
16. APPENDICES

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16.1.1 Protocol and Protocol Amendments

[SM 17-03 Study Protocol v. 1.1 05FEB2018](#)

Clinical Study Protocol

Investigational Product	ZYN®
Study Code	SM 17-03
Protocol Version and Date	1.1, 05Feb2018

STUDY TITLE

Nicotine pharmacokinetics and subjective effects of a single dose of a non-tobacco-based nicotine pouch (ZYN®) compared with conventional, tobacco-based Swedish snus among current, daily snus users.

Design	Open, randomized, five-way cross-over, single dose administration. The study will include 18 subjects.
Test products and dosage	<p>1= ZYN Smooth containing 3 mg nicotine per portion</p> <p>2= ZYN Smooth containing 6 mg nicotine per portion</p> <p>3= ZYN Smooth containing 3 mg nicotine per portion (alternative manufacturing process)</p> <p>4= ZYN Smooth containing 6 mg nicotine per portion (alternative manufacturing process)</p>
Comparator product and dosage	5= Swedish portion snus PSWL 1.0 g (8 mg nicotine/g)

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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)
1	05Feb2018	Final 1.0 05Oct2017

2 STUDY SYNOPSIS

Study Title	
Nicotine pharmacokinetics and subjective effects of a single dose of a non-tobacco-based nicotine pouch (ZYN®) compared with conventional, tobacco-based Swedish snus among current, daily snus users.	
Study code	
SM 17-03	
Study period	
Estimated date of first subject enrolled: Q4 2017	
Estimated date of last subject completed: Q1 2018	
Principal Investigator	
Jan Erik Berglund, MD, PhD CTC Clinical Trial Consultants AB	
Study design	
Open, randomized, five-way cross-over, single dose administration.	
Objectives	
<u>Primary objective(s)</u>	
To compare each subject's AUC_{inf} based on plasma concentrations of nicotine after administration of one single dose of a novel, non-tobacco-based nicotine pouch containing 3 and 6 mg of nicotine, to that of one single dose from a 1 g Swedish snus pouch containing 8 mg of nicotine.	
<u>Secondary objectives</u>	
<ol style="list-style-type: none"> 1. To compare AUC_{60min}, C_{max}, T_{max}, AUC_{0-t} and terminal half-life of a novel, non-tobacco-based nicotine pouch to that of a Swedish snus pouch. 2. To compare the estimated <i>in-vivo</i> extracted amount of nicotine from a novel, non-tobacco-based nicotine pouch containing 3 and 6 mg of nicotine, respectively, with that from a 1 g Swedish snus pouch containing 8 mg of nicotine. 3. To compare heart rate and subjective effects ("head buzz") after study product administration (as proxy for <i>in vivo</i> nicotine uptake). 4. Collection of adverse events 	

Number of subjects planned

The study will include 18 subjects.

Diagnosis and main eligibility criteria

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 $\leq 1\%$) or two or more cans (brands with nicotine content $> 1\%$). Subjects who are pregnant or who have a history of hypertension or any cardiovascular disease are excluded. Subjects shall be abstinent from snus and all other nicotine containing products from 8.00 p.m. the night before each trial day.

Methodology

Before entry to the study subjects undergo screening evaluations including medical history and pulse rate measurements before/after application of their usual brand of Swedish snus.

Subjects report to the clinic on separate days for the 5 experimental sessions. The subjects are instructed to abstain from snus or other nicotine delivery products as from the evening before and smoking 24 hours prior to all visits to the clinic. All sessions are performed during the morning hours to facilitate abstinence. The subjects should certify abstinence before each treatment is started.

The treatments are administered as single doses in a pre-determined randomized order. The subject keeps the pouch still between the upper lip and the gum for 60 minutes and are instructed not to manipulate the pouch with the tongue or lips. The subjects are instructed not to eat or drink from 30 minutes before and during application of investigational products and 30 minutes after the investigational product have been taken out. [5].

Each used pouch is collected and frozen (-20°C) pending analyses of nicotine. Unused pouches are collected and frozen (-20°C) pending analysis and serve as references in the calculations of extracted doses.

Investigational Products, dosage and mode of administration**Test articles:**

1= ZYN Smooth containing 3 mg nicotine per portion

2= ZYN Smooth containing 6 mg nicotine per portion

3= ZYN Smooth containing 3 mg nicotine per portion (alternative manufacturing process)

4= ZYN Smooth containing 6 mg nicotine per portion (alternative manufacturing process)

Reference articles:

5= Swedish portion snus PSWL 1.0 g (8 mg nicotine/g)

Duration of treatment

The treatments are administered as single doses in a pre-determined randomized order. The subject keeps the pouch still between the upper lip and the gum for 60 minutes. Plasma concentrations of nicotine are followed over 6 hours.

Duration of subject's involvement in the study

Each Subject will participate in the study approximately 20-84 days.

Efficacy assessments

Pharmacokinetics assessments - WinNonlin computer program (Certara Corp., USA) will be used for pharmacokinetic calculations. Nicotine plasma concentrations are determined at preset time points, before (0), 5, 10, 15, 30 and 60 minutes, 1.5, 2, 4 and 6 hours after administration.

Pulse rate – Pulse rate will be measured at the following time points: before (0), 5, 10, 15, 30 and 60 minutes after each product is administered.

Subjective effects – Each subject's rating of product "strength" using a Visual Analogue Scale (VAS): (head "buzz", "head rush", "hit", feeling alert, overall "product strength"), anchored with "not at all" to "extremely". VAS scores will be obtained at the following time points before (0), 5, 10, 15, 30 and 60 minutes after each product is administered.

Safety assessments

Adverse Events will be collected starting with administration of the Investigational Product until the last follow-up from the first dose.

Statistical methods

The study will include 18 subjects. A previous study (Lunell E & Curvall M 2011) has made the calculation of sample size possible. Nicotine extraction from 1 g Swedish portion snus containing 8 mg nicotine/pouch was estimated at 2.18 ± 0.92 mg per 1 g portion. Under the assumption of a complete dissolution and extraction of the 3 and 6 mg ZYN® products, respectively, versus the 2.18 ± 0.92 mg nicotine, and a standard deviation of 5.0 the estimated sample size is 16 with a power of 80% and $\alpha=0.05$.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or term	Explanation
AE	Adverse event
ATC	Anatomical therapeutic chemical
BP	Blood pressure
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
IP	Investigational product
MedDRA	Medical dictionary for regulatory activities
min	minute
N	number
NRT	Nicotine replacement therapy
NSAID	Non-steroid anti-inflammatory drug
SAR	Serious adverse reaction
PPAS	Per protocol analysis set
PSWL	Pouched Snus White portion Large
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
VAS	Visual Analogue Scale
WHO	World Health Organization

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
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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 investigational products will be administered by site personnel under medical surveillance. In cases of accidental overdose, standard supportive measures should be adopted as required (see Section 7.3.1).

Overdose should be recorded as follows:

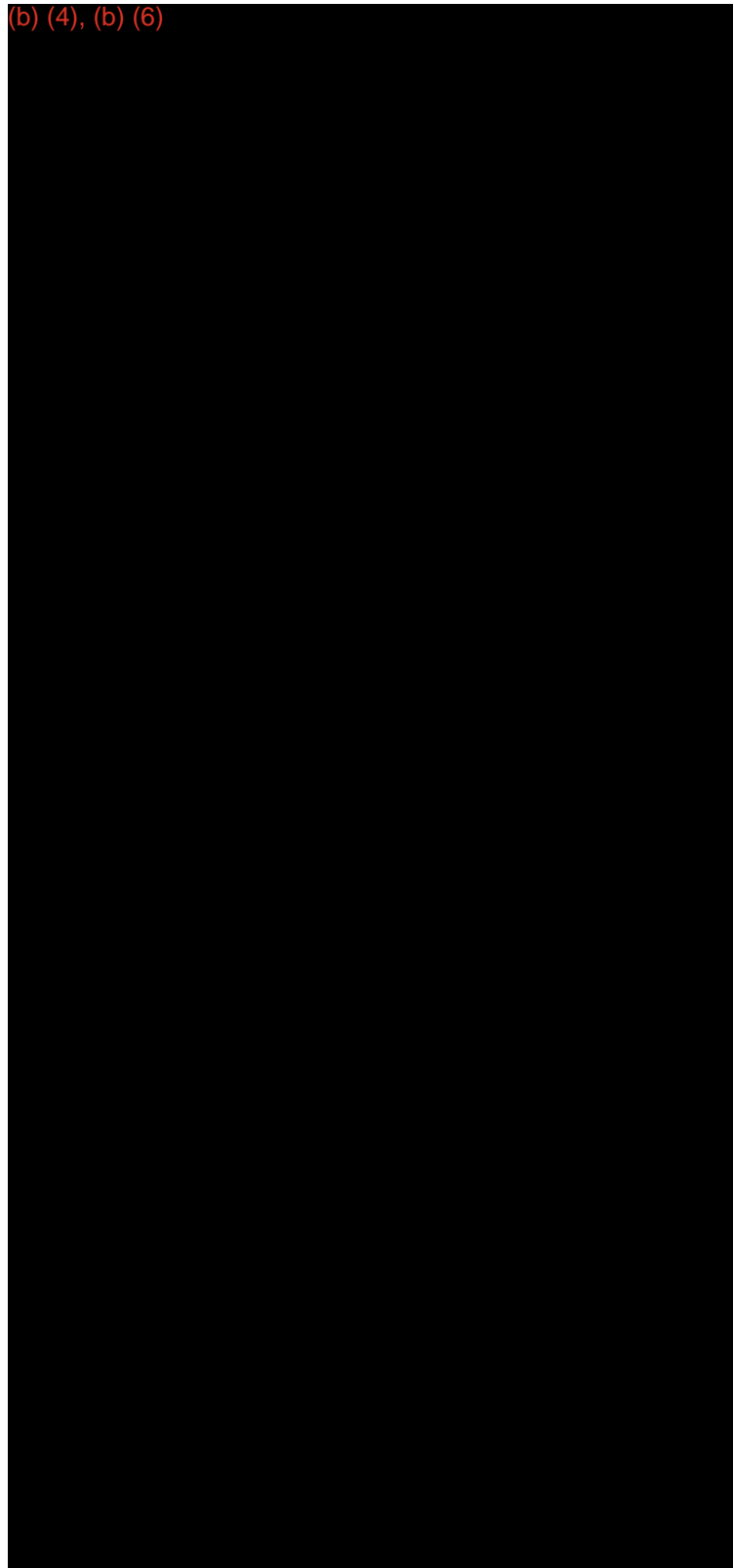
- An overdose with associated adverse event (AE) is recorded as the AE diagnosis/symptoms on the relevant AE modules in the case report form (CRF).
- An overdose without associated symptoms is only reported in the subject's medical records.

6 INVESTIGATOR(S) AND STUDY ADMINISTRATIVE STRUCTURE

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6.1.1 Investigational Product manufacturing and packaging

The investigational and reference products will be manufactured and packaged compliant with Swedish law on food production. The investigational and reference products will be transferred from the original container, weighed and individually packaged in identical sealed food approved test containers at Swedish Match analytical lab.

6.1.2 Identity of investigational products

Each dose of the investigational and reference products will be delivered in separate identical food approved glass containers labeled with unique identification numbers.

Signatures required are provided in [Appendix 18.1](#).

7 INTRODUCTION

7.1 Project background

Sweden displays the lowest prevalence of smoking in Europe, particularly among males. Population surveys have indicated that snus is the most frequently used smoking cessation aid. Snus is sometimes used as a last resort for people who have failed stopping smoking with the available, pharmaceutical smoking cessation aids. Smokeless tobacco is capable of rapidly delivering nicotine to the bloodstream (Fant et al 1999), and therefore may be more satisfactory among smokers than currently available pharmaceutical nicotine products. Traditionally there has been no non-tobacco-based nicotine product on the Swedish market intended for recreational use similar to Swedish snus. Despite the vast risk differential between snus and cigarettes in terms of adverse long-term health effects including cancer, cardiovascular disease and chronic lung disease, snus remains a controversial product as it contains tobacco and is intended for recreational use. The tobacco component of snus explains why it contains measurable amounts of hazardous constituents such as potentially carcinogenic nitrosamines, albeit at very low concentrations.

Recently, a novel, non-tobacco-based nicotine product (ZYN®) has been developed. It has some features that are similar to snus: it comes in pouches with a nicotine content of 3 or 6 mg; it is used the same way as snus, that is, it is placed under the upper lip. In contrast to snus the product contains no nitrosamines or polycyclic hydrocarbons (PAHs), which are the two main classes of unwanted substances in snus that are classified as potentially carcinogenic. Other unwanted substances in ZYN® are present in comparable or lower concentrations than in snus. The toxicological safety profile of ZYN® thus represents a significant improvement over snus with the exception of the nicotine content which is only marginally lower than in snus (3 or 6 mg in ZYN® versus e.g. 8-12 mg in a conventional 1.0 g snus pouch).

Commercially available snus products have a nicotine content ranging between 1-2%. Previous studies (Lunell E and Curvall M 2011), have indicated that on average about 15-20% of the total nicotine content is extracted and absorbed, with large inter-individual variation. Extraction is generally not linear with pouch size: surface area, saliva penetration and diffusion factors may be important determinants of nicotine uptake.

The nicotine delivery profile of a tobacco-free product like ZYN® is probably a main determinant of its efficacy to function as an alternative to cigarettes and snus. In view of these circumstances, it is highly justified to study the nicotine delivery profile of ZYN® in comparison with commercially available snus products (which have a documented ability to replace cigarettes as a source of recreational nicotine among current tobacco consumers). The Sponsor has previously conducted studies of nicotine chewing gum with different nicotine content versus snus products. We now intend to extend those observations by comparing the ZYN® product with Swedish snus.

The main aim of the present study is to document the *in-vivo* extraction of nicotine from ZYN® pouches and the resulting uptake to the systemic blood circulation, measured as AUC_{inf}, based on plasma concentrations of nicotine, versus a conventional snus pouch. The extraction and plasma data will be supplemented with assessments of subjective effects of “product strength” and pulse rate measurements, both of which constitute proxies for systemic nicotine uptake.

7.2 Investigational products

7.2.1 Product characteristics

Test and reference products will be delivered in identical containers labeled with unique identification numbers.

