYN® Peppermint or ZYN® Cinnamon, with a nicotine strength of 3 mg or 6 mg. You are encouraged to replace as much of your regular snus use as possible with ZYN snus.

The Regional Ethical Review Board in Gothenburg has approved the implementation of the study.

Participation in the study

Participation in the study is fully voluntary. You have the right to discontinue your participation in the study at any time without providing an explanation. The researcher in charge may decide to discontinue your participation in the study if it is deemed necessary for you or if you fail to comply with the restrictions participation in the study requires. The study's sponsor can decide to discontinue the study. If your participation in the study is discontinued for any reason, it is important that you come in for the follow-up visits the researcher considers necessary for your safety.

The study will be carried out in two parts and your participation is requested in the second part, what is known as the 6-week follow-up stage. In this part of the study, you will be given one treatment, one of the study products that you choose yourself, which you will use for approximately six weeks freely as an alternative to your usual snus brand. You are encouraged to replace as much of your regular snus use as possible with ZYN snus.

You will be continuously informed of new and important study data that may have an impact on your decision to continue participation.

What does the 6-week follow-up stage of the study entail?

During the study, examinations will be performed at the research laboratory at the Department of Cariology, Institute of Odontology, at Gothenburg University. In the 6-week follow-up stage of the study, 60 healthy volunteer men and women over the age of 19 will participate.



The study product, which is a "portion snus", is placed inside the upper lip in the same manner as regular snus. During the study period, you can replace your regular snus with the study product and are therefore able to decide for yourself how much you will use, however, you are encouraged to replace your regular snus as much as possible.

Your participation in the 6-week follow-up stage of the study will consist of a total of up to 5 visits to the laboratory and a phone follow-up. The first visit is a screening, where you will be examined to determine your suitability as a study participant. At the end of the screening visit, you will bring samples of different types of the study product home, which you will try out for two to four days so that on visit two you will be given the right amount of study product to last the next 2 weeks. Visits three through five are treatment visits and are described in detail below. During the time you use the study product at home, you will fill out a log indicating whether you have used the product.

A final follow-up call will be made 5-10 days after the final treatment visit. Your participation in this study will last about seven weeks. More detailed information about each visit is given below.

Visit 1 (approximately 1 hour) Screening visit

During this visit, you will be provided with information about the study and have the opportunity to ask questions individually. If you decide to participate in the study, you will be required to sign a consent form. You will then be asked to fill out a questionnaire with questions about your past and present illnesses and use of medications and homeopathic remedies. You will be asked to provide urine samples for a pregnancy test (female participants). You will undergo an oral examination that will be photographed. The laboratory will measure the degree of acidity (pH) in your mouth, assess the amount of plaque and take samples to assess which bacteria are present. If you are found to be a suitable study participant, you will be called in for visit 2 and so on. If you decide you would like to participate in the study, before you go home, you will be given samples of the study product to try for a few days until you come back for visit 2.

Visit 2 (approx. 30 min)

During the visit, you will notify us which study product you have chosen, and you will be given an adequate supply of the product to last the next two weeks until the next visit.

Visits 3-5 (approximately 1.5 hours) treatment visit

The study will have a total of three visits at about 1.5 hours each, with a gap of two weeks between each visit. You will book your test date with the staff at the laboratory.

At each visit, the staff will ask you how you have been feeling since the last visit and if you have used any medications. The following evaluations will also be performed:

- Oral examination and photo documentation.
- Measurements of oral acidity (pH).
- Assessment of plaque amounts.
- Sample collection for evaluation of bacteria

After the evaluations have been completed, you will be able to book a time for the next visit and collect the study product you need for the next two weeks.

A follow-up call will be made 5-10 days after the final treatment visit

You will be called in to the laboratory five to ten days after your final visit and we will follow up on your general health and any medications you may be taking.

What do I need to consider during the study period?

- In order for the results of the study to be as reliable as possible, certain restrictions must be observed.
- You may not participate in any other medical study during the time you participate in this study.

- You must not use dental floss in the 72 hours before your visit to the laboratory.
- You must not brush your teeth in the 48 hours before your visit to the laboratory.
- You must not eat or drink in the two hours before your visit until you receive your dose.
- You may not use any drugs. If you need to take any medications during the study period, you must notify the lead researcher before the test day or when you arrive at the laboratory.
- Women must not become pregnant during the study period.
- You must not take antibiotics in the four-week period before the study and during the study period.



Side effects, risks and symptoms

As with normal snus products, the test product can cause a stinging sensation under the lip. However, this is not likely for habitual snus users. The test product is expected to provide the same approximate nicotine dose as a portion pouch of regular tobacco-based snus, therefore providing the same "nicotine buzz". In the event that the dose you receive is higher than what you are used to, common symptoms include increased saliva production, mild nausea, hiccups, dizziness or heart palpitations. In general, nicotine has an effect on blood circulation, increases heart rate and constricts blood vessels. Individuals with a history of heart problems, such as irregular heartbeat or angina, should therefore avoid nicotine. The study will be interrupted if serious symptoms arise.

If, during the course of the study, you feel any discomfort or other symptoms, you should immediately talk with one of the study staff members.

Benefits of participation in the study

You will not receive any direct benefit for participating in the study nor will you benefit directly from the results of the study other than the fact that you will receive a thorough dental examination.

Insurance

The study sponsor has taken out insurance that covers the cost of potential injury that may be attributed to the use of its product. Gothenburg University also holds liability insurance that covers any injury that may arise when you are present at the laboratory. If you believe your participation in the study has resulted in an injury, you must contact the researcher in charge.

Processing of personal data (Personal Data Act SFS 1998:204)

We will collect your personal data during the study (this is collectively called "Study data"). Study data includes your date of birth, sex, health information (such as previous illnesses) and results from examinations during the study. Your consent to the processing of study data will remain applicable unless you decide to withdraw your consent. All information in the study is handled in accordance with applicable confidentiality regulations.

All study data will be encoded, i.e., your name and personal identity number will not be collected but will be replaced with a code. Only the researcher in charge and his or her and staff members will be able to access the code key that allows the personal data to be directly linked to you. The collected study data will be processed, (i.e. stored, processed and compiled) both manually and using computerised technology. The study data will be processed for research purposes. Once a year, you have the right to submit a written request to learn what personal data has been recorded, from where this data was obtained and to which categories of recipients this data may have been disclosed. Gothenburg University is the data controller for your personal data. You are welcome to contact the university office if you would like to receive an extract of the personal data that has been stored and for any assistance with data rectification (University Lawyer Kristina Ullgren, Universitetsledningens kansli, Box 100, 405 30 Gothenburg, telephone 031- 7861092). The application must be signed and contain the study name. You also have the right to have inaccurate personal data corrected. If you would like to exercise this right, you should contact the researcher in charge.

Collected study data will be transferred to the company in charge, the sponsor and companies working on behalf of the sponsor. The sponsor and Gothenburg University are each responsible for following the Personal Data Act. Your study data may be transferred to recipients in countries outside Sweden and the European Union (EU). These countries may have laws that do not require the same high level of protection with regard to the processing of personal data.

Results may be published in a medical journal, however, this will be done in a way that does not disclose your identity. If you have any questions about this, you are welcome to contact the researcher in charge.

If you decide to withdraw your consent, the researcher in charge will not collect or process any new study data. However, the study data collected before you withdrew your consent will be used and processed by the study sponsor.

Financial remuneration



For your participation in the 6-week follow-up stage of the study, you will receive taxable remuneration amounting to SEK 4,900.

No remuneration is provided for lost income or travel expenses. If you only participated in the initial study visit, the health check, no remuneration will be paid.

Your participation may be discontinued before the end of the study for a number of reasons:

- if you decide to discontinue your participation
- if continuation of the study would be harmful for you
- if you need to take a medication that is not permitted during the study
- if you fail to follow established restrictions
- if all of the treatments cannot be carried out due to results from the previous groups.

If the researcher/study sponsor in charge decides to discontinue your participation before the end of the study, you will receive remuneration in proportion to your actual participation.

If you have any further questions or need to contact us, you are welcome to call:

	Name	Telephone
Researcher in charge:	Professor Peter Lingström	(b) (6), (b) (4)
Research assistant in charge:	(b) (4), (b) (6) = [REDACTED] [REDACTED]	(b) (6), (b) (4)



Screening number: _____

CONSENT OF RESEARCH SUBJECTS

I have been verbally informed of the study described above and reviewed the attached printed information containing the details of the study.

I have been provided with the opportunity to submit questions and have any questions answered.

I hereby consent:

- To participate in the study
- For my study data (personal data) to be processed as described and that my data may be transferred to countries outside Sweden and the European Union (EU).
- For a person designated by the study sponsor or a person working for a supervisory authority, under a duty of professional secrecy, to compare collected study data with relevant information in my medical record.
- For my samples to be used as described.
- To my oral cavity's being photo documented.

I am aware that my participation in the study is fully voluntary. I am aware that I can discontinue my participation at any time without providing further explanation and without this affecting my future dental care.

Signature of research subject:

.....
Signature

.....
date (research subject signature date)

.....
Printed name

Signature of the researcher who has provided the information and received this signed form:

.....
Signature

.....
Date

.....
Printed name



English
It is hereby certified that this translation into *Swedish* agrees with the original document in and was carried out by the officially registered translation agency A & Adekvat AB in accordance with established Swedish law.
A & ADEKVAT AB, Djursholmsvägen 91, S-183 57 TÄBY
Tel. +46 8 756 67 08 info@adekvat.se, Stockholm

(b) (6)

LEO KANTOR
Head translator

Regionala etikprövningsnämnden i Göteborg

Projektansvarig:

Peter Lingström
GU/Sahlgrenska akademien
Inst för odontologi, avd f cariologi
Box 450
405 30 Göteborg

Dnr: Exp. 2017-10-12
778-17 2017-10-25

Forskningshuvudman: Göteborgs universitet

Närvarande beslutande:

Göran Bodin, *ordförande*
Staffan Björck, *bitr. vetenskaplig sekreterare*

Ledamöter med vetenskaplig kompetens:

Peter Andiné
Jane Carlsson
Ingrid Emanuelsson
Per-Anders Jansson
Margareta Kreuter
Max Levin (*deltog ej i ärende 737-17 p g a jäv*)
Per Ramberg
Per Örtenwall
Anna-Lena Östberg (*deltog ej i ärende 763-17 p g a jäv*)

Granskad och godkänd som sekreterarärende
Göteborg (b) (6)

Staffan Björck, docent, bitr vetenskapl sekr
Avdelning för Medicinsk forskning 1
Regionala Etikprövningsnämnden i Göteborg

Ledamöter som företräder allmänna intressen:

Bengt Andersson
Jane Bredin
Britt Dovmyr
Ulla-Britt Hagström (*deltog ej i ärende 738-17 p g a jäv, deltog ej i ärenden 769-17, 775-17, 776-17, 778-17 samt 779-17*)
Heléna Okomdal Holmgren

Projekttitel: En öppen observationsstudie som undersöker effekt på munhälsa hos dagliga snus användare vid användning av tobaksfria nikotinpods (ZYN(R))

Projekt ID: SM 17-02

Version: XXSEP2017

Beslutsprotokoll från sammanträde med Regionala etikprövningsnämnden i Göteborg, Medicinska avdelningen (M 1), den 9 oktober 2017

Föredragande: Anna-Lena Östberg (*deltog ej i diskussion och beslut*)

Sekreterarärende efter komplettering

Nämnden önskar viss komplettering innan godkännande kan ske. Från vilken oberoende grupp kommer monitorn till studien? Varifrån kommer sjuksköterskan som tar första kontakten med patienterna? Nämnden önskar en förklaring till varför det finns två annonstexter. Ska dessa publiceras samtidigt? Vilken är det som gäller?

Patientinformationerna bör ses över då det finns en del svåra ord och begrepp, t ex cross-over, negativ kontroll etc. I patientinformationen beskrivs att forskningsdata kan komma att överföras till mottagare i andra länder. Detta bör också beskrivas i ansökan under punkt 2:6.

De specifika kompletteringar som görs bör anges i ett separat underskrivet följebrev. Textavsnitt som ändras i ansökningshandlingarna/forskningspersonsinformationens bör tydligt markeras.

Komplettering av ärendet (1 ex) ska ha kommit in till Etikprövningsnämnden inom tre månader från beslutsdatum då ärendet tas upp på nytt. Om komplettering inte inkommit kan ärendet komma att avgöras i befintligt skick.

Att denna avskrift i transumt överensstämmer med originalet intygar

(b) (6)

Lisa D. Hillström, administrativ sekreterare

Screeningnummer: _____

Information till forskningsperson i del 1, Överkorsningsdel med flera behandlingar

Studie nummer: SM17-02

Studietitel: En studie som undersöker munhälsa hos dagliga snus användare vid användning av tobaksfria nikotinpods (ZYN®).

Förfrågan om deltagande

Du tillfrågas härmed om du vill delta i en studie för att undersöka tandhälsa efter användning av tobaksfritt nikotin innehållande snus och tobaksbaserat snus som utförs av företaget Swedish Match AB, Sverige (sponsor) i samarbete med Professor Peter Lingström vid Göteborgs Universitet.

Sponsor i studien har tagit fram en produkt som i likhet med vanligt snus innehåller nikotin men som saknar tobak vilken man vill utvärdera med avseende på påverkan på tandhälsa.

Studien består av två delar och du tillfrågas om deltagande i den första delen, överkorsningsdel med flera behandlingar.

Denna information beskriver varför studien görs, hur den går till samt tänkbara risker och obehag som studien kan medföra. Dessutom beskrivs hur insamlade uppgifter att behandlas.

Ta gärna god tid på dig att läsa denna information. Om något är oklart är det viktigt att du frågar prövaren om detta. Om du väljer att delta kommer du att få med dig denna information hem, samt en kopia på det undertecknade samtyckesformuläret.

Bakgrund och syfte

Det finns ca 1 miljon snusare i Sverige. Snus som är baserat på tobak kan innehålla små mängder cancerframkallande ämnen. Ett tobaksfritt snus skulle därför vara ett bra substitut för tobaksinnehållande produkter. Avsikten med studien är att undersöka påverkan på tandhälsan från ett icke-tobaksbaserat portionssnus vilket i överkorsningsdelen kommer att göras genom att mäta surhetsgrad (pH) i plack. Två typer av tobaksfria pods ska testas, ZYN Smooth 3 mg och ZYN Peppermint 3 mg, vilka har en nikotinstyrka som är något lägre än i de vanligaste typerna av portionssnus. Utöver dessa två pods finns det också positiv kontroll, en behandling som man kommer ge en högre surhetsgrad i plack, samt negativ kontroll, en behandling som man vet inte kommer påverka surhetsgraden i plack. Positiv kontroll i studien kommer vara en sockerlösning och negativ kontroll kommer vara en xylitollösning

Regionala Etikprövningsnämnden i Göteborg har gett sitt godkännande till att studien genomförs.