The test product of non-tobacco-based nicotine contains 3 and 6 mg of nicotine, respectively, in a pouch.

The reference product of 1 g Swedish snus pouch contains 8 mg of nicotine.

Administration of the pouch will be between the upper lip and the gum.

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. However, 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. Preliminary data from the manufacturer (J. Lindholm, personal communication) indicate that the amount of nicotine extracted from the test articles is comparable to that from tobacco-based snus, despite the fact that the overall nicotine content and content of free nicotine in the ZYN® pouches, 3 and 6 mg, is lower than in conventional tobacco-based snus (8 mg). This suggests that adverse effects from the nicotine exposure from the test and reference articles are unlikely to occur among the research subjects.

Aside from the nicotine, all ingredients used in the test products are food-approved (similar to ingredients in conventional snus). The nicotine in ZYN® is of pharmaceutical grade, i.e. the same as the nicotine in nicotine replacement products (gum, lozenges, mouth spray etc.). ZYN® is currently commercially available on the U.S. and Swedish markets.

The study does not involve invasive procedures, beside the collection of venous blood samples. So far, no adverse effects have been reported associated with the use of ZYN® apart from effects likely to be related to the nicotine exposure (such as salivation, nausea, and dyspepsia).

Pregnant women or individuals with a history of hypertension or any cardiovascular disease, who may be particularly vulnerable to nicotine exposure, are excluded from participation.

The potential adverse effects of the study procedures, which are likely to be minor and/or clinically insignificant, are from a research ethics perspective counterbalanced by the potential positive effects of the novel nicotine pouch as a reduced toxicity alternative to conventional snus. As the nicotine delivery profile of a product is likely to be central to its acceptability among current tobacco users, it is reasonable to conduct formal clinical studies to assess this feature in more detail.

7.3.1 Summary of risk management

Subjects will remain in the research clinic for 6 hour after the administration of the Investigational Product and will be closely monitored by medical staff.

8 STUDY OBJECTIVES AND ENDPOINTS

8.1 Primary objective(s)

To compare each subject's AUC_{inf} based on plasma concentrations of nicotine after administration of one single dose of a novel, non-tobacco-based nicotine pouch containing 3 and 6 mg of nicotine, to that of one single dose from a 1 g Swedish snus pouch containing 8 mg of nicotine.

8.1.1 Primary endpoint (s)

AUC_{inf} based on plasma concentrations of nicotine after administration of one single dose of a novel, non-tobacco-based nicotine pouch containing 3 and 6 mg of nicotine, to that of one single dose from a 1 g Swedish snus pouch containing 8 mg of nicotine.

8.2 Secondary objectives

1. To compare AUC_{60min} , C_{max} , T_{max} , AUC_{0-t} and terminal half-life of a novel, non-tobacco-based nicotine pouch to that of a Swedish snus pouch.
2. To compare the estimated *in-vivo* extracted amount of nicotine from a novel, non-tobacco-based nicotine pouch containing 3 and 6 mg of nicotine, respectively, with that from a 1 g Swedish snus pouch containing 8 mg of nicotine.
3. Comparison of pulse rate and subjective effects ("head buzz") after study product administration (proxy for *in vivo* nicotine uptake).
4. Adverse events

8.2.1 Secondary endpoints

1. AUC_{60min} , C_{max} , T_{max} , AUC_{0-t} and terminal half-life of a novel, non-tobacco-based nicotine pouch to that of a Swedish snus pouch.
2. *In-vivo* extracted amount of nicotine
3. To assess the correlation between the estimates of AUC_{inf} and the total amount of nicotine extracted from the ZYN® pouches.
4. Pulse rate and VAS for measure "head buzz" (head rush, "hit", feeling alert, overall "product strength"), using a 100-mm visual analogue scale (VAS) anchored with "not at all" to "extremely" at preset time points up to 60 minutes (predose, + 5min, +10 min, + 15 min, +30 min, +60 min after each dose), respectively, after study product administration (proxy for systemic uptake).
5. Collection of adverse events

9 INVESTIGATIONAL PLAN

9.1 Overall study design and schedule of events

The study will be conducted as an open, randomized, five-way cross-over, single dose administration. The study will include 18 subjects.

The subjects included will be healthy males and females 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 $\leq 1\%$) or two or more cans (brands with nicotine content $> 1\%$). Subjects who are pregnant or who have a history of hypertension or any cardiovascular disease are excluded. Subjects shall be abstinent from snus and all other nicotine containing products from 8.00 p.m. the night before each trial day.

Before entry to the study subjects undergo screening evaluations including smoking and snus use, medical history and pulse rate measurements before/after application of their usual brand of snus. The pulse rate assessment will be made in abstinent condition from 8 p.m. the night before.

A pulse rate increase of ≥ 10 beats/min in the morning before use of any nicotine containing product will classify the subject as eligible for participation the study.

Subjects report to the clinic on separate days for the 5 experimental sessions. The subjects are instructed to abstain from snus, cigarettes or other nicotine delivery products as from 8 pm the evening before. All sessions are performed during the morning hours to facilitate abstinence. The subjects should certify abstinence before each treatment is started.

The treatments are administered as single doses in a pre-determined randomized order. The subject keeps the pouch still between the upper lip and the gum for 60 minutes and are instructed not to manipulate the pouch with the tongue or lips. The subjects are instructed not to eat, drink, chew chewing gum or brush teeth from 30 minutes before application of treatment, during application of investigational products and 30 minutes after the investigational product have been taken out. [5].

Each used pouch is collected and frozen (-20°C) pending analyses of nicotine.

Table 1 Overall Schedule of Events

Assessment	Screening	Cross-over phase	Follow-up Phone contact
	Visit 1 ¹	Visit 2-6 ²	Visit 7
	Day -14 to -1	Day 1 followed by 1-14 day(s) of wash-out. Repeated for each dose time point	7 Days after last dose – 3/+7 days
Informed consent	X		
Eligibility	X	X ⁸	
Demographics	X		
Prior and Concomitant medication	X	X	X
Medical history	X		
Urine pregnancy test ³	X		
HIV, Hepatitis B and C test	X		
Drug screen	X ⁴	X ⁴	
CO measurement	X	X	
Pulse rate	X ⁵	X ⁶	
Visual Analogue Scale		X ⁶	
Investigational Product administration		X	
Collection of pouches		X	
PK blood sampling		X ⁷	
Baseline Symptoms	X	X ⁸	
Adverse Events		X	X

¹ Visit 1 could be performed during 2 days

² Refer to Schedule of Events per visit for details.

³ Female subjects only

⁴ Drug tests during the treatment period may be performed randomly.

⁵ Before and 15 min after application of the subject's usual brand and amount of Swedish snus

⁶ Before and 5, 10, 15, 30 and 60 min after application of the investigational products

⁷ Before and 5, 10, 15, 30, 60, 90, 120, 240 and 360 min after application of the investigational products

⁸ Only prior to dose administration on visit 2.

9.2 Rationale for study design and dose groups

Pouched Swedish snus has recently been studied in a report by Lunell and Curvall (2011). The snus investigated in that report, Swedish portion snus PSWL 1.0 g (8 mg nicotine/g), released an average 2.18 mg nicotine following use over 30 minutes. Non-tobacco-based products with similar nicotine content are investigated in the present study. The rationale for the choice of the 3 mg and 6 mg dose of the non-tobacco-based nicotine pouch is that 6 mg proved safe in a previous study (Molander L and Lunell E 2001). In view of these circumstances, it is highly justified to study the nicotine delivery profile of the non-tobacco-based nicotine pouch (ZYN®) in comparison with commercially available snus products. We thus intend to extend those observations by comparing a nicotine non-tobacco-based nicotine pouch (ZYN®) with Swedish snus, PSWL 1.0 g (8 mg nicotine/g).

10 STUDY POPULATION

10.1 Recruitment

The subjects will be recruited from a list of healthy volunteers at CTC and from advertising in media.

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 screening 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 randomized will be assigned a subject number (101, 102 and 103 etc.).

10.3 Number of subjects

The study will include 18 subjects.

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 <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 .
4. Willing and able to comply with study procedures.

5. A heart rate increase ≥ 10 beats/min with first use of snus in the morning after overnight abstinence from any nicotine exposure.

10.5 Exclusion criteria

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

1. Smoker, defined as "smoking during the last 24 hours according to self-report and CO in exhaled air >10 ppm at clinical visits".
2. A history or presence of diagnosed hypertension or any cardiovascular disease.
3. 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.
4. Any surgical or medical condition, which, in the judgment of the clinical investigator, might interfere with the absorption, distribution, metabolism or excretion of the investigational product.
5. History of any clinically significant disease or disorder which, in the opinion of the Investigator, may either put the subject at risk because of participation in the study, or influence the results or the subject's ability to participate in the study.
6. Pregnancy or planning to get pregnant during the study.
7. Positive screen for drugs of abuse at screening or on admission to the unit prior to administration of the investigational product.
8. Any positive result on screening for serum hepatitis B surface antigen, hepatitis C antibody and Human Immunodeficiency Virus (HIV).
9. Current or history of alcohol abuse and/or use of anabolic steroids or drugs of abuse.
10. Use of any prescribed or non-prescribed medication including antacids, analgesics and herbal remedies within two weeks prior to the first administration of IP, except occasional intake of paracetamol (maximum 2 000 mg/day; and not exceeding 3 000 mg/week), at the discretion of the Investigator.
11. Plasma donation within 1 month of Screening or any blood donation/blood loss >450 mL during the 3 months prior to Screening.
12. Investigator considers the subject unlikely to comply with study procedures, restrictions and requirements.

10.6 Restrictions during the study

1. Subjects shall be abstinent from snus and all other nicotine containing products from 8.00 p.m. the night before each trial day.
2. Subjects shall abstain from smoking the last 24 before each study day.

3. The subjects are not allowed to eat or drink, or use any other mouth related procedure (e.g. tooth brushing) 30 minutes before dose administration, during application of investigational products and 30 minutes after the investigational product have been taken out. [5].
4. 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.
5. The female volunteers are expected to be sexually abstinent or use contraceptives to prevent pregnancy during the study period
6. Consumption of grapefruit and/or grapefruit containing products is not allowed 1 week before IP dosing until last PK day.
7. Xanthine or taurine containing products/beverages, e.g. Redbull, are not allowed during the study.
8. Abstain from drugs of abuse from Screening to Follow-up visit.
9. The subjects must not donate blood or plasma during the study until three months after the Follow-up Visit.
10. 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 he/she 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 will not be replaced.

10.8 Randomization

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

Test articles:

1= ZYN Smooth containing 3 mg nicotine per portion

2= ZYN Smooth containing 6 mg nicotine per portion

3= ZYN Smooth containing 3 mg nicotine per portion (alternative manufacturing process)

4= ZYN Smooth containing 6 mg nicotine per portion (alternative manufacturing process)

Reference articles:

5= Swedish portion snus PSWL 1.0 g (8 mg nicotine/g)

11.2 Packaging and labelling

Investigational products will be delivered to the study site in identical containers labeled with unique identification numbers by Swedish Match in accordance with the randomization list.

11.3 Conditions for storage

The Investigational Product will be stored in the access-controlled storage area at CTC, as per storage conditions specified by the Sponsor.

11.4 Dispensing and accountability

Investigational Product will be dispensed as per randomization schedule by site personnel.

CTC AB and the Investigator will maintain an *Investigational Product Accountability Log* and *Investigational Product dispensing log* detailing the dates and quantities of Investigational Product received, dispensed to and used by each subject and Investigational Product returned or destroyed at the end of the study. Any discrepancies between dispensed and returned Investigational Product 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

A single dose will be given on the morning of each study day (see specific dosing instruction).

11.6 Treatment compliance

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

11.7 Return and destruction of investigational products

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 returned to the Sponsor 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 ([Table 1 Overall Schedule of Events](#), Section [9.1](#)). A detailed schedule of events with assessment time points during treatment days is presented below.

12.1 Screening assessments

Before entry to the study subjects undergo screening evaluations including smoking and snus use, medical history and pulse rate measurements before/after application of their usual brand of snus.

12.2 Visits after Investigational product administration

The subjects should certify abstinence before each treatment is started. A detailed list of event after the administration of the investigational product is displayed in Table 2 below.

Table 2 Detailed Schedule of Events, Visit 2-6.

EVENT	COLLECTION OF PLASMA SAMPLES	PULSE RATE	VAS ASSESSMENT	COLLECTION OF USED POUCH SAMPLE (±1 MIN)	AE INTERVIEW
<i>Predose</i>	✓	✓	✓		✓
<i>5 min</i>	✓	✓	✓		
<i>10 min</i>	✓	✓	✓		
<i>15 min</i>	✓	✓	✓		
<i>30 min</i>	✓	✓	✓		
<i>60 min</i>	✓	✓	✓	✓	
<i>90 min</i>	✓				
<i>2 hrs</i>	✓				
<i>4 hrs</i>	✓				
<i>6 hrs</i>	✓				✓

12.3 Recording of data

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

Serial plasma samples are drawn before, and at regular time intervals up to 6 hours after administration (10 samples). It is important that assessments are performed as close as possible to scheduled time. In order to achieve this, the timing priority order at a particular time point is:

1. Pulse rate
2. Collection of plasma sample
3. VAS

The time points for measurements will start from the start time of placing the snus between the upper lip and the gum. The plasma sample may be drawn with $\pm 5\%$ deviation from the time stated in the protocol.

The actual pouch sampling time should always be recorded in the CRF. Pre-dose assessments may be performed up to 10 minutes prior to dosing (if not specified in the schedule of events).

12.4 Demographics and other baseline characteristics

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 in order to verify that the eligibility criteria are met.

12.4.4 HIV and Hepatitis B/C

Subjects will be tested for HIV and hepatitis B/C prior to inclusion into the study in order to protect personnel handling the blood samples.

12.4.5 Urine drug screen

Urine will be screened for drugs of abuse at screening using the AlereTM Drug Screen Test Panel. Additional random tests can be performed during the study period.

The following substances will be included in the screen panel:

Amphetamine, Barbiturates, Benzodiazepines, Buprenorphine, Clonazepam, Cocaine, Fentanyl, Ketamine, Marijuana (Tetrahydrocannabinol [THC]), Methadone, Methamphetamine, Methylenedioxymethamphetamine (MDMA), Morphine, Opiate, Oxycodone, Phencyclidine, Propoxyphene, Tramadol, Tricyclic antidepressants (TCA)

12.4.6 Pregnancy urine test

Pregnancy urine test will be performed at screening visit (females only).

12.4.7 CO test

Measurement of Carbonmonoxide in exhaled air will be performed at visits to the clinic.

12.4.8 Prior and concomitant medication

Prior medication, medication 2 weeks prior to screening, will be obtained by interview and documented in the subjects CRF.

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, dose, unit, indication, reason for administration, dose form, frequency, route, start and stop dates) must be recorded. All changes in medication should be noted in the CRF.

12.4.9 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 Investigational Product (*i.e.* during the screening period)

12.5 Study assessments

12.5.1 Pharmacokinetics assessments

Nicotine plasma concentrations are determined at preset time points, before (0), 5, 10, 15, 30 and 60 minutes, and 1.5, 2, 4 and 6 hours after administration. Frozen plasma samples collected for nicotine determinations will be shipped to a certified contract laboratory. The analysis of the plasma samples will be performed by a validated LC-MS/MS assay at ABS Laboratories Ltd, UK. To quantify nicotine a multilevel calibration at eight concentrations will be performed over a range of 0 to 50 ng/mL. The calibration line will be fitted by means of linear regression weighted by $1/\text{concentration}^2$. The samples will be assayed once. Incurred sample reproducibility will be performed according to the EMA and FDA guidelines so that 10% of the analysed study samples up to 1000 will be reanalysed and then 5% of the number above 1000. The analysis batch acceptance criteria will be: The calibration standards must have a back-calculated accuracy within $100 \pm 15\%$, except at the lower limit of quantification (LLOQ) where it must be within $100 \pm 20\%$. The standard curve must be constructed from at least three quarters (*i.e.* 12) of the calibration standards, excluding the zero concentration calibration standards. Duplicate quality control samples at low, medium and high concentrations will be included in each analysis batch. The accuracy of at least two thirds of the quality control samples must be within $100 \pm 15\%$. Half of the quality control samples at each concentration must be within $100 \pm 15\%$. At least half of the blank samples with internal standard and half of the blank samples without internal standard, placed immediately before the calibration standards, must be free of interference. Overall two thirds of the total number of blank samples must be free of interference. Interference is defined as a detectable response, at the retention time of the analyte, greater than 20% of the mean response of the lowest concentration (LLOQ) standards. WinNonlin computer program (Certara Corp., USA) will be used for pharmacokinetic calculations. Main variables will be AUC_{inf} , C_{max} , T_{max} .

12.5.2 Visual Analogue Scale and Vital signs

VAS for measure "head buzz" (head rush, "hit", feeling alert, overall "product strength"), using a 100-mm visual analogue scale (VAS) anchored with "not at all" to "extremely" at preset time points up to 60 minutes, after study product administration (as a proxy for systemic uptake). VAS assessment will be performed with a VAS-ruler. Pulse rate will be measured with automatic device in sitting position after 10 minutes of rest.

12.5.3 Collection of pouches and analysis

Pouches for the determination of nicotine after administration of the Investigational Product will be collected after 60 minutes (see [Overall study design and schedule of events](#) in Section 9.1). The following time window will apply for the pouch sampling:

- ± 1 min.
- The date and time of collection of each pouch will be recorded in the CRF.

All the collected pouches will be collected and frozen immediately at -20°C.

Pouches for extraction of nicotine will be analyzed by Swedish Match. Pouches from all evaluable subjects excluding withdrawn or dropout subjects will be analyzed.

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.

12.6.1.2 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.

12.6.1.3 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'.

12.6.1.4 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

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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)

The same information must also be sent to the CTC SAE email inbox: sae@ctc-ab.se.

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.

12.7 Appropriateness of measurements

Measurements of nicotine extraction, pulse rate and Visual Analogue Scales are standard assessments in nicotine research.

Standardized methods for measurements of safety and tolerability will be used.

13 PROCEDURES FOR SAMPLING AND ANALYSIS OF NICOTINE

13.1 PK plasma samples

13.1.1 Sample collection

Blood samples (5 mL) for the determination of plasma concentrations of nicotine will be collected at the specified time-points on Visits 2 to 6. The plasma fraction of the samples will be collected and divided into two cryo tubes containing approx. 1 ml each. For further details refer to the separate lab manual. The date and time of collection of each sample will be recorded in the eCRF.

The samples will be registered in a tissue-bank 893 at CTC and stored at -20°C until analyzed. The samples will be disposed after the Clinical Study Report (CSR) has been finalized.

13.1.2 Analysis of PK plasma samples

Samples for determination of plasma concentrations of nicotine will be analysed by ABS Laboratories LTD (United Kingdom), by means of a validated LC-MS/MS method. The details of the analytical method used will be described in a separate bioanalytical report.

Samples will be collected, stored, and shipped to the laboratory for analysis in accordance with study-specific instructions.

For additional information on the analysis of PK parameters, refer to Section [12.5.1](#).

13.2 Nicotine extraction

13.2.1 Sample collection

The nicotine content per portion of used and unused pouches, respectively, will be estimated. Each used pouch is collected and frozen (-20°C) pending analysis of nicotine. Frozen samples of used pouches collected for nicotine determinations will be shipped to Swedish Match laboratories.

13.2.2 Analysis of nicotine in pouches

Nicotine in used and unused pouches will be analyzed at the Swedish Match laboratories using a validated method.

14 ETHICAL AND REGULATORY REQUIREMENTS

14.1 Ethical conduct of the study

The study 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.

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

14.2 Ethics and regulatory review

It may be considered problematic to expose research subjects to a novel nicotine delivery product the properties of which are not yet fully known. However, 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. Preliminary data from the manufacturer (J. Lindholm, personal communication) indicate that the nicotine extraction from the test articles is comparable to that from tobacco-based snus, despite the fact that the overall nicotine content and content of free nicotine in the ZYN® pouches, 3 and 6 mg, is lower than in conventional tobacco-based snus (8 mg). This suggests that adverse effects from the nicotine exposure from the test and reference articles are unlikely to occur among the research subjects.

Aside from the nicotine, all ingredients used in the test products are food-approved (similar to ingredients in conventional snus). ZYN® is currently commercially available on the U.S. and Swedish markets. The nicotine in ZYN® is of pharmaceutical grade, i.e. the same as the nicotine in nicotine replacement products (gum, lozenges, mouth spray etc.).

So far, no adverse effects have been reported associated with the use of ZYN® apart from well-known effects likely to be related to the nicotine exposure (such as salivation, nausea, and dyspepsia).

Pregnant women or individuals with a history of hypertension or any cardiovascular disease, who may be particularly vulnerable to nicotine exposure, are excluded from participation.

The study does not involve invasive procedures, besides collection of venous blood samples from an antecubital vein using an inserted cannula (Venflon®).

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

The study will not be started until approval of the protocol, the Subject Information and the Informed Consent Forms have been obtained from the Independent Ethics Committee in Uppsala, Sweden. It is the responsibility of the Investigator to forward a copy of the written approval and, where possible, a list of the members, their titles or occupations, and their institutional affiliations, to CTC/the Sponsor. The approval should include a study identification and the date of review. The study will not be started until receipt by CTC of written approval from the IEC.

14.3 Subject information and consent

It is the responsibility of the Investigator or designee to give each subject prior to inclusion in the study, full and adequate verbal and written information regarding the objectives and procedures of the study and the possible risks involved. The subjects must be informed about their right to withdraw from the study at any time. Written subject information should be given to each subject before enrolment. The written subject information must not be changed without prior discussion with CTC/the Sponsor. All subjects are required to provide informed consent prior to any study procedures. Furthermore, it is the responsibility of the Investigator or designee to obtain signed Informed Consent Form from all subjects prior to inclusion in the study.

The signed Informed Consent Form should be filed by the Investigator or designee for review by the Monitor. The Investigator will confirm receipt of the Informed Consent Form from each subject by signing the appropriate page of the Case Report Form.

14.4 Subject data protection

The Investigator should keep a subject identification list not to be available to the Sponsor, including sufficient information to link records, i.e. CRFs and hospital records. The subjects should be informed that the data will be stored and analyzed by computer, that Swedish and local regulations for the handling of computerized data will be followed and described in the written subject information and that identification of individual subject data will only be

possible for the Investigator. Furthermore, the subjects should be informed about the possibility of inspection of relevant parts of the records by representatives of CTC AB and/or Authorities.

14.5 Changes to the approved clinical study protocol

Any variation in procedure from that specified in the Final Study Protocol may lead to results of the trial being questioned and in some cases rejected. Any proposed protocol change must therefore be discussed with and approved by the Sponsor and submitted for Independent Ethics Committee approval or notification. Any protocol change should be documented in a Protocol Amendment.

14.6 Audits and inspections

Authorized 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, analyzed, and accurately reported according to the protocol, ICH-GCP guidelines and any applicable regulatory requirements.

14.7 Insurance

The Sponsor is liable under law and in accordance with generally accepted standards for unexpected injuries, including death, that the use of the study drug may cause subjects.

The Sponsor will indemnify and hold the Investigator as well as any hospital, institution, ethics committee or the alike, harmless from any claims for damages caused by such injuries but only to the extent that the claim is not caused by gross negligence or failure to comply with the protocol and/or governmental regulation by the indemnified.

The Sponsor will require the Investigator to indemnify and hold the Sponsor harmless from any claim caused by gross negligence and/or failure to comply with the protocol and/or governmental regulation by the Investigator.

The Investigator agrees to notify the Sponsor whenever he becomes aware of a claim or action and to co-operate with and authorize the Sponsor to carry out sole management of such claim or action.

The Sponsor's responsibility is covered by product liability insurance. The insurance also covers the Sponsor's liability under law and generally accepted liability standards within industry toward any third parties, including subjects, as Sponsor of the Study. The Investigator's responsibility is covered by liability insurance for scientific studies in human subject. CTC has a company insurance covering services performed by CTC.

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) utilized.

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, including detailed knowledge of and training in all procedures to be followed.

Curriculum vitae will be collected from all personnel and be kept in the Trial Master File.

15.2 Clinical monitoring

The study site will be monitored periodically during the study, as agreed with the Investigator. The Monitor will ensure that all aspects of the protocol are followed, including the randomization procedure, the accurate recording of results, the reporting of Adverse Events, Product Accountability and record keeping.

Furthermore, it will be verified that the clinical facilities remain accurate, and that the Case Report Forms are in agreement with source data. For this purpose, the Monitor will be given access to hospital records, original laboratory data, etc., as far as they relate to the study, without jeopardizing subject integrity and as agreed with the Investigator prior to the study. Case Report Forms for all included subjects will be made available to the Monitor for review and collection as agreed with the Investigator. It is important that the Investigator and other 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

Monitoring visits will be made during the trial, to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of agreement with data on CRFs.

A separate *Source Data Verification List* will be generated 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 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 be enrolled.

15.5 Study time table and end of study

Ethics committee application will be submitted in October 2017. Performance of clinical part of study is expected to be finished in the beginning of 2018.

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

15.6 Discontinuation of the study

The Sponsor reserves the right to discontinue the study prior to inclusion of the intended number of subjects, but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the Investigator must call in all participating subjects. At this visit, all delivered unused study products and other study materials must be collected and all CRFs be completed as far as possible.

15.7 Reporting and publication

15.7.1 Clinical study report

A summarizing report should be submitted to the applicable IEC within 12 months after completion of the study.

A clinical study report (CSR), in compliance with ICH E3; *Structure and content of clinical study reports*, describing the conduct of the study, *the statistical analysis performed* 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.

15.7.2 Confidentiality and ownership of study data

All information not previously published concerning the test product and the Sponsor's research, including patent applications, manufacturing processes, basic scientific data, etc., is considered confidential and should remain the sole property of the Sponsor. The Investigator agrees to use this information only in connection with this study and will not use it for other purposes without the written permission from the Sponsor.

15.7.3 Publication

It is agreed that the Sponsor has the ownership of all results. Before publication, if publication is agreed upon, the Sponsor will be given the opportunity to review and comment upon the manuscript. The time for review should not exceed 30 days after receipt of the manuscript. If the Investigator has not submitted the results for publication within 6 months after completion of the final CSR, the Sponsor will have the right to publish. In this case the Investigator will be given 30 days to review and comment on the manuscript prior to submission to the publisher.

15.8 Archiving

To enable any further evaluations and/or audits from Health Authorities/the Sponsor, the Investigator agrees to keep records, including the identity of all participating subjects, all original signed Informed Consent Forms, copies of all CRFs and detailed records of drug

disposition. To comply with international regulations, the records should be retained by the Investigator for 15 years.

16 DATA MANAGEMENT

16.1 Case report form

Data will be collected in CRFs specifically designed for this study. The Investigator or an authorized 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 will sign off the CRF 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 initialed and dated. Correction fluid must not be used. Only persons authorized by the Investigator are allowed to make entries to the CRF.

16.2 Database management plan and database design

Detailed information on data management will be described in a study-specific 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 computerized edit checks and queries for identifying data values that are outside the allowed range, protocol violations, incomplete or inconsistent. The Data Validation Plan (DVP) 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 done 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 WHO Anatomic Therapeutic Chemical (ATC) classification system.

All coding will be approved by CTC.

16.5 Database lock

When all data have been entered, discrepancies solved the database will be locked and the data will be analyzed.

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) that 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

Continuous data will be presented using summary statistics. Data will be presented in terms of number (N), arithmetic mean, standard deviation (SD), 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.

A significance level of 5% with two-sided tests will be used in all comparisons.

The test articles below will in all analyses be compared to the reference product.

Any comparisons between the test articles will be described in the SAP.

Test articles:

1= ZYN Smooth containing 3 mg nicotine per portion

2= ZYN Smooth containing 6 mg nicotine per portion

3= ZYN Smooth containing 3 mg nicotine per portion (alternative manufacturing process)

4= ZYN Smooth containing 6 mg nicotine per portion (alternative manufacturing process)

Reference articles:

5= Swedish portion snus PSWL 1.0 g (8 mg nicotine/g)

17.2 Determination of sample size

The primary endpoint is nicotine extraction. The study will include 18 subjects. A previous study [Lunell E & Curvall M 2011] has made the calculation of sample size possible. Nicotine extraction from a 1 g Swedish portion snus (PSWL) containing 8mg nicotine/pouch was estimated at 2.18 ± 0.92 mg per portion. Under the assumption of a complete dissolution and *in-vivo* extraction of the 3 and 6 mg ZYN® products, respectively, versus the 2.18 ± 0.92 mg nicotine, and a standard deviation of 5.0 the estimated sample size is 16 with a power of 80% and $\alpha=0.05$. The randomization will be performed using Latin Squares approach.