Deltagande i studien

Ditt deltagande i studien är helt frivilligt. Du har rätt att när som helst och utan närmare förklaring avbryta ditt deltagande. Ansvarig forskare kan besluta att avbryta ditt deltagande i studien om det bedöms som nödvändigt för dig eller om du inte följer de restriktioner som studien kräver. Studiens sponsor kan besluta att avbryta studien. Om ditt deltagande i studien avbryts är det viktigt att du kommer till de uppföljningsbesök som forskaren anser behövas för din säkerhet.

Studien består av två delar och du tillfrågas om deltagande i den första delen, den s.k. överkorsningsdelen. I denna del av studien ges en behandling, en av studieprodukterna, positiv-, eller negativ kontroll, vid varje besök under ungefär fyra veckors tid.

Du kommer att fortlöpande informeras om nya och viktiga studiedata som kan komma att påverka ditt beslut om fortsatt deltagande.

Hur går överkorsningsdelen av studien till?

Studien kommer att utföras på forskningslaboratoriet vid Avdelningen för cariologi, Institutionen för odontologi, Göteborgs universitet. I överkorsningsdelen av studien kommer 20 friska frivilliga män eller kvinnor över 19 år att delta.

Studieprodukten ges som en "portionssnus" som placeras innanför överläppen medan negativ- och positiv

kontroll är en lösning som sköljs i munnen.

Ditt deltagande i överkorsningsdelen av studien består av totalt upp till 5 besök på laboratoriet samt ett uppföljningssamtal via telefon. Första besöket är ett screeningbesök då du undersöks för lämplighet att delta i studien medan besök två till fem är behandlingsbesök vilka beskrivs nedan.

Ett avslutande uppföljningssamtal görs 5-10 dagar efter sista behandlingsbesök. Ditt deltagande i studie pågår under cirka fem veckor. Nedan ges detaljerad information om varje besök.

Besök 1 (ca 1 timme), screeningbesök

Vid besöket får du information om studien och har möjlighet att ställa frågor enskilt. Om du bestämmer dig för att delta i studien kommer du att få skriva under ett samtycke till att delta. Efter detta får du fylla i ett frågeformulär där du blir tillfrågad om tidigare och nuvarande sjukdomar och användning av läkemedel och naturläkemedel. Du får lämna urinprov för graviditetstest (endast kvinnor). Om du är lämplig att delta i studien blir du kallad till besök 2 och framåt.

Besök 2 till 5, (ca 1,5 timme) behandlingsbesök

Studien omfattar totalt 4 försöksdagar om vardera ca 1,5 timmar, med minst en veckas uppehåll mellan varje försöksdag. Du bokar in försöksdatumen med personal på laboratoriet.

På varje behandlingsbesök kommer personalen fråga dig om hur du mått sedan senaste besöket och om du använt några läkemedel sedan kommer en av följande doseringar att ges:

1. En portionspåse av en tobaksfri pod ZYN® Smooth 3 mg i 60 minuter.
2. En portionspåse av en tobaksfri pod ZYN® Peppermint 3 mg i 60 minuter.
3. Negativ kontroll, 10% xylitolösning som sköljs i munnen under 60 sekunder.
4. Positiv kontroll, 10 % sockerlösning som sköljs i munnen under 60 sekunder.

I vilken ordning som just du får de olika preparaten, bestäms av ett på förhand uppgjort schema. Då varje person som deltar i studien får alla behandlingar kan man säga att behandlingarna korsas vilket gjort att delen av studien kallas överkorsningsdel med flera behandlingar.

Du kommer att instrueras att hålla portionspåsen under överläppen 60 minuter medan mätningar av surhetsgrad (pH) sker i munhålan. Vid de besök du får negativ- eller positiv kontroll får du skölja munnen med respektive lösning under 60 sekunder varefter den spottas ut. Därefter görs mätningar av surhetsgrad (pH) i munhålan under 60 minuter.

Uppföljningssamtal 5-10 dagar efter sista behandlingsbesöket

Du blir uppringt av laboratoriet fem till tio dagar efter det sista besöket och vi följer upp hur det är med din hälsa och din övriga eventuella medicinering.

Vad måste du tänka på under studietiden?

- För att resultaten av studien skall bli så tillförlitliga som möjligt, måste du följa vissa restriktioner.
- Du får inte delta i någon annan medicinsk studie samtidigt med denna.
- Du får inte använda tandtråd 72 timmar innan besöken till laboratoriet.
- Du får inte borsta tänderna 48 timmar innan besöken till laboratoriet.
- Du får inte äta eller dricka från två timmar innan ett besök tills efter doseringen.
- Du får inte använda några droger. Om du behöver ta något läkemedel under studiens gång, måste du meddela försöksledningen detta innan försöksdagen eller när du kommer till forskningslaboratoriet.
- Du som är kvinna får inte bli gravid under studiens gång.
- Du får inte använt antibiotika fyra veckor innan samt under studieperioden.

Eventuella biverkningar, risker och obehag

Liksom vanligt snus kan testprodukten svida under läppen. Detta är dock inte sannolikt bland vanesnusare. Testprodukten förväntas avge ungefär samma nikotindos som en portionsprilla av vanligt tobaksbaserat snus och därmed ge samma "nikotinkick". Vanliga besvär om dosen skulle bli högre än vad du är van vid är ökad salivproduktion, lätt illamående, hicka, känsla av yrsel eller hjärtklappning. Generellt

påverkar nikotin blodcirkulationen, höjer pulsen och drar samman blodkärlen. Personer med olika typer av hjärtproblem, såsom oregelbunden hjärtrytm eller kärlkramp bör därför undvika nikotin. Försöket avbryts om svåra besvär skulle uppstå.

Om Du under studiens gång skulle känna obehag eller besvär skall Du genast tala med någon av personalen.

Fördelar med att delta i studien

Du kommer själv inte att ha någon direkt nytta av att delta i studien eller dra nytta av resultaten som framkommer i studien, förutom att du får en grundlig tandhälsoundersökning.

Försäkring

Sponsorn har tecknat en försäkring som täcker kostnader för skada som anses vara orsakad av deras produkt. Göteborgs universitet har också en ansvarsförsäkring som täcker eventuell skada som uppstår när du vistas på Laboratoriet. Om du tror att du fått en skada som följd av ditt deltagande i studien ska du kontakta ansvarig forskare.

Behandling av personuppgifter (Personuppgiftslagen SFS 1998:204)

Under studien kommer vi att samla in dina personuppgifter (dessa kallas gemensamt för "Studiedata"). Studiedata inkluderar födelsedatum, kön, hälsodata (såsom tidigare sjukdomar) samt resultat av undersökningar i studien. Ditt samtycke till behandling av studiedata gäller för all framtid såvida du inte drar tillbaka det. All information i studien hanteras enligt gällande sekretessbestämmelser.

All studiedata kommer att vara kodad, d.v.s. ditt namn och personnummer samlas inte in, utan ersätts med en kod. Endast ansvarig forskare och dennes medarbetare har tillgång till kodnyckeln med vilken det går att koppla personuppgifterna till dig. Insamlad studiedata behandlas, (d.v.s. lagras, bearbetas och sammanställs) både manuellt och med datorteknik. Ändamålet med behandlingen av studiedata är forskning. Du har rätt att skriftligen en gång om året begära att få veta vilka personuppgifter som har registrerats om dig, varifrån dessa uppgifter har hämtats och till vilka kategorier av mottagare uppgifter eventuellt har lämnats ut. Ansvarig för behandling av dina personuppgifter är Göteborgs Universitet. Du kan vända dig till universitets kansli om du önskar utdrag över de personuppgifter som finns registrerade på dig och eventuell hjälp till rättelse (Universitetsjurist Kristina Ullgren, Universitetsledningens kansli, Box 100, 405 30 Göteborg, telefon 031-7861092). Ansökan ska vara undertecknad och innehålla information om studiens namn. Du kan även begära att felaktiga uppgifter om dig rättas. Du ska i så fall vända dig till studieansvarig forskare.