17.3 Analysis data sets

17.3.1 Full analysis set

The FAS will consist of all subjects who have been randomized and received at least one dose of IMP.

17.3.2 Per protocol analysis

The PP population will consist of all subjects who have been randomized, completed the study period and without any major protocol violations. All violations will be presented and discussed at the clean file meeting.

The baseline and safety data will be presented using the FAS population. All data regarding extraction of nicotine will use the PP population.

17.4 Description of study population

17.4.1 Demographics and baseline characteristics

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

17.4.2 Medical/surgical history and prior/concomitant medication

Medical/surgical history and prior/concomitant medications will be presented by descriptive statistics by dose group.

17.4.3 Treatment compliance

The number of subjects treated in each by dose group will be tabulated.

17.5 Analysis of primary endpoint

AUC_{inf} based on plasma concentrations of nicotine after administration of one single dose of a novel, non-tobacco-based nicotine pouch containing 3 and 6 mg of nicotine, to that of one single dose from a 1 g Swedish snus pouch containing 8 mg of nicotine will be described using summary statistics and non-parametric signed Wilcoxon rank sum test for within subject difference.

17.6 Analysis of secondary endpoints

The mean + SD extracted dose of nicotine from each pouch, will be calculated. The extracted dose of nicotine will be analyzed using the signed Wilcoxon rank sum test and Students t-test for within subject difference. The correlation between the AUC and the total amount of nicotine extracted from the pouch will be analyzed using Proc corr. in SAS.

The mean + SD of AUC_{inf} based on plasma concentrations of nicotine after administration of each pouch, will be calculated. AUC_{60min}, C_{max}, T_{max}, AUC_{0-t} and terminal half-life will also be calculated.

AUC_{60min}, C_{max}, T_{max}, AUC_{0-t} and terminal half-life of a novel, non-tobacco-based nicotine pouch to that of a Swedish snus pouch will be described using summary statistics and analyzed using signed Wilcoxon rank sum test for within subject difference.

Pulse rate and VAS for measure of subjective "head buzz" (head rush, "hit", feeling alert, overall "product strength"), will be summarized by treatment and period using descriptive statistics.

The intra subject difference of pulse rate will be analyzed using the signed Wilcoxon rank sum test and Students t-test for within subject difference.

The intra subject difference of VAS scales for "head buzz" (head rush, "hit", feeling alert, overall "product strength") will be analyzed using the signed Wilcoxon rank sum test and Students t-test for within subject difference.

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

17.7 Statistical/analytical issues

17.7.1 Adjustments for covariates

No adjustments for covariates will be performed.

17.7.2 Handling of dropouts or missing data

Missing data will not be imputed.

17.7.3 Multiple comparison/multiplicity

Even though many pairwise comparison will be made, will no p-value adjustments will be enforced. However, a medical/clinical judgement will be applied to all significance tests, in order to avoid any conclusions based solely on statistical significance and without any clinical relevance.

17.7.4 Examination of subgroups

No subgroup analysis will be performed.

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 signature

(b) (4)



14Feb2018
Date

Principal Investigator

(b) (4)



CONFIDENTIAL

43 (45)

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. Fant RV, Henningfield JE, Nelson RA and Pickworth WB. Pharmacokinetics and pharmacodynamics of moist of snuff in humans. *Tob. Control* 1999;8;387-392.
2. Molander L and Lunell E. Pharmacokinetic investigation of a nicotine sublingual tablet. *Eur J Clin Pharmacol.* 2001;56:813-819.
3. Lunell E and Curvall M. Nicotine Delivery and Subjective Effects of Swedish Portion Snus Compared With 4 mg Nicotine Polacrilex Chewing Gum. *Nicotine Tob Res* 2011;13(7): 573-578.
4. Chow S-C, Shao J and H Wang (2003) Sample Size Calculations in Clinical Research. Marcel Dekker, New York, pp 102-103.
5. Henningfield JE, Radzius A, Cooper TM, Clayton RR. Drinking coffee and carbonated beverages blocks absorption of nicotine from nicotine polacrilex gum. *JAMA* 1990;264:1560-4.

16.1.2 Sample Case Report Form (Unique Pages Only)

[Swedish Match 17-03 CRF Flow](#)

[Swedish Match 17-03 CRF pages 3.1 Annotated](#)

Swedish match 148 [3.1]



Assigned. Last edited : 2017-12-13 12:00 Validated

This report contains information about the design project and version as stated above. It summarizes the most important settings in the design. For full details, please check the design version in Viedoc Designer.



DESIGN CONFIGURATION REPORT
PRINTED: 2019-01-08 15:05
VIEDOC 4.47.6914.33354

Table of contents

Details	1	Study workflow	4	Edit checks	7
Languages	2	Roles	5		
Forms in use	3	Study settings	6		

1 Details

This section describes the name, version and possible revision of the project.

Internal Description		Study Name	
Swedish match 148		Swedish match 148	
Version	Revised Version		
3	1		
Study Description			
-			
Protocol Name		Protocol Version	
SM 17-03		1.0	

2 Languages

The below languages have been used in all or some of the forms in the study.

Default Language

English

Additional Languages

-

3 Forms in use

The below forms with respective IDs are used in the design. The table indicates if they include any additional languages and if they are expected to be completed through the API and/or ViedocMe. Detailed contents of each form can be found in the Annotated CRF file.

#	Name	Id	Visibility	API	ViedocMe	Addl languages
(b) (4)						

4 Study workflow

This section describes the study workflow including activities, visit window, available forms and any conditions used.

4.1 Study Start

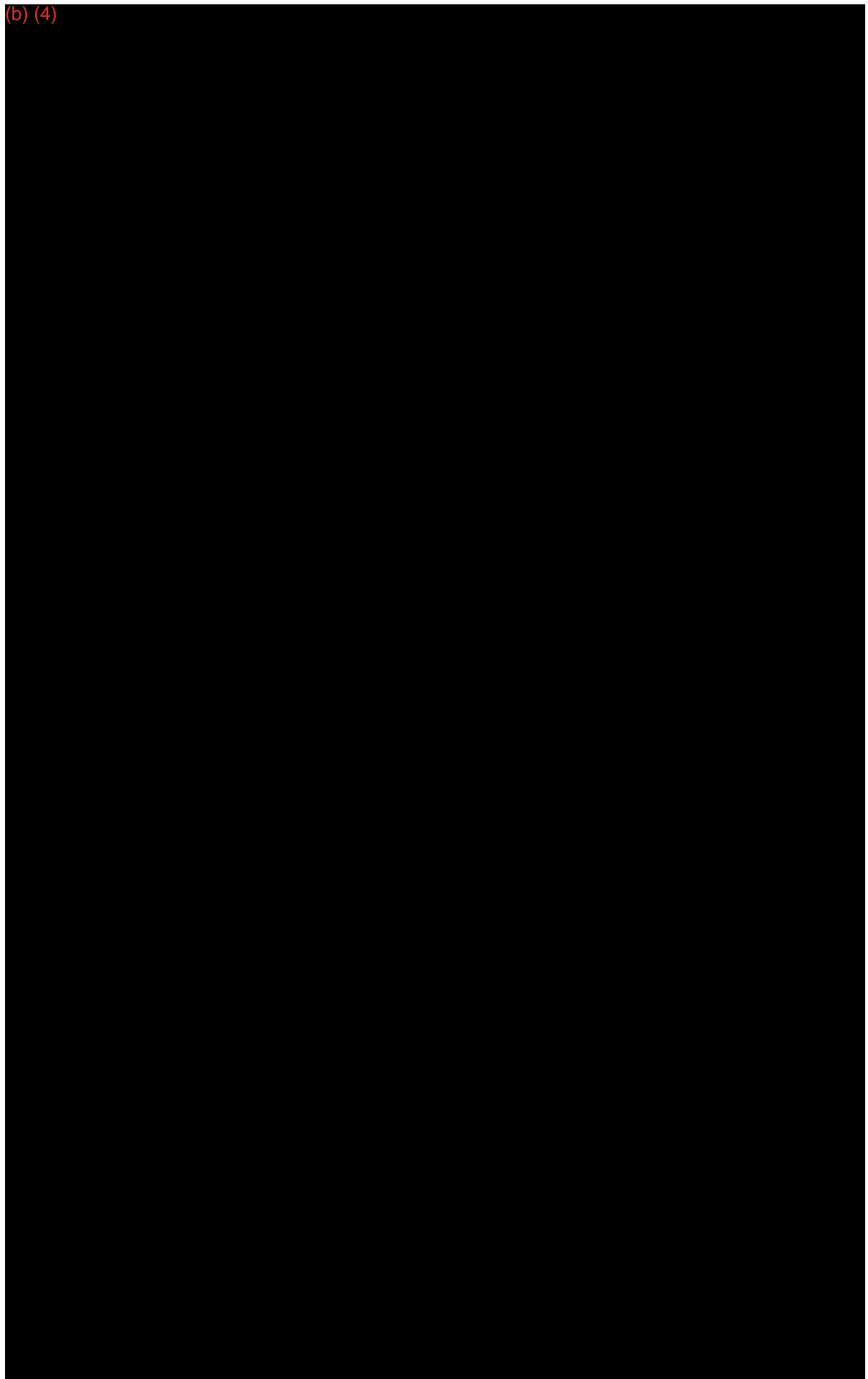
(b) (4)

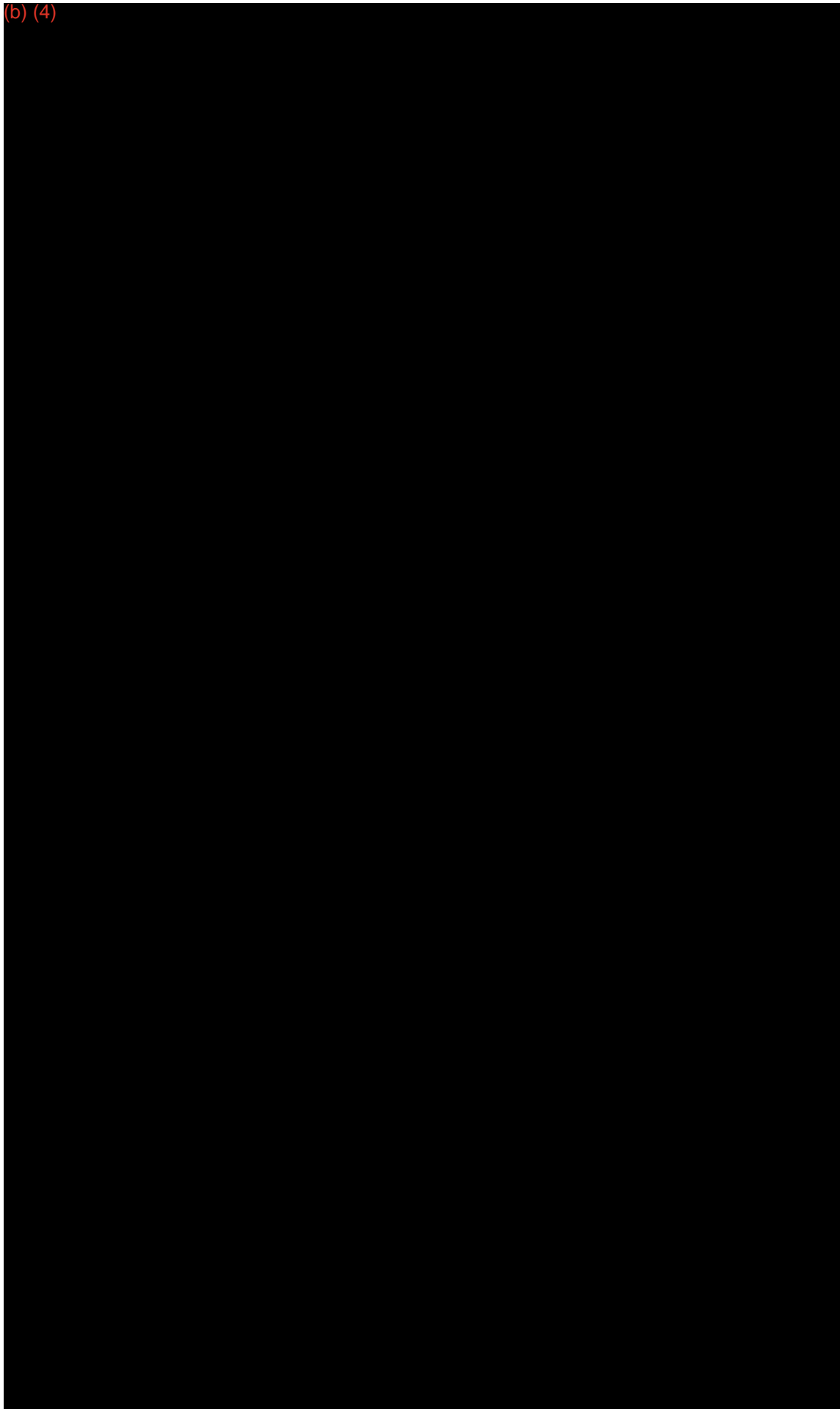
A large black rectangular redaction box covering the content of section 4.1.