Insamlad studiedata kommer att överföras till ansvarigt företag, sponsor och till företag som arbetar på uppdrag av sponsor. Sponsor och Göteborgs universitet är var och en ansvariga att följa PUL. Dina studiedata kan komma att överföras till mottagare i länder utanför Sverige och Europeiska Unionen (EU). Dessa länder kan ha lagar som inte har samma höga skydd när det gäller behandling av personuppgifter.

Resultat kan komma att publiceras i en medicinsk tidskrift, dock utan att din identitet uppges. Har du frågor om detta är du välkommen att vända dig till studieansvarig forskare.

Om du drar tillbaka ditt samtycke, kommer ansvarig forskare inte att fortsätta samla in eller behandla nya studiedata. De studiedata som samlats in innan du drog tillbaka ditt samtycke kommer dock att användas och behandlas av sponsor.

Ekonomisk ersättning

För ditt deltagande i överkorsningsdelen av studien kommer du att erhålla en skattepliktig ersättning på 2900 kr.

Ingen ersättning för förlorad arbetsinkomst eller resor utgår. Om du endast gjort det första studiebesöket, hälsokontrollen, utgår ingen ersättning.

Ditt deltagande kan avbrytas i förtid av olika orsaker:

- om du själv väljer att avbryta
- om det skulle vara skadligt för dig att fortsätta studien

- om du skulle behöva ta ett läkemedel som inte är tillåtet i studien
- om du inte följer de restriktioner som finns
- om alla behandlingar inte kan genomföras pga. resultaten av de tidigare grupperna.

Om den ansvarige forskare/ sponsor bestämmer att du skall avsluta ditt deltagande i förtid, ersätts du i förhållande till ditt faktiska deltagande.

Om det är något ytterligare du undrar över eller behöver komma i kontakt med oss är du välkommen att ringa:

	Namn	Telefon
Ansvarig forskare:	Professor Peter Lingström	(b) (6)
Ansvarig forskningsassistent:	(b) (6)	(b) (6)

Screeningnummer: _____

FORSKNINGSPERSONENS SAMTYCKE

Jag har muntligen informerats om ovanstående studie och läst bifogad skriftlig information om vad som ska ske i studien.

Jag har fått tillfälle att ställa frågor och fått eventuella frågor besvarade.

Jag samtycker till:

- Att delta i studien
- Att mina studiedata (personuppgifter) får behandlas som beskrivits samt att data får överföras till länder utanför Sverige och Europeiska Unionen (EU).
- Att en person utsedd av sponsor eller en myndighetsperson under förbehåll av sekretess får jämföra insamlade studiedata med relevant information i min medicinska journal.
- Att mina prover får användas som beskrivits.

Jag känner till att mitt deltagande är helt frivilligt. Jag är medveten om att jag när som helst och utan närmare förklaring kan avbryta mitt deltagande utan att det påverkar mitt framtida omhändertagande i tandvården.

Underskrift av forskningsperson:

.....
namnteckning

.....
datum (forskningspersons egen datering)

.....
namnförtydligande

Underskrift av den forskare som har informerat och tagit emot detta underskrivna formulär:

.....
namnteckning

.....
datum

.....
namnförtydligande

Screeningnummer: _____

Information till forskningsperson i del 2, 6-veckors uppföljningsdel

Studie nummer: SM17-02

Studietitel: En öppen observationsstudie som undersöker effekt på munhälsa hos dagliga snusanvändare vid användning av tobaksfria nikotinpods (ZYN®).

Förfrågan om deltagande

Du tillfrågas härmed om du vill delta i en studie för att undersöka tandhälsa efter användning av tobaksfritt nikotinnehållande portionssnus som utförs av företaget Swedish Match AB, Sverige (sponsor) i samarbete med Professor Peter Lingström vid Göteborgs Universitet.

Sponsor i studien har tagit fram en produkt som i likhet med vanligt snus innehåller nikotin men som saknar tobak vilken man vill utvärdera med avseende på påverkan på tandhälsa.

Studien består av två delar och du tillfrågas här om deltagande i den andra delen, en 6-veckors uppföljningsdel.

Denna information beskriver varför studien görs, hur den går till samt tänkbara risker och obehag som studien kan medföra. Dessutom beskrivs hur insamlade uppgifter att behandlas.

Ta gärna god tid på dig att läsa denna information. Om något är oklart är det viktigt att du frågar prövaren om detta. Om du väljer att delta kommer du att få med dig denna information hem, samt en kopia på det undertecknade samtyckesformuläret.

Bakgrund och syfte

Det finns ca 1 miljon snusare i Sverige. Snus som är baserat på tobak kan innehålla små mängder cancerframkallande ämnen. Ett tobaksfritt snus skulle därför vara ett bra substitut för tobaksinnehållande produkter. Avsikten med studien är att undersöka påverkan på tandhälsan från ett icke-tobaksbaserat portionssnus av olika styrkor och smaker. Du kommer under studien att fritt få välja att använda dig av ZYN® Smooth, ZYN® Peppermint eller ZYN® Cinnamon, med en nikotinstyrka på 3 mg eller 6 mg. Du uppmuntras att byta ut så mycket som möjligt av ditt vanliga snus mot ZYN.

Regionala Etikprövningsnämnden i Göteborg har gett sitt godkännande till att studien genomförs.

Deltagande i studien

Ditt deltagande i studien är helt frivilligt. Du har rätt att när som helst och utan närmare förklaring avbryta ditt deltagande. Ansvarig forskare kan besluta att avbryta ditt deltagande i studien om det bedöms som nödvändigt för dig eller om du inte följer de restriktioner som studien kräver. Studiens sponsor kan besluta att avbryta studien. Om ditt deltagande i studien avbryts är det viktigt att du kommer till de uppföljningsbesök som forskaren anser behövas för din säkerhet.

Studien består av två delar och du tillfrågas om deltagande i den andra delen, den s.k. 6-veckors uppföljningsdelen. I denna del av studien ges en behandling, en av studieprodukterna som du själv väljer under ungefär sex veckors tid då du själv använder produkten fritt som ett alternativ till ditt vanliga snus. Du uppmuntras att byta ut så mycket som möjligt av ditt vanliga snus mot ZYN.

Du kommer att fortlöpande informeras om nya och viktiga studiedata som kan komma att påverka ditt beslut om fortsatt deltagande.

Hur går 6-veckors uppföljningsdelen av studien till?

Under studien kommer undersökningar att utföras på forskningslaboratoriet vid Avdelningen för cariologi, Institutionen för odontologi, Göteborgs universitet. I 6-veckors uppföljningsdelen av studien kommer 60 friska frivilliga män eller kvinnor över 19 år att delta.

Studieprodukten, som är en "portionssnus", placeras innanför överläppen precis som ditt vanliga snus. Du kommer under studieperioden få byta ut ditt vanliga snus mot studieprodukten och bestämmer därför själv hur mycket du ska använda, men uppmuntras att byta ut så mycket som möjligt.

Ditt deltagande i 6-veckors uppföljningsdelen av studien består av totalt upp till 5 besök på laboratoriet samt ett uppföljningssamtal via telefon. Första besöket är ett screeningbesök då du undersöks för lämplighet att delta i studien. Vid slutet av screeningbesöket får du med dig prover av olika typer av studieprodukt hem vilka du testar under två till fyra dagar för att på besök två hämta den mängd studieprodukt du behöver för de kommande 2 veckorna. Besök tre till fem är behandlingsbesök vilka beskrivs nedan. Under de dagar du tar studieprodukten hemma kommer du att få fylla i om du har tagit produkten i en dagbok.

Ett avslutande uppföljningssamtal görs 5-10 dagar efter sista behandlingsbesök. Ditt deltagande i studie pågår under cirka sju veckor. Nedan ges detaljerad information om varje besök.

Besök 1 (ca 1 timme), Screeningbesök

Vid besöket får du information om studien och har möjlighet att ställa frågor enskilt. Om du bestämmer dig för att delta i studien kommer du att få skriva under ett samtycke till att delta. Efter detta får du fylla i ett frågeformulär där du blir tillfrågad om tidigare och nuvarande sjukdomar och användning av läkemedel och naturläkemedel. Du får lämna urinprov för graviditetstest (endast kvinnor). Din munhåla kommer att undersökas och fotodokumenteras. Laboratoriet kommer att mäta surhetsgrad(pH) i din mun, utvärdera mängden plack och ta prover för att utvärdera vilka bakterier som finns där. Om du är lämplig att delta i studien blir du kallad till besök 2 och framåt. Om du vill delta i studien får du, innan du går hem, med dig prover av studieprodukterna hem som du får prova under några dagar fram till besök 2.

Besök 2 (ca 30 min)

Vid besöket får du meddela vilken studieprodukt du valt och hämta ut tillräcklig mängd för de kommande två veckorna fram till nästa besök.

Besök 3 till 5, (ca 1,5 timme) behandlingsbesök

Studien omfattar totalt tre besök om vardera ca 1,5 timmar, med två veckors mellanrum. Du bokar in försöksdatumen med personal på laboratoriet.

På varje besök kommer personalen fråga dig om hur du mått sedan senaste besöket och om du använt några läkemedel samt utföra följande utvärderingar:

- Undersökning av munhålan samt fotodokumentering.
- Mätning av surhetsgrad i munhålan.
- Utvärdering av plackmängd.
- Provtagning för utvärdering av bakterier

Efter att utvärderingarna gjorts får du boka in en tid för nästa besök och hämta ut studieprodukt för de kommande två veckorna.

Uppföljningssamtal 5-10 dagar efter sista behandlingsbesöket

Du blir uppringd av laboratoriet fem till tio dagar efter det sista besöket och vi följer upp hur det är med din hälsa och din övriga eventuella medicinering.

Vad måste du tänka på under studietiden?

- För att resultaten av studien skall bli så tillförlitliga som möjligt, måste du följa vissa restriktioner.
- Du får inte delta i någon annan medicinsk studie samtidigt med denna.
- Du får inte använda tandtråd 72 timmar innan besöken till laboratoriet.
- Du får inte borsta tänderna 48 timmar innan besöken till laboratoriet.
- Du får inte äta eller dricka från två timmar innan ett besök tills efter doseringen.
- Du får inte använda några droger. Om du behöver ta något läkemedel under studiens gång, måste du meddela försöksledningen detta innan försöksdagen eller när du kommer till forskningslaboratoriet.
- Du som är kvinna får inte bli gravid under studiens gång.
- Du får inte använt antibiotika fyra veckor innan samt under studieperioden.

Eventuella biverkningar, risker och obehag

Liksom vanligt snus kan testprodukten svida under läppen. Detta är dock inte sannolikt bland vanesnusare. Testprodukten förväntas avge ungefär samma nikotindos som en portionsprilla av vanligt tobaksbaserat snus och därmed ge samma "nikotinkick". Vanliga besvär om dosen skulle bli högre än vad du är van vid är ökad salivproduktion, lätt illamående, hicka, känsla av yrsel eller hjärtklappning. Generellt påverkar nikotin blodcirkulationen, höjer pulsen och drar samman blodkärlen. Personer med olika typer av hjärtproblem, såsom oregelbunden hjärtrytm eller kärlkramp bör därför undvika nikotin. Försöket avbryts om svåra besvär skulle uppstå.

Om Du under studiens gång skulle känna obehag eller besvär skall Du genast tala med någon av personalen.

Fördelar med att delta i studien

Du kommer själv inte att ha någon direkt nytta av att delta i studien eller dra nytta av resultaten som framkommer i studien, förutom att du får en grundlig tandhälsoundersökning.

Försäkring

Sponsorn har tecknat en försäkring som täcker kostnader för skada som anses vara orsakad av deras produkt. Göteborgs universitet har också en ansvarsförsäkring som täcker eventuell skada som uppstår när du vistas på Laboratoriet. Om du tror att du fått en skada som följd av ditt deltagande i studien ska du kontakta ansvarig forskare.

Behandling av personuppgifter (Personuppgiftslagen SFS 1998:204)

Under studien kommer vi att samla in dina personuppgifter (dessa kallas gemensamt för "Studiedata"). Studiedata inkluderar födelsedatum, kön, hälsodata (såsom tidigare sjukdomar) samt resultat av undersökningar i studien. Ditt samtycke till behandling av studiedata gäller för all framtid såvida du inte drar tillbaka det. All information i studien hanteras enligt gällande sekretessbestämmelser.

All studiedata kommer att vara kodad, d.v.s. ditt namn och personnummer samlas inte in, utan ersätts med en kod. Endast ansvarig forskare och dennes medarbetare har tillgång till kodnyckeln med vilken det går att koppla personuppgifterna till dig. Insamlad studiedata behandlas, (d.v.s. lagras, bearbetas och sammanställs) både manuellt och med datorteknik. Ändamålet med behandlingen av studiedata är forskning. Du har rätt att skriftligen en gång om året begära att få veta vilka personuppgifter som har registrerats om dig, varifrån dessa uppgifter har hämtats och till vilka kategorier av mottagare uppgifter eventuellt har lämnats ut. Ansvarig för behandling av dina personuppgifter är Göteborgs Universitet. Du kan vända dig till universitets kansli om du önskar utdrag över de personuppgifter som finns registrerade på dig och eventuell hjälp till rättelse (Universitetsjurist Kristina Ullgren, Universitetsledningens kansli, Box 100, 405 30 Göteborg, telefon 031-7861092). Ansökan ska vara undertecknad och innehålla information om studiens namn. Du kan även begära att felaktiga uppgifter om dig rättas. Du ska i så fall vända dig till studieansvarig forskare.

Insamlad studiedata kommer att överföras till ansvarigt företag, sponsor och till företag som arbetar på uppdrag av sponsor. Sponsor och Göteborgs universitet är var och en ansvariga att följa PUL. Dina studiedata kan komma att överföras till mottagare i länder utanför Sverige och Europeiska Unionen (EU). Dessa länder kan ha lagar som inte har samma höga skydd när det gäller behandling av personuppgifter.

Resultat kan komma att publiceras i en medicinsk tidskrift, dock utan att din identitet uppges. Har du frågor om detta är du välkommen att vända dig till studieansvarig forskare.

Om du drar tillbaka ditt samtycke, kommer ansvarig forskare inte att fortsätta samla in eller behandla nya studiedata. De studiedata som samlats in innan du drog tillbaka ditt samtycke kommer dock att användas och behandlas av sponsor.

Ekonomisk ersättning

För ditt deltagande i 6-veckors uppföljningsdelen av studien kommer du att erhålla en skattepliktig ersättning på 4900 kr.

Ingen ersättning för förlorad arbetsinkomst eller resor utgår. Om du endast gjort det första studiebesöket, hälsokontrollen, utgår ingen ersättning.

Ditt deltagande kan avbrytas i förtid av olika orsaker:

- om du själv väljer att avbryta
- om det skulle vara skadligt för dig att fortsätta studien
- om du skulle behöva ta ett läkemedel som inte är tillåtet i studien
- om du inte följer de restriktioner som finns
- om alla behandlingar inte kan genomföras pga. resultaten av de tidigare grupperna.