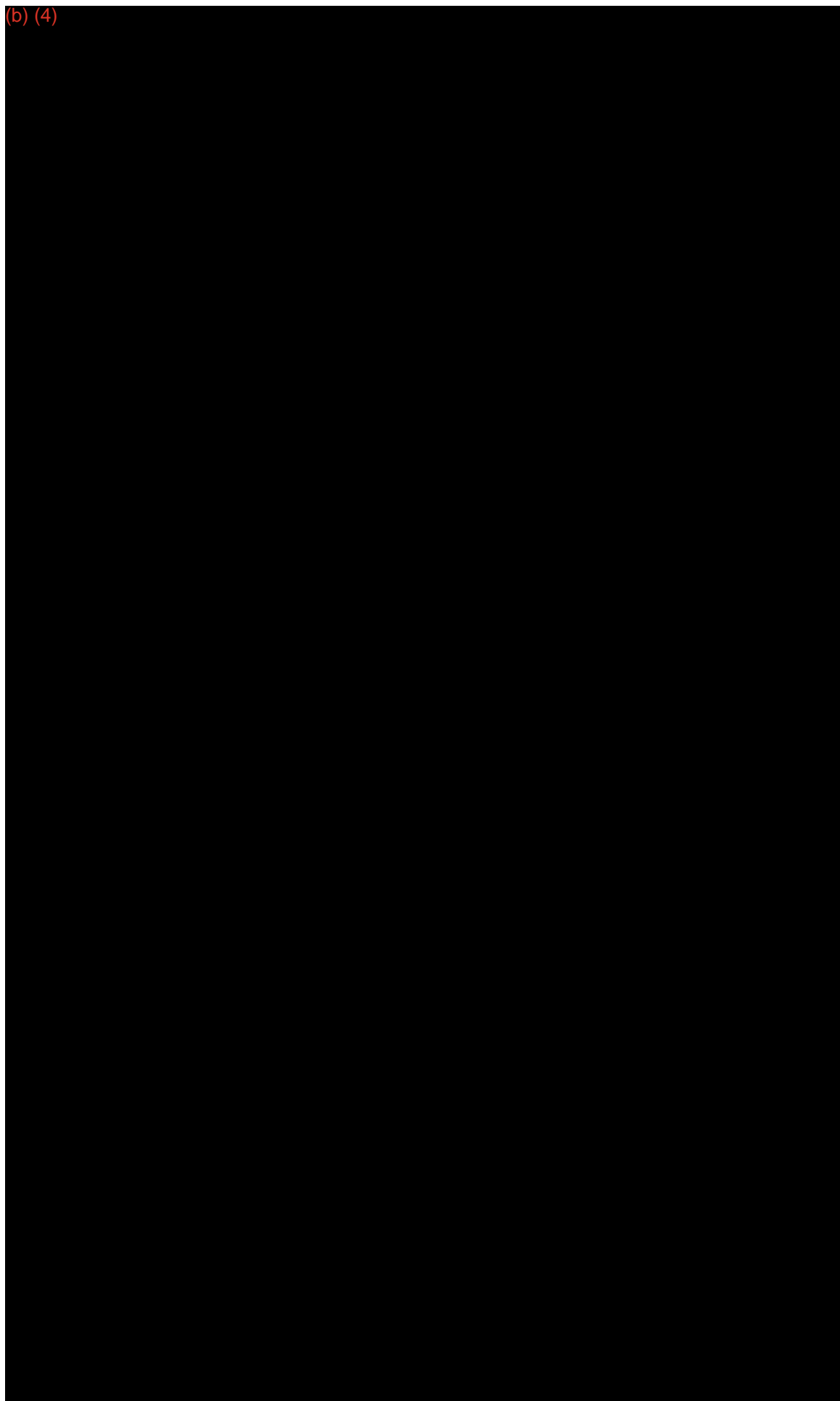
4.2 Scheduled Events

(b) (4)

A large black rectangular redaction box covering the content of section 4.2.







(b) (4)

A large black rectangular redaction box covering the top portion of the page content.

4.3 **Unscheduled Events**

-

4.4 **Common Events**

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5 Roles

5.1 Enabled

The roles described below are enabled in the design and have settings configured according to the text under rights. Any eLearning program attached to a role is also specified.

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5.2 Disabled

6 Study settings

This section contains a summary of the settings in the design.

6.1 Selection View Settings

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6.2 Subject Id Generation Settings

(b) (4)



6.3 SDV

(b) (4)



6.4 Miscellaneous

(b) (4)



6.5 Alerts

-

6.6 Subject Status

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6.7 Randomizations

-

6.8 eLearning

The following eLearning programs are enabled in the design

Site User Training, Monitoring Training

—

7 Edit checks

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(b) (4)



Abstinence - Code Lists

(b) (4)



(b) (4)



(b) (4)



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

Approval IEC: Regional Ethics Committee in Uppsala, chair Madelaine Tunudd

SM 17-03 Subject Information and Informed Consent Form v. 2.0 16NOV2017

Screening number: _____

INFORMATION FOR RESEARCH SUBJECTS IN STUDY SM 17-03

You have been asked if You would like to participate in a research project. Before making a decision, we ask that you review this information carefully. You will also be provided with information verbally and have the chance to ask questions. You will receive a copy of this

STUDY TITLE

A study investigating the metabolism (pharmacokinetic profile) and perceived effect of nicotine from single doses of tobacco-free nicotine pods (ZYN®) in comparison to tobacco-based snus in subjects who are daily snus users.

REQUEST FOR PARTICIPATION

You are hereby asked to participate in a clinical study investigating the metabolism (how much is absorbed in the body and how quickly it is removed) of nicotine from a non-tobacco-based portion snus in comparison to regular snus portions in 18 habitual snus users.

The study will be carried out by Swedish Match (sponsor) in collaboration with Clinical Trial Consultants AB (CTC).

BACKGROUND

There are approximately 1 million snus users in Sweden. But snus is a product based on tobacco that can contain small amounts of carcinogenic substances. Tobacco-free snus would be a welcome alternative. The purpose of the study is to compare nicotine absorption from different strengths of non-tobacco-based portion snus with traditional snus. The tobacco-free pods will be tested in two strengths, 3 mg and 6 mg, which is somewhat lower than the strength of the most commonly used portion snus.

PURPOSE OF THE STUDY

We will investigate the amount of nicotine extracted from non-tobacco-based portion snus and how quickly this is extracted as well as how quickly it is removed from the body and excreted in comparison to regular portion snus. We will also compare the increase in heart rate after using tobacco-free pods with the increase in heart rate after using a portion of regular snus. You will also be asked to note any "nicotine buzz" in a VAS scale visual analogue scale).

THE STUDY'S DESIGN

The study will consist of 7 visits, the initial visit being a screening visit where we determine your suitability for participation in the study and the last being a follow-up by phone. In between the initial visit and final follow-up, you will make 5 visits to CTC's clinic in Uppsala, where you will be asked to use a portion of either a tobacco-free test product or a portion of regular snus.

Visit 1 (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) and a drug test along with an exhalation test to determine whether you have smoked within the last 24 hours. You will also submit a blood sample for HIV and jaundice tests. We will measure your heart rate immediately before and 15 minutes after you use your usual snus brand. If you are found to be a suitable study participant, you will be called in for visit 2 and so on. Visit 1 may be split up over two days.

Visits 2-6 (a time commitment of approximately 6 hours at the clinic)

The study consists of a total of 5 test days of 6 hours each, with a minimum one day break in between each test day. All visits are scheduled in the morning. You will book your test date with the research leader.

Information for research subjects SM17-03 v.2.0



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it is hereby certified that this translation into English agrees with the original document in Swedish 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. +48 8 756 67 08, info@adekvat.se, Stockholm

19.11.2019

On each test day, one of the following dosages will be given:

- 1) A single portion pouch of a tobacco-free pod (containing 3 mg or 6 mg of nicotine) for 60 minutes over 4 occasions.
- 2) A single portion pouch of a typical Swedish Snus brand, with a strength corresponding to General snus (containing 8 mg of nicotine) for 60 minutes on 1 occasion.

The exact order in which you receive the different preparations will be pre-determined according to an established schedule. You will be instructed to keep the portion pouch under your upper lip for 60 minutes. We will then collect the used portion pouch for analysis. Blood samples will be drawn via a venous catheter over a 6-hour period, starting just before you place the portion pouch into the mouth. Your heart rate will be measured at regular intervals before and after you use the snus pouch. You will also be asked regularly about your experience of any "nicotine buzz" after you place the portion pouch under your lip. This is done on what is known as a VAS scale, which is rated from "None at all" to "Highest possible". At each visit, an exhalation test will be performed to determine whether you have smoked within the last 24 hours. Additional drug tests may be performed during the study.

Visit 7

Approximately 7 days after completion of the study, you will do a short follow-up by phone in which you will be asked about side effects and other concomitant medications (other prescriptions, dietary supplements, etc.) since the previous visit and the study is then concluded.

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 be able to learn more about tobacco-free snus.

SIDE EFFECTS AND POSSIBLE RISKS

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.

REGULATORY AUTHORITIES AND INSURANCE

The study has been approved by the Regional Ethical Review Board in Uppsala.

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

SPECIAL RULES

- You must not use snus or any other nicotine-containing product after 20:00 the night before the test day until the test dose is complete.
- You must not smoke within 24 hours of each test day.
- You must not eat, drink or place anything in your mouth (e.g. brushing your teeth or chewing gum) from 30 minutes before or during the dose delivery until 30 minutes after the test dose is complete.
- Before receiving the test dose, you will be asked to rest for 10 minutes, after which your heart rate will be measured.
- 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 on the morning of the test.

- Women are expected to use contraception or remain abstinent to avoid becoming pregnant during the study.
- You must not eat grapefruit or products that contain grapefruit for one week before you are scheduled to receive the first dose until the final study visit.
- You must not ingest energy drinks, such as Redbull, during the study period.
- You must not donate blood or plasma during the study or 3 months after your final follow-up visit.
- You may not participate in any other medical study during the time you participate in this study.

VOLUNTARY.

Participation in the study is fully voluntary. You may stop your participation in the study at any time without being required to provide a reason and without any consequences for you. However, it is important that you notify us.

Your personal doctor and the responsible manufacturing company also have the right to stop your participation if new information arises. You may also be excluded from the study if you are unable to adhere to the study schedule. If new information regarding the study preparation becomes known, you will be informed immediately.

HANDLING OF STUDY DATA

Data that is collected about you during the study will be processed by CTC AB (the research company) or by an outside data processing specialist hired for the study. All data will be treated as confidential and encoded in such a way that your identity cannot be determined. 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. If you would like to make such a request, you must apply for this in writing to the data protection officer, Anders Millerhovf, CTC Clinical Trial Consultants AB, Akademiska Sjukhuset, 751 85 Uppsala. 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 a study doctor/nurse in charge. Authorised persons from regulatory authorities may need to access your study record, while under a duty of professional secrecy, in order to verify that the study has been conducted correctly. By consenting to participate in this study, you authorise the study doctor in charge to disclose such information. In the medical research field, personal data is protected under the *Public Access to Information and Secrecy Act (2009:400)* which contains provisions on public authorities' and certain other bodies' handling of personal data in relation to recording, disclosure and other handling of public documents and this data is also subject to the duty of confidentiality and the *Public Access to Information and Secrecy Ordinance (2009:641)* which regulates who may access or request individual or public documents.

Provisions on the withdrawal of consent, the right to a register extract at no cost and the right to rectification of incorrect or misleading personal data are found in the *Personal Data Act (1998:204)* which is intended to protect individuals from violations of their right to privacy in the processing of personal data and the *Patient Data Act (2008:355)*, which regulates how personal data and medical records shall be handled within the public healthcare sector and by private healthcare providers.

HANDLING OF BLOOD SAMPLES

The blood samples collected during the study for HIV and jaundice testing we will be analysed at the laboratory for clinical microbiology at the Akademiska University Hospital in Uppsala and will be destroyed after analysis is complete. In the event of positive results in the tests for HIV and jaundice (hepatitis), the results, according to current regulations, will be reported to the European Centre for Disease Prevention and Control.

Blood samples taken to measure nicotine levels in your blood will be sent to a laboratory within the

Information for research subjects SM17-03 v.2.0



EU/EEA for analysis. Samples will be destroyed after the study report is completed. Urine samples collected for drug and pregnancy testing will be discarded after analysis.

REMUNERATION

If you complete the study, you will receive taxable remuneration amounting to SEK 5275. No remuneration is provided for lost income. For longer trips, travel costs to and from the clinic can be reimbursed after providing receipts or you may receive mileage reimbursement according to the Swedish Tax Agency's rules. *If, on any occasion, you are found to be in violation of the rules requiring you to refrain from smoking for 24 hours before your appointment on test day, using snus or other nicotine-containing products after 20:00 on the evening before test day, no remuneration will be provided for that test day and you will be asked to book a new test day with the lead researcher.*

STUDY DOCTOR IN CHARGE AND LEAD RESEARCHER

If you have any questions or need more information about the study, you are welcome to contact any member of the study team.

Jan Erik Berglund
XXX

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Screening number [] [] []

WRITTEN CONSENT

- I have received information about the study verbally and I have read the written information provided.
- I have been informed that the personal data collected during the study will be subject to confidentiality and encoded in such a way that my identity will not be disclosed to unauthorised persons. I provide my consent for the personal data collected to be processed by CTC Clinical Trial Consultants AB (the research company) and transferred to another country.
- I hereby allow samples I submit during the study to be registered in a biobank and used and analysed as described in this information.
- I have been informed of my right to receive a register extract once annually regarding the information that has been collected and any sample materials collected.
- I provide my consent for the personal data collected during the study, in its original form, to be disclosed by the study doctor in charge to medical supervisory authorities in different countries, or to staff working in the study, provided that customary confidentiality is observed.
- I have received answers to my questions and consent to participate in the study. I understand that my participation is completely voluntary and that I can withdraw my consent at any time without providing a reason.
- I have been informed that staff or representatives of the company concerned and any relevant supervisory authority may compare data collected in the study with data contained in my study record and hereby provide my consent to this. The above may occur under the condition that the data that is made available to the aforementioned parties is not disclosed further. Only the data that is relevant to the study will be accessed.

.....
Signature of research subject.....
Date.....
Printed name

I have informed the research subject verbally and in writing and have received consent.
The research subject will receive a copy of this information.

.....
Informing physician's signature.....
Date.....
Printed name

Reg no 2017/433

DECISION
01/11/2017**APPLYING PRINCIPAL RESEARCH BODY**

CTC Clinical Study Consultants AB

Researchers performing the project:

Jan-Erik Berglund

**INFORMATION ON THE RESEARCH PROJECT ACCORDING TO
THE APPLICATION RECEIVED BY THE BOARD ON 06/10/2017.****Project title:**

A study investigating the metabolism (pharmacokinetic profile) and perceived effect of nicotine from single doses of tobacco-free nicotine pods (ZYN®) in comparison to tobacco-based snus in subjects who are daily snus users.

Project number/ID:

AM 17-03, version Final05Oct2017

The Regional Ethical Review Board in Uppsala hereby provides notification of the following

DECISION

The board hereby approves the application and, by virtue of Section 6 of the Act concerning the Ethical Review of Research Involving Humans (SFS 2003:460), grants permission to conduct the study described in the application.

Condition

In the information for the research subjects, the following must be changed:

1. Under the header, Handling of study data, the word "Confidential" shall be replaced by "encoded".



Address	Telephone	Fax	Email
Box 1964 751 49 Uppsala	018-4717400	018-4717410	registrator@uppsala.epn.se

Reg no 2017/433

2. In the information about the Personal Data Act, it must be stated that there is no charge for the test subject to access the information recorded about him/her under the framework of the study.
3. Under the header, "Handling of blood samples", the information "*In the event of positive results in the tests for HIV and jaundice (hepatitis), the results, according to current regulations, will be reported to the European Centre for Disease Prevention and Control*" shall be added.
4. The abbreviation PK test must be removed and the full name of the test must be written out.
5. In the consent form, "*confidential*" shall be replaced with "*encoded*".
6. Additionally, "*record*" should be replaced with "*study record*" for the sake of clarity (alt. "*study protocol*").

Reminder

This approval will cease to apply if the study in the application is not commenced within two years of the final decision.

THIS DECISION MAY BE APPEALED

See instructions.

On behalf of the Ethical Review Board

[SIGNATURE]

Madelaine Tunudd
Chair

Decision-making party:

Madelaine Tunudd, judge, chair

Members with scientific expertise:

Jan-Erik Broman, psychiatry, Ulla Friberg, ear nose and throat, Jan Gustafsson, paediatrics, Martin Höglund, haematology, scientific secretary, Marieann Högman, respiratory physiology, Anneli Stavreus-Evers, gynaecology and reproductive medicine, Christer Sundström, pathology, scientific secretary, Agneta Yngve-rapporteur, nutrition, Lars Wiklund anaesthesiology and Anna Cristina Åberg, geriatrics.



Address	Telephone	Fax	Email
Box 1964 751 49 Uppsala	018-4717400	018-4717410	registrator@uppsala.epn.se

Reg no 2017/433**Members representing the public interest:**

Tommy Berger, Ann-Mari Bergström, Daniel Didricksson and Hanna Karin Linck.

Dispatched to:

Researcher: Jan-Erik Berglund

Principle research body's representative: CEO Anders Millerhovf



Address
Box 1964
751 49 Uppsala

Telephone
018-4717400

Fax
018-4717410

Email
registrator@uppsala.epn.se

Reg no 2017/433

How to appeal the Ethical Review Board's decision

Who may appeal?

Any appeal shall be made by the **principle research body/authorised representative**. Authorized representatives may provide written authorisation to researchers who are carrying out the project.

Where should appeals be sent?

The Board's decision can be appealed to the Central Ethical Review Board in Stockholm. However, the appeal must be sent or submitted to: The Regional Ethical Review Board in Uppsala Box 1964, 751 49 UPPSALA.

If the appeal is received before the prescribed deadline, the Board will submit the appeal and documentation to the Central Ethical Review Board.

What is the deadline for appeal?

The appeal must be received by the Board **within three weeks** from the date you received the decision.

What needs to be included in the appeal?

The appeal must be made in writing and must be signed.

In the appeal, indicate

- Your name, personal identity number/company registration number and telephone number,
- which decision you are appealing, e.g., by specifying the decision date and the case registration number,
- how you believe the Board's decision should be changed and why it should be changed.



any power of attorney forms as an attachment.

(b) (6)

It is hereby certified that this translation into *English* agrees with the original document in *Swedish* 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. +48 8 756 67 08, info@adekvat.se, Stockholm *19-11-2019*

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Box 1964
751 49 Uppsala

Telephone
018-4717400

Fax
018-4717410

Email
registrator@uppsala.epn.se

Dnr 2017/433

BESLUT
2017-11-01**SÖKANDE FORSKNINGSHUVUDMAN**

CTC Clinical Trial Consultants AB

Forskare som genomför projektet:

Jan-Erik Berglund

**UPPGIFTER OM FORSKNINGSPROJEKTET ENLIGT ANSÖKAN
INKOMMEN TILL NÄMNDEN 2017-10-06.****Projekttitel:**

En studie som undersöker omsättning i kroppen (farmakokinetisk profil) och upplevd effekt av nikotin från singeldoser av tobaksfria nikotinpods (ZYN) jämfört med tobaksbaserat snus hos dagliga snusanvändare.

Projektnummer/identitet:

AM 17-03, version Final05Oct2017

Regionala etikprövningsnämnden i Uppsala meddelar följande

BESLUT

Nämnden bifaller ansökan och godkänner med stöd av 6 § lagen (2003:460) om etikprövning av forskning som avser människor den forskning som anges i ansökan.

Villkor

I informationen till forskningspersonerna ska följande ändras:

1. Under rubriken Hantering av studiedata ska ordet "*Konfidentiell*" bytas ut till "*kodat*".

Dnr 2017/433

2. I informationen om personuppgiftslagen ska det framgå att det är kostnadsfritt för försökspersonen att få ut vilka uppgifter om denne(a) som är registrerade inom ramen för studien.
3. Under rubriken "Hantering av blodprover" ska upplysningen om att "*Vid ev. positiva fynd i testarna för HIV och gulsot (hepatit) kommer resultatet, enligt gällande bestämmelser, att rapporteras till Smittskyddsmyndigheten*" läggas till.
4. Förkortningen PK-test ska tas bort och testets fullständiga namn skrivas ut.
5. I samtyckesblanketten ska "*konfidentiellt*" bytas ut till "*kodat*".
6. Vidare ska "*journal*" för tydlighets skull ersättas med "*studiejournal*" (alt. "studieprotokoll").

Erinran

Godkännandet upphör att gälla om forskningen inte har påbörjats inom två år efter slutgiltigt beslut.

BESLUTET FÅR ÖVERKLAGAS

Se anvisning.



Madelaine Tunudd
ordförande

Beslutande:

Madelaine Tunudd, rådman, ordförande

Ledamöter med vetenskaplig kompetens:

Jan-Erik Broman, psykiatri, Ulla Friberg, öron-näsa-hals, Jan Gustafsson, pediatrik, Martin Höglund, hematologi, vetenskaplig sekreterare, Marieann Högman, respirationsfysiologi, Anneli Stavreus-Evers, gynekologi och reproduktiv medicin, Christer Sundström, patologi, vetenskaplig sekreterare, Agneta Yngve-föredragande, nutrition, Lars Wiklund, anestesiology och Anna Cristina Åberg, geriatrik.

Ledamöter som företräder allmänna intressen:

**Dnr 2017/433**

Tommy Berger, Ann-Mari Bergström, Daniel Didricksson och Hanna Karin
Linck.

Expedieras till:

Forskare: Jan-Erik Berglund

Forskningshuvudmannens företrädare: VD Anders Millerhovf

Dnr 2017/433

Hur man överklagar etikprövningsnämndens beslut

Vem får överklaga?

Överklagandet ska göras av **forskningshuvudmannen/ behörig företrädare**. Behörig företrädare får lämna skriftlig fullmakt till forskare som genomför projektet.

Var ska beslutet överklagas?

Nämndens beslut kan överklagas hos Centrala etikprövningsnämnden, Stockholm. Överklagandet ska dock skickas eller lämnas till: Regionala etikprövningsnämnden i Uppsala, Box 1964, 751 49 UPPSALA.

Har överklagandet inkommit i rätt tid överlämnar nämnden överklagandet och handlingarna till Centrala etikprövningsnämnden.

När ska beslutet senast överklagas?

Överklagandet ska ha kommit in till nämnden **inom tre veckor** från den dag Ni fick del av beslutet.

Vad ska överklagandet innehålla?

Överklagandet ska vara skriftligt och det ska vara undertecknat.

I skrivelsen ska Ni ange

- Ert namn, adress, personnummer/organisationsnummer och telefonnummer,
- vilket beslut som Ni överklagar t.ex. genom att ange beslutsdatum och ärendets diarienummer,
- hur Ni anser att nämndens beslut ska ändras och varför det ska ändras.
- eventuell fullmakt som bilaga.

Screeningnummer: _____

INFORMATION TILL FORSKNINGSPERSONER I STUDIE SM 17-03

Du har tillfrågats om Du vill delta i ett forskningsprojekt. Innan Du bestämmer dig ber vi att Du läser igenom denna information noggrant. Du kommer också att få muntlig information och ges möjlighet att ställa frågor. Du kommer att få en kopia på denna information med dig hem.

STUDIETITEL

En studie som undersöker omsättning i kroppen (farmakokinetisk profil) och upplevd effekt av nikotin från singeldoser av tobaksfria nikotinpods (ZYN®) jämfört med tobaksbaserat snus hos dagliga snusanvändare.

FÖRFRÅGAN OM DELTAGANDE

Du tillfrågas härmed om du vill delta i en klinisk studie som undersöker omsättning i kroppen (hur mycket som tas upp av kroppen och hur snabbt det försvinner) av nikotin från ett icke-tobaksbaserat portionssnus jämfört med vanliga snusportioner hos 18 stycken vanesnusare.

Studien utförs av Swedish Match (sponsor) i samarbete med Clinical Trial Consultants AB (CTC).

BAKGRUND

Det finns ca 1 miljon snusare i Sverige. Men snus är baserat på tobak som kan innehålla små mängder cancerframkallande ämnen. Ett tobaksfritt snus skulle vara välkommet. Avsikten med studien är att jämföra nikotinupptaget från ett icke-tobaksbaserat portionssnus av olika styrkor med traditionellt snus. Två styrkor av tobaksfria pods ska testas, 3 mg och 6 mg, vilket är något lägre än i de vanligaste typerna av portionssnus.

SYFTE MED STUDIEN

Vi vill undersöka hur mycket och hur snabbt nikotin tas upp och försvinner från kroppen samt utsöndras från icke-tobaksbaserat portionssnus jämfört med en portion av vanligt snus. Vi vill också jämföra pulsökningen efter tobaksfria pods med pulsökningen efter en portion vanligt snus. Du får också markera eventuell "nikotinkick" i en s.k. VAS-skala (visuell analog skala).

STUDIENS UPPLÄGG

Studien består av 7 besök varav det första är ett screeningbesök där vi kontrollerar om du kan delta i studien, och det sista ett uppföljningsbesök via telefon. Däremellan görs 5 besök på CTCs klinik i Uppsala då du får använda en portion av antingen en tobaksfri testprodukt eller en portion vanligt snus.

Besök 1 (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) och drogtest samt får göra ett utandningstest för att se om du rökt de senaste 24 timmarna. Du får även lämna ett blodprov för kontroll av HIV och gulsot. Vi mäter din puls strax före och 15 minuter efter intag av ditt vanliga snusmärke. Om du är lämplig att delta i studien blir du kallad till besök 2 och framåt. Besök 1 kan delas upp på två dagar.

Besök 2-6 (tidsåtgång ca 6 timmar på kliniken)

Studien omfattar totalt 5 försöksdagar om vardera ca 6 timmar, med minst en dags uppehåll mellan varje försöksdag. Alla besök görs på morgonen. Du bokar in försöksdatumen med försöksledaren.

På varje försöksdag kommer en av följande doseringar att ges:

- 1) En portionspåse av en tobaksfri pod (innehåller 3 mg eller 6 mg nikotin) i 60 minuter vid 4 tillfällen.
- 2) En portionspåse av normalt svenskt snus, ungefär lika starkt som General (innehåller 8 mg nikotin) i 60 minuter vid 1 tillfälle.

I vilken ordning som just du får de olika preparaten, bestäms av ett på förhand uppgjort schema. Du kommer att instrueras att hålla portionspåsen stilla under överläppen i 60 minuter. Därefter samlas din använda portionspåse in för analys. Blodprover kommer att tas via en venkateter under 6 timmar med start strax innan du lagt in portionspåsen i munnen. Din puls mäts före och efter snusintag med regelbundna intervall. Du kommer också att regelbundet tillfrågas om eventuell "nikotinkick" efter att du har lagt in portionspåsen. Detta görs med hjälp av en så kallad VAS-skala som är graderad från "Inget alls" till "Mest tänkbara".

Vid varje besök kommer ett utandningstest att göras för att se om du rökt de senaste 24 timmarna. Ytterligare drogtest kan komma att utföras under studien.

Besök 7

Omkring 7 dagar efter studiens slut görs en kort uppföljning via telefon då du tillfrågas om biverkningar och annan samtidig medicinering sedan föregående besök och därefter avslutas studien.

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 erbjuds ta del av kunskap om tobaksfritt snus.

BIVERKNINGAR OCH MÖJLIGA RISKER

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.

MYNDIGHETER OCH FÖRSÄKRING

Studien är godkänd av Regionala etikprövningsnämnden i Uppsala.

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

SPECIELLA FÖRHÅLLNINGSGREGLER

- Du får inte snusa eller använda någon annan form av nikotin från klockan 20.00 kvällen före varje försöksdag tills efter doseringen.
- Du får inte röka 24 timmar innan varje försöksdag.
- Du får inte äta, dricka eller ha något i munnen (t.ex. borsta tänderna eller tugga tuggummi) från 30 minuter innan eller under dosering, samt 30 minuter efter doseringen.
- Innan försöket startar får du vila i 10 minuter, varefter din puls mäts.
- 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 på morgonen.

- Du som är kvinna förväntas använda preventivmedel eller iaktta avhållsamhet för att undvika gravid under studiens gång.
- Du får inte äta grapefrukt eller grapefrukthinnehållande produkter från en vecka innan första doseringsdagen till sista studiebesöket.
- Du ska avstå från energidrycker, t.ex Redbull, under studieperioden.
- Du får inte donera blod eller plasma under studien eller 3 månader efter det sista uppföljningsbesöket.
- Du får inte delta i någon annan medicinsk studie samtidigt med denna.

FRIVILLIGHET.

Ditt deltagande i studien är helt frivilligt. Du kan när som helst avbryta ditt deltagande utan att behöva ange något skäl och utan att det medför några konsekvenser för dig. Det är dock viktigt att du meddelar oss detta.