Om den ansvarige forskaren/ sponsor bestämmer att du skall avsluta ditt deltagande i förtid, ersätts du i förhållande till ditt faktiska deltagande.

Om det är något ytterligare du undrar över eller behöver komma i kontakt med oss är du välkommen att ringa:

	Namn	Telefon
Ansvarig forskare:	Professor Peter Lingström	(b) (6)
Ansvarig forskningsassistent:	(b) (6)	(b) (6)

Screeningnummer: _____

FORSKNINGSPERSONENS SAMTYCKE

Jag har muntligen informerats om ovanstående studie och läst bifogad skriftlig information om vad som ska ske i studien.

Jag har fått tillfälle att ställa frågor och fått eventuella frågor besvarade.

Jag samtycker till:

- Att delta i studien
- Att mina studiedata (personuppgifter) får behandlas som beskrivits samt att data får överföras till länder utanför Sverige och Europeiska Unionen (EU).
- Att en person utsedd av sponsor eller en myndighetsperson under förbehåll av sekretess får jämföra insamlade studiedata med relevant information i min medicinska journal.
- Att mina prover får användas som beskrivits.
- Att min munhåla fotodokumenteras.

Jag känner till att mitt deltagande är helt frivilligt. Jag är medveten om att jag när som helst och utan närmare förklaring kan avbryta mitt deltagande utan att det påverkar mitt framtida omhändertagande i tandvården.

Underskrift av forskningsperson:

.....
namnteckning

.....
datum (forskningspersons egen datering)

.....
namnförtydligande

Underskrift av den forskare som har informerat och tagit emot detta underskrivna formulär:

.....
namnteckning

.....
datum

.....
namnförtydligande

16.1.4 List and Description of Investigators and Other Important Participants in the Study, Including Brief (1 page) CVs or Equivalent Summaries of Training and Experience Relevant to the Performance of the Clinical Study

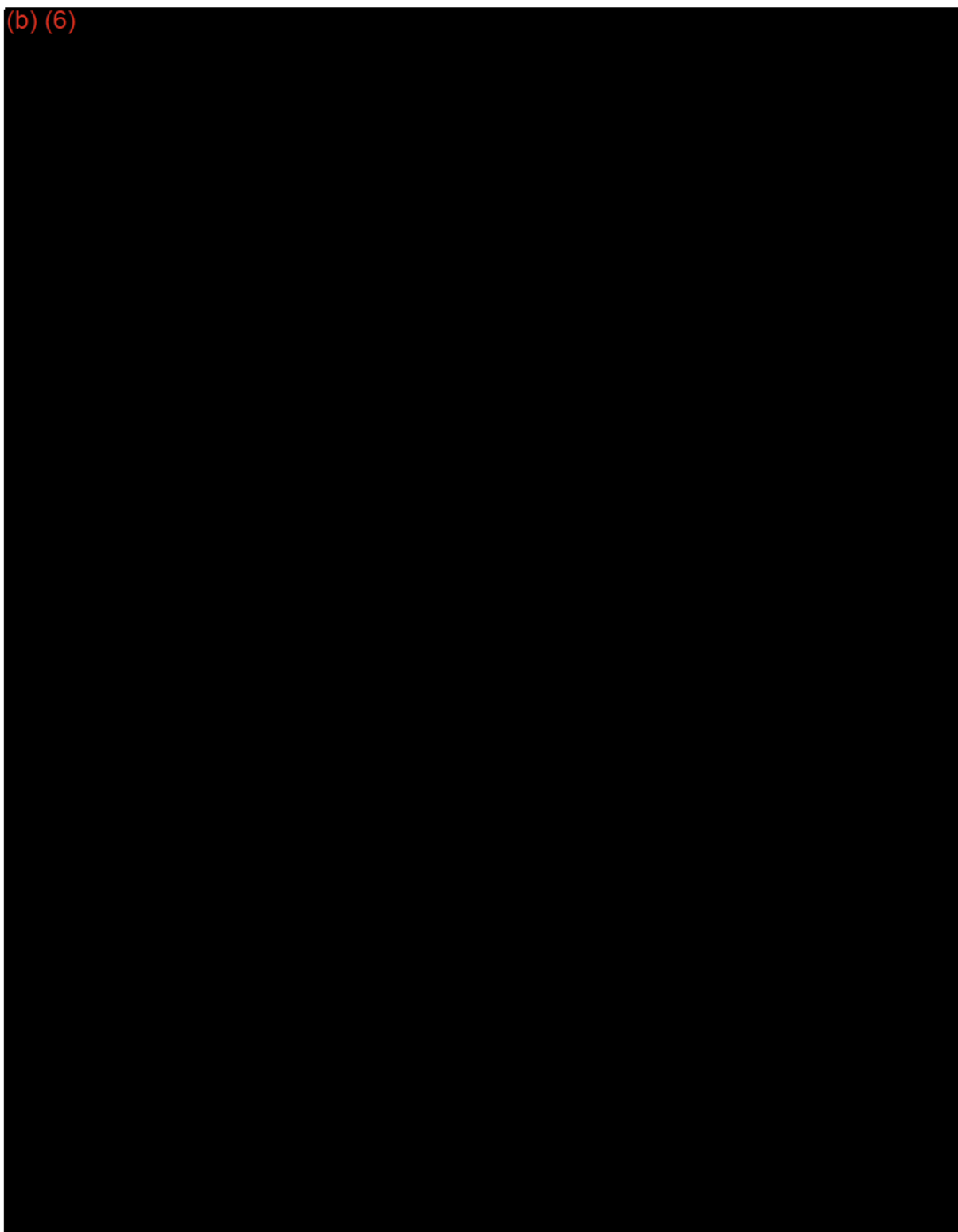
[CV Peter Lingström](#)