Din läkare och ansvarigt tillverkningsföretag har också rätt att avbryta ditt deltagande om ny information framkommer. Du kan även bli utesluten ur studien om det visar sig att du inte kan följa försöksplanen. Om någon ny information om studiepreparatet blir tillgänglig kommer du genast att bli informerad.

HANTERING AV STUDIEDATA

De uppgifter som samlats in om dig i studien kommer att bearbetas av CTC AB (forskningsföretaget) eller av en anlitad specialist på databearbetning. Uppgifterna kommer att behandlas kodat och på ett sådant sätt att Din identitet inte kan avslöjas. 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. Du ska i då ansöka om detta skriftligen till Personuppgiftsombudet, Anders Millerhovf, CTC Clinical Trial Consultants AB, Akademiska Sjukhuset, 751 85 Uppsala. Ansökan ska vara undertecknad och innehålla information om studiens namn. Du kan även begära att felaktiga uppgifter om dig rättas. Du ska i då vända dig till studieansvarig läkare/sköterska. Behöriga personer från myndigheter kan behöva titta i din studiejournal, för att under tystnadsplikt kontrollera att studien utförts på ett korrekt sätt. Ditt samtycke att delta i studien innebär att Du ger ansvarig läkare tillstånd att lämna ut sådana uppgifter. Personuppgifter i medicinsk forskning skyddas av *Offentlighets- och Sekretesslag (2009:400)* vilken innehåller bestämmelser om myndigheters och vissa andra organs handläggning vid registrering, utlämnande och övrig hantering av allmänna handlingar men även tystnadsplikt samt *Offentlighets- och Sekretessförordning (2009:641)* som styr vem som får ta del av eller begära ut enskilda eller allmänna handlingar.

Bestämmelser om återkallande av samtycke, rätt till gratis registerutdrag och rättelse av felaktiga eller missvisande personuppgifter finns i *Personuppgiftslag (1998:204)* som syftar till att skydda människor mot att deras personliga integritet kränks genom behandling av personuppgifter samt *Patientdatalag (2008:355)* vilken styr hur personuppgifter och studiejournalhandlingar ska hanteras inom hälso- och sjukvården men också hos privata vårdgivare.

HANTERING AV BLODPROVER

De blodprov som tas under studien för kontroll av HIV och gulsot kommer att analyseras vid laboratoriet för klinisk mikrobiologi på Akademiska sjukhuset i Uppsala och förstörs efter att analysen är klar. Vid ev. positiva fynd i testerna för HIV och gulsot (hepatit) kommer resultatet, enligt gällande bestämmelser, att rapporteras till Smittskyddsmyndigheten,

Blodprover som tas för mätning av nikotinnivåerna i ditt blod kommer att skickas till laboratorium inom EU/EES för analys. Proverna kommer att destrueras efter det att studierapporten har slutförts.

De urinprov som samlas in för drogtest och graviditetstest kommer slängas efter analys.

ERSÄTTNING


Om du fullföljer studien kommer du att erhålla en skattepliktig ersättning på 5275 kr. Ingen ersättning för förlorad arbetsinkomst utgår. Vid längre resor kan resekostnader till och från kliniken ersättas mot kvitto eller med milersättning enligt Skatteverkets regler. *Om du vid något tillfälle bryter mot regeln att avstå ifrån rökning 24 timmar innan en försöksdag alternativt snus eller andra nikotinprodukter från kl 20.00 kvällen före försöksdag utgår ingen ersättning för den försöksdagen utan du bokar in ny försöksdag med försöksledningen.*

ANSVARIG LÄKARE OCH FÖRSÖKSLEDNING

Om du har några frågor eller behöver mer information om denna studie, kontakta någon av oss som arbetar med studien.

Jan Erik Berglund
XXX

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

A large black rectangular redaction box covers the contact information for Jan Erik Berglund.

Screeningnummer | _ | _ |

SKRIFTLIGT SAMTYCKE

- Jag har muntligen informerats om studien och jag har läst den skriftliga informationen.
- Jag har fått information att de uppgifter som samlats in om mig i studien kommer att behandlas kodat, på ett sådant sätt att min identitet inte kommer att avslöjas för obehöriga. Jag godkänner att uppgifterna som samlas in får bearbetas av CTC Clinical Trial Consultants AB (forskningsföretaget) och överföras till annat land.
- Jag tillåter att prover som lämnas av mig i studien registreras i en biobank samt används och analyseras som beskrivits i denna information.
- Jag är informerad om rättigheten att få registerutdrag en gång per år över vilka uppgifter och eventuellt provmaterial som samlats in.
- Jag tillåter att i studien insamlade uppgifter i original kan utlämnas av ansvarig läkare till medicinska kontrollmyndigheter i olika länder, eller till personal som arbetar med studien under förutsättning att sedvanlig sekretess upprätthålls.
- Jag har fått svar på mina frågor och jag samtycker till att delta i studien. Mitt deltagande är frivilligt och jag kan avbryta när som helst utan förklaring.
- Jag har informerats om och samtycker härmed till att personal från berört företag eller dess representant och eventuell kontrollmyndighet får jämföra uppgifter i studien med uppgifter som finns i min studiejournal. Detta får ske under förutsättning att den information som därvid blir tillgänglig inte förs vidare. Endast de uppgifter som har betydelse för studien kommer att kontrolleras.

.....
Forskningspersonens underskrift.....
Datum.....
Namnförtydligande

Jag har informerat forskningspersonen muntligt och skriftligt och mottagit samtycke.
Forskningspersonen erhåller en kopia av denna information.

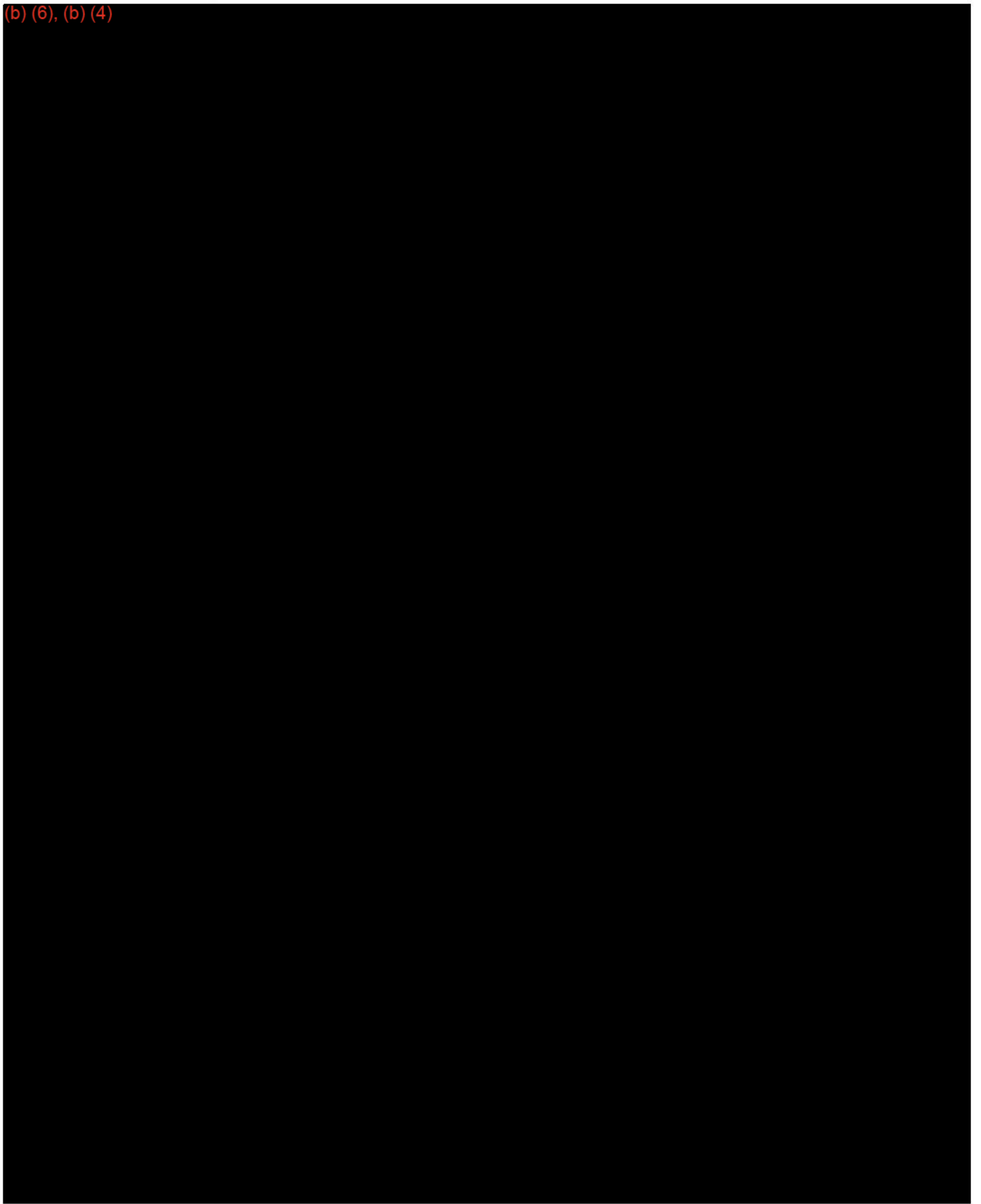
.....
Informerande läkares underskrift.....
Datum.....
Namnförtydligande

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

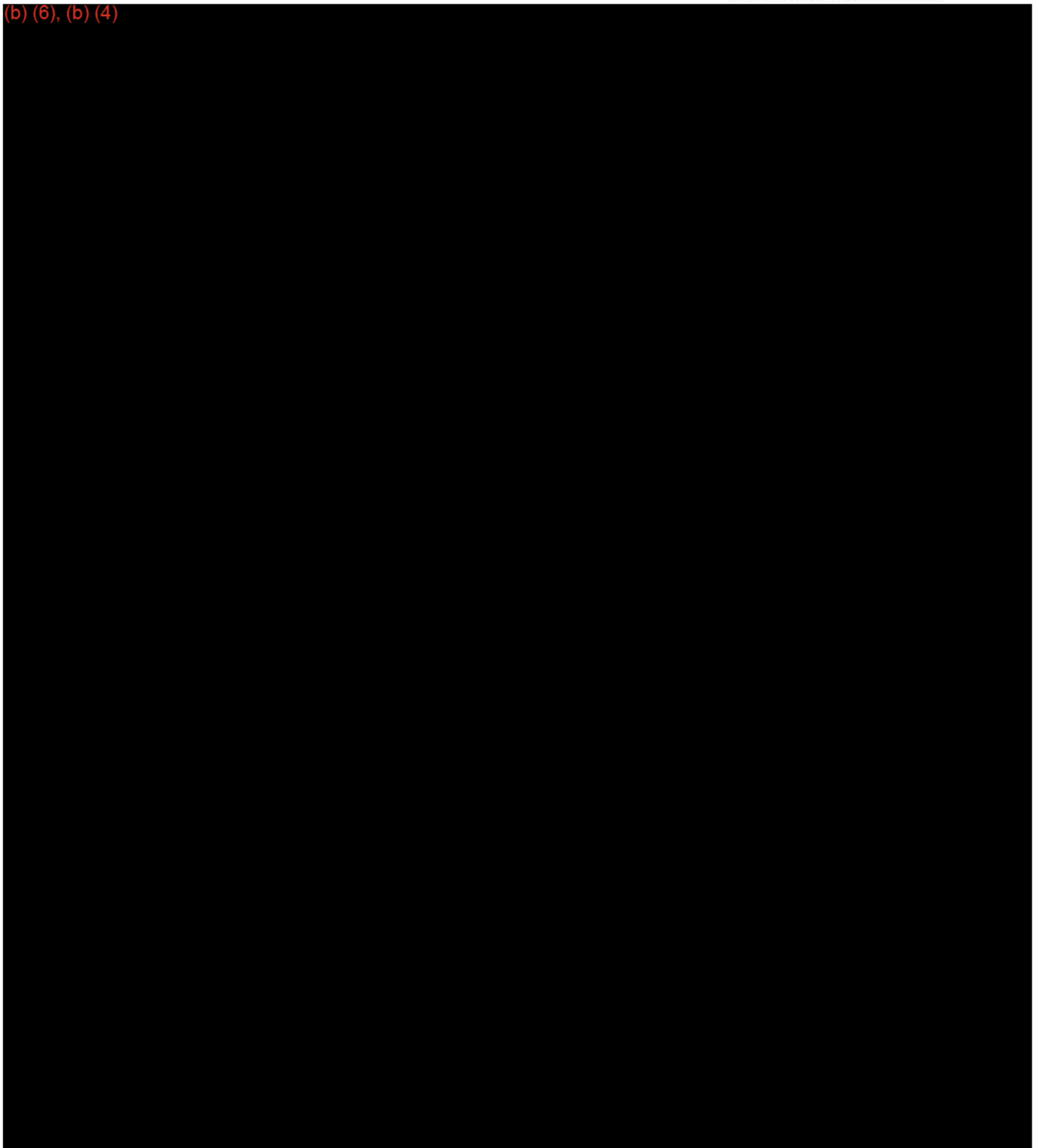
[CV Jan Erik Berglund](#)

[CV Erik Hedin](#)