Curriculum Vitae

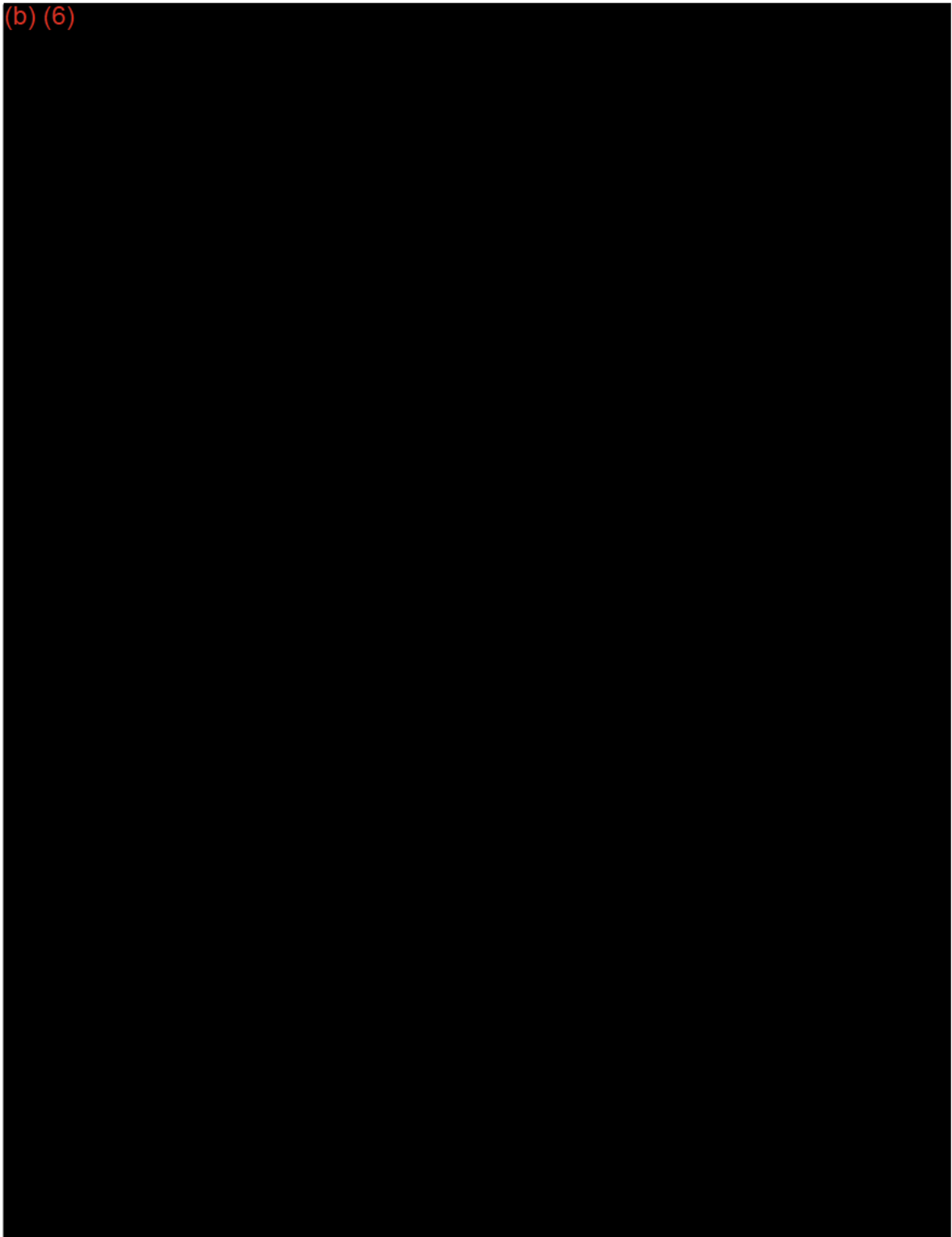
(b) (6)



(b) (6)



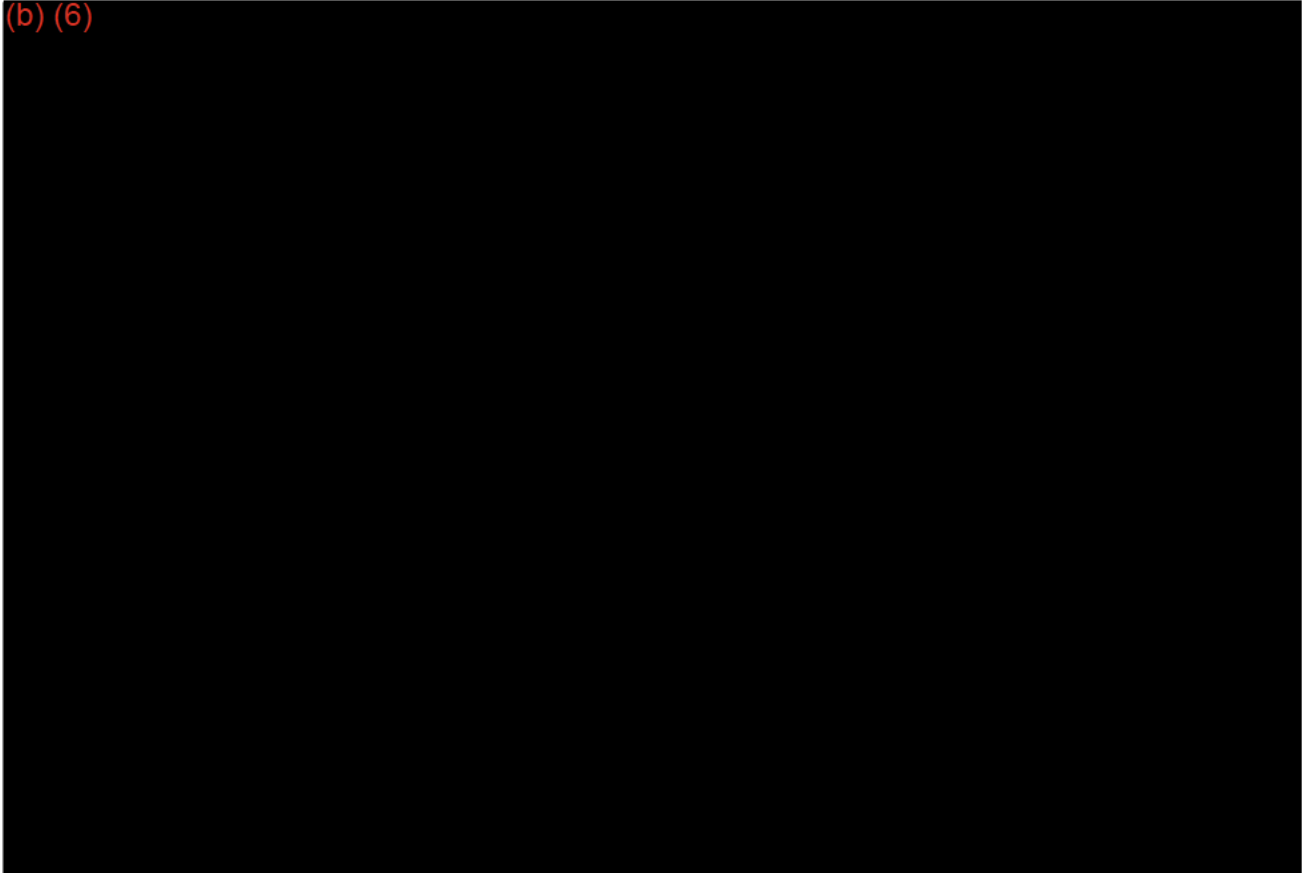
(b) (6)



(b) (6)




(b) (6)



16.1.5 Signatures of Sponsor, Statistician and Principal Investigator

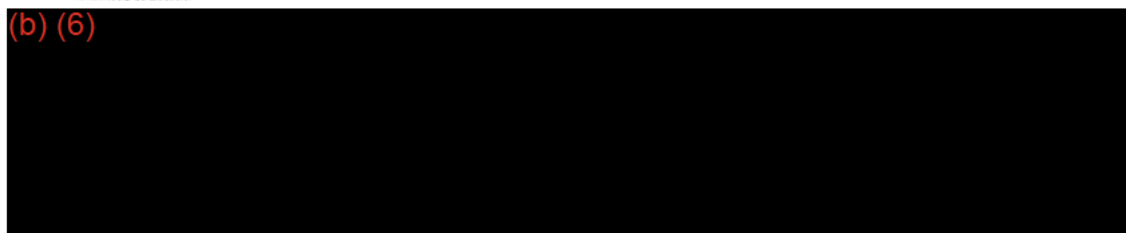
Sponsor signature

(b) (6)

A large black rectangular redaction box covering the signature area.

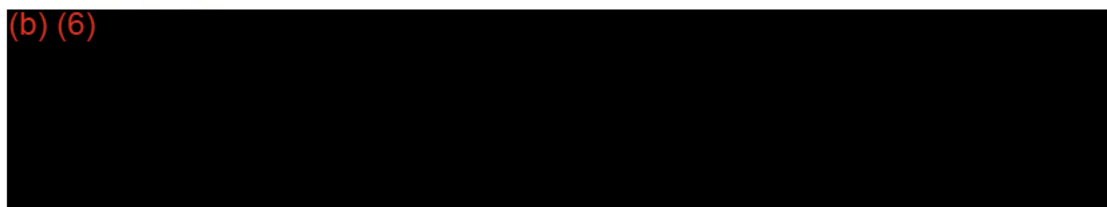
Statistician

(b) (6)

A large black rectangular redaction box covering the signature area.

Principal Investigator

(b) (6)

A large black rectangular redaction box covering the signature area.

16.1.6 Listing of Subjects Receiving Investigational Product(s) From Specific Batches, where More than One Batch was used

Not applicable.

16.1.7 Randomization Scheme and Codes (Subject Identification and Treatment Assigned)

(b) (4)

A large black rectangular redaction box covers the majority of the content in this section, starting below the section header and extending across the width of the text area.

(b) (4)

1

RANDOMIZATION LIST - FINAL - (b) (4)
Swedish Match AB
Clinical trial no: SM 17-02
Title: Open oral safety of a non-tobacco based nicotine pouch (ZYN®)
among current daily snus users

Principal investigator: Peter Lingström, Professor
CTC Clinical Trial Consultants AB

(b) (4)

RANDOMIZATION LIST - FINAL - (b) (4)
Swedish Match AB
Clinical trial no: SM 17-02
Title: Open oral safety of a non-tobacco based nicotine pouch (ZYN®)
among current daily snus users

Principal investigator: Peter Lingström, Professor
CTC Clinical Trial Consultants AB

(b) (4)

RANDOMIZATION LIST - FINAL - (b) (4)
Swedish Match AB
Clinical trial no: SM 17-02
Title: Open oral safety of a non-tobacco based nicotine pouch (ZYN®)
among current daily snus users

Principal investigator: Peter Lingström, Professor
CTC Clinical Trial Consultants AB

(b) (4)

RANDOMIZATION LIST - FINAL - (b) (4)
Swedish Match AB
Clinical trial no: SM 17-02
Title: Open oral safety of a non-tobacco based nicotine pouch (ZYN®)
among current daily snus users

Principal investigator: Peter Lingström, Professor
CTC Clinical Trial Consultants AB

(b) (4)

RANDOMIZATION LIST - FINAL - (b) (4)
Swedish Match AB
Clinical trial no: SM 17-02
Title: Open oral safety of a non-tobacco based nicotine pouch (ZYN®)
among current daily snus users

Principal investigator: Peter Lingström, Professor
CTC Clinical Trial Consultants AB

(b) (4)

RANDOMIZATION LIST - FINAL - (b) (4)
Swedish Match AB
Clinical trial no: SM 17-02
Title: Open oral safety of a non-tobacco based nicotine pouch (ZYN®)
among current daily snus users

Principal investigator: Peter Lingström, Professor
CTC Clinical Trial Consultants AB

(b) (4)

RANDOMIZATION LIST - FINAL - (b) (4)
Swedish Match AB
Clinical trial no: SM 17-02
Title: Open oral safety of a non-tobacco based nicotine pouch (ZYN®)
among current daily snus users

Principal investigator: Peter Lingström, Professor
CTC Clinical Trial Consultants AB

(b) (4)

RANDOMIZATION LIST - FINAL - (b) (4)
Swedish Match AB
Clinical trial no: SM 17-02
Title: Open oral safety of a non-tobacco based nicotine pouch (ZYN®)
among current daily snus users

Principal investigator: Peter Lingström, Professor
CTC Clinical Trial Consultants AB

(b) (4)

RANDOMIZATION LIST - FINAL - (b) (4)
Swedish Match AB
Clinical trial no: SM 17-02
Title: Open oral safety of a non-tobacco based nicotine pouch (ZYN®)
among current daily snus users

Principal investigator: Peter Lingström, Professor
CTC Clinical Trial Consultants AB

(b) (4)

RANDOMIZATION LIST - FINAL - (b) (4)
Swedish Match AB
Clinical trial no: SM 17-02
Title: Open oral safety of a non-tobacco based nicotine pouch (ZYN®)
among current daily snus users

Principal investigator: Peter Lingström, Professor
CTC Clinical Trial Consultants AB

(b) (4)

RANDOMIZATION LIST - FINAL - (b) (4)
Swedish Match AB
Clinical trial no: SM 17-02
Title: Open oral safety of a non-tobacco based nicotine pouch (ZYN®)
among current daily snus users

Principal investigator: Peter Lingström, Professor
CTC Clinical Trial Consultants AB

(b) (4)

RANDOMIZATION LIST - FINAL - (b) (4)
Swedish Match AB
Clinical trial no: SM 17-02
Title: Open oral safety of a non-tobacco based nicotine pouch (ZYN®)
among current daily snus users

Principal investigator: Peter Lingström, Professor
CTC Clinical Trial Consultants AB

(b) (4)

RANDOMIZATION LIST - FINAL - (b) (4)
Swedish Match AB
Clinical trial no: SM 17-02
Title: Open oral safety of a non-tobacco based nicotine pouch (ZYN®)
among current daily snus users

Principal investigator: Peter Lingström, Professor
CTC Clinical Trial Consultants AB

(b) (4)

RANDOMIZATION LIST - FINAL - (b) (4)
Swedish Match AB
Clinical trial no: SM 17-02
Title: Open oral safety of a non-tobacco based nicotine pouch (ZYN®)
among current daily snus users

Principal investigator: Peter Lingström, Professor
CTC Clinical Trial Consultants AB

(b) (4)

RANDOMIZATION LIST - FINAL - (b) (4)
Swedish Match AB
Clinical trial no: SM 17-02
Title: Open oral safety of a non-tobacco based nicotine pouch (ZYN®)
among current daily snus users

Principal investigator: Peter Lingström, Professor
CTC Clinical Trial Consultants AB

(b) (4)

RANDOMIZATION LIST - FINAL - (b) (4)
Swedish Match AB
Clinical trial no: SM 17-02
Title: Open oral safety of a non-tobacco based nicotine pouch (ZYN®)
among current daily snus users

Principal investigator: Peter Lingström, Professor
CTC Clinical Trial Consultants AB

(b) (4)

RANDOMIZATION LIST - FINAL - (b) (4)
Swedish Match AB
Clinical trial no: SM 17-02
Title: Open oral safety of a non-tobacco based nicotine pouch (ZYN®)
among current daily snus users

Principal investigator: Peter Lingström, Professor
CTC Clinical Trial Consultants AB

(b) (4)

RANDOMIZATION LIST - FINAL - (b) (4)
Swedish Match AB
Clinical trial no: SM 17-02
Title: Open oral safety of a non-tobacco based nicotine pouch (ZYN®)
among current daily snus users

Principal investigator: Peter Lingström, Professor
CTC Clinical Trial Consultants AB

(b) (4)

RANDOMIZATION LIST - FINAL - (b) (4)
Swedish Match AB
Clinical trial no: SM 17-02
Title: Open oral safety of a non-tobacco based nicotine pouch (ZYN®)
among current daily snus users

Principal investigator: Peter Lingström, Professor
CTC Clinical Trial Consultants AB

(b) (4)

RANDOMIZATION LIST - FINAL - (b) (4)
Swedish Match AB
Clinical trial no: SM 17-02
Title: Open oral safety of a non-tobacco based nicotine pouch (ZYN®)
among current daily snus users

Principal investigator: Peter Lingström, Professor
CTC Clinical Trial Consultants AB

(b) (4)

16.1.8 Audit Certificates (If Available)

Not applicable.

16.1.9 Documentation of Statistical Methods

Not applicable.

16.1.10 Documentation of Inter-Laboratory Standardization Methods and Quality Assurance Procedures if Used

Not applicable.

16.1.11 Publications Based on the Study

Not applicable.

16.1.12 Important Publications Referenced in the Report

Not applicable.