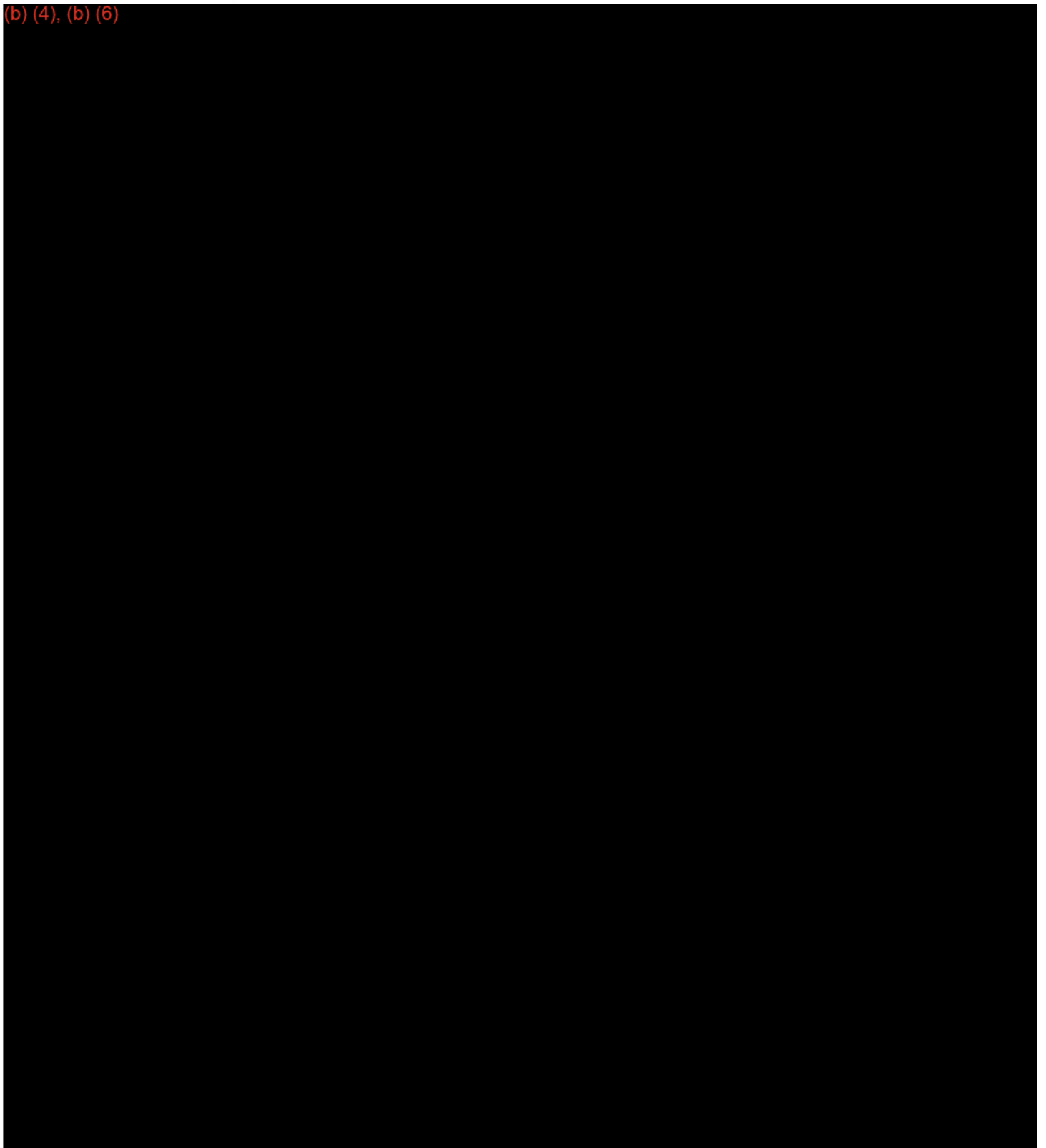
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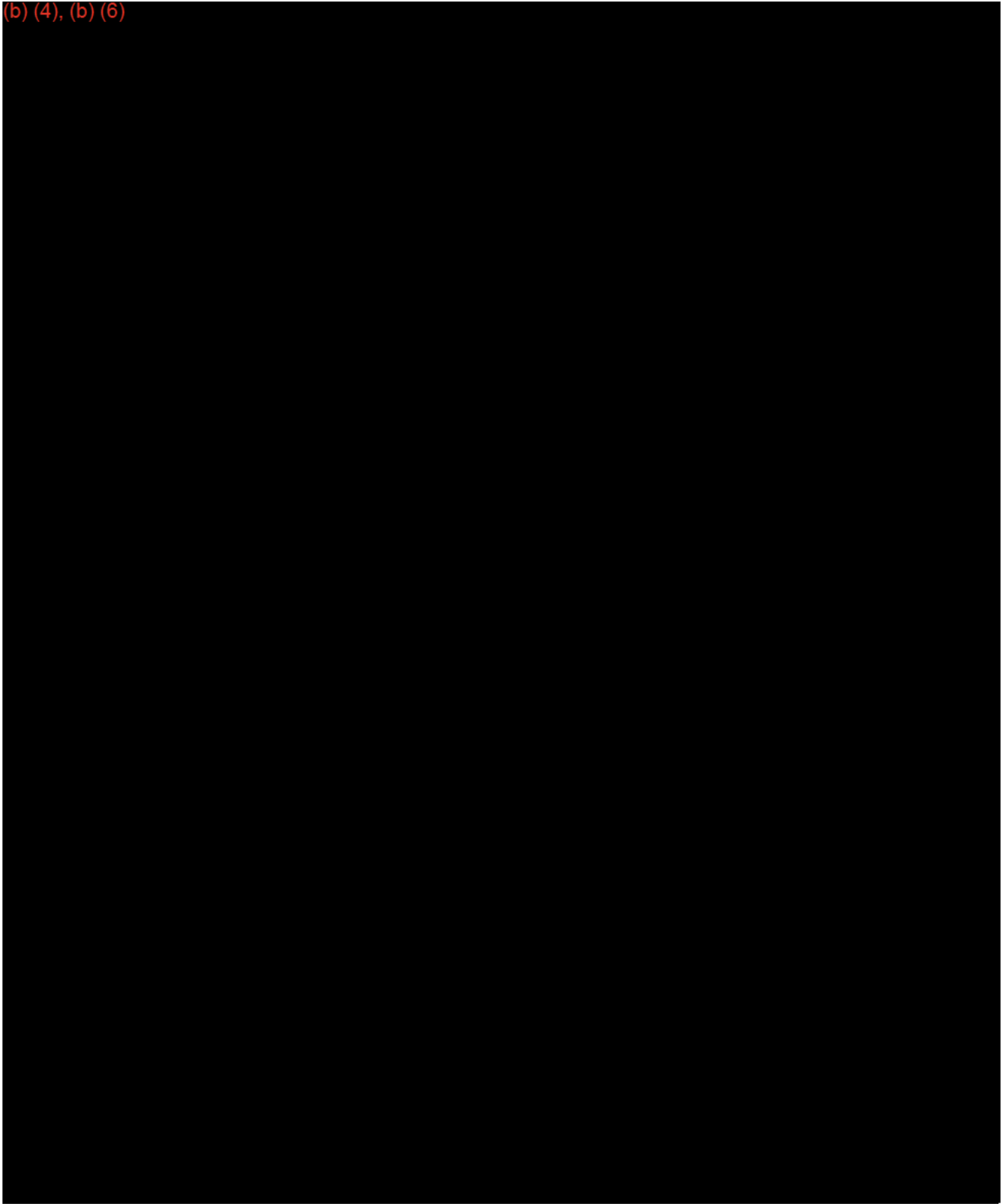
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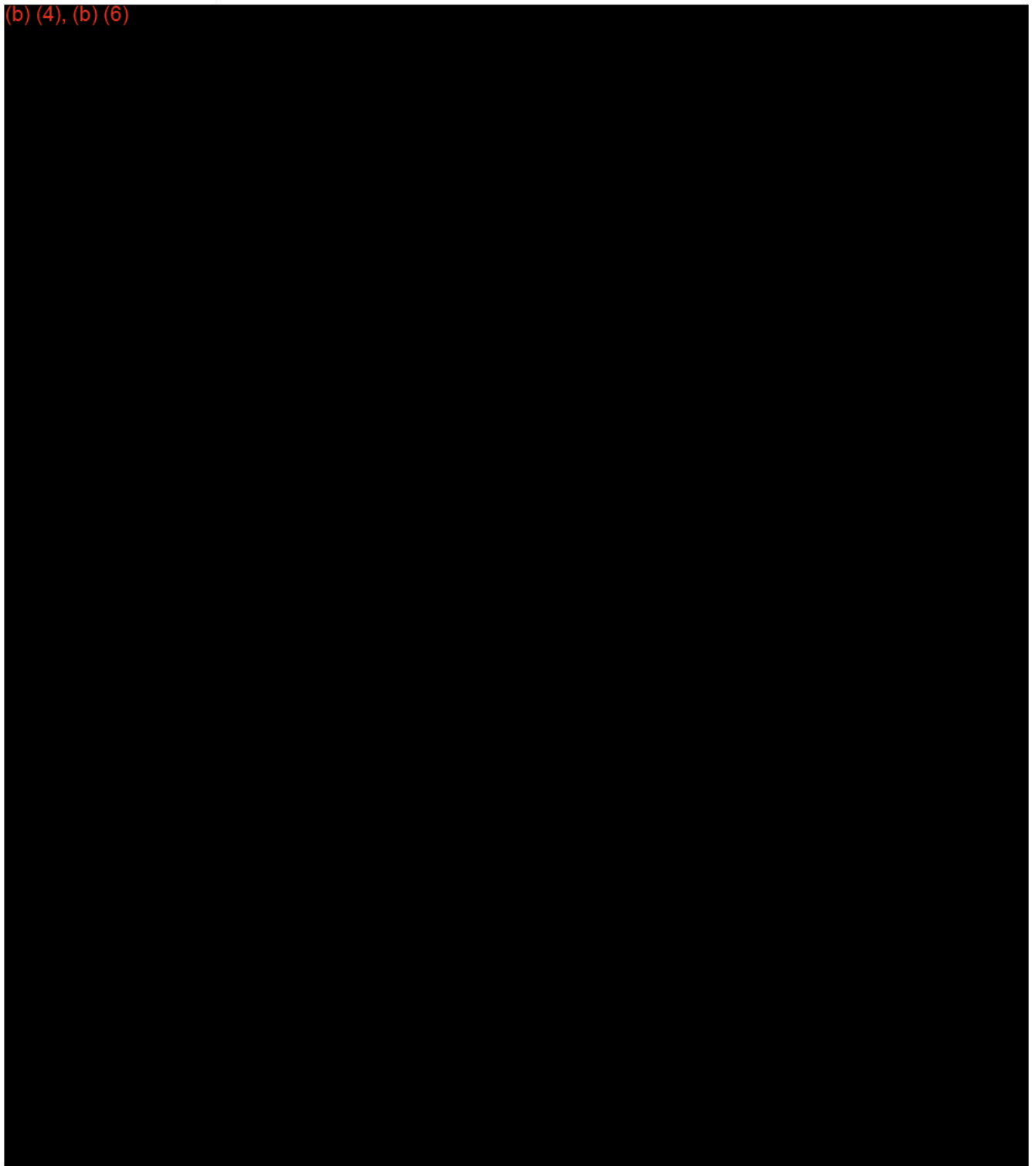
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(b) (4), (b) (6)



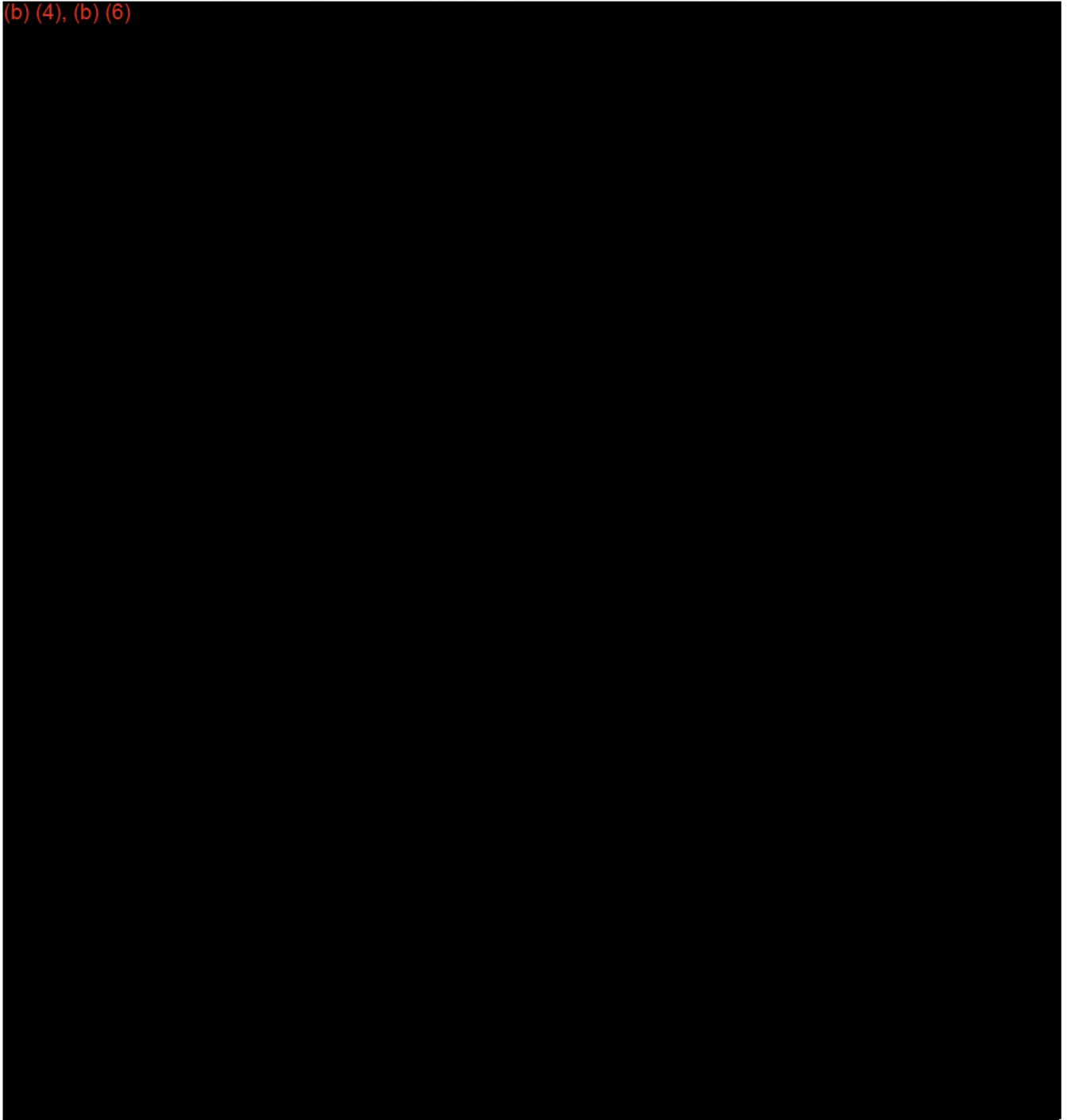
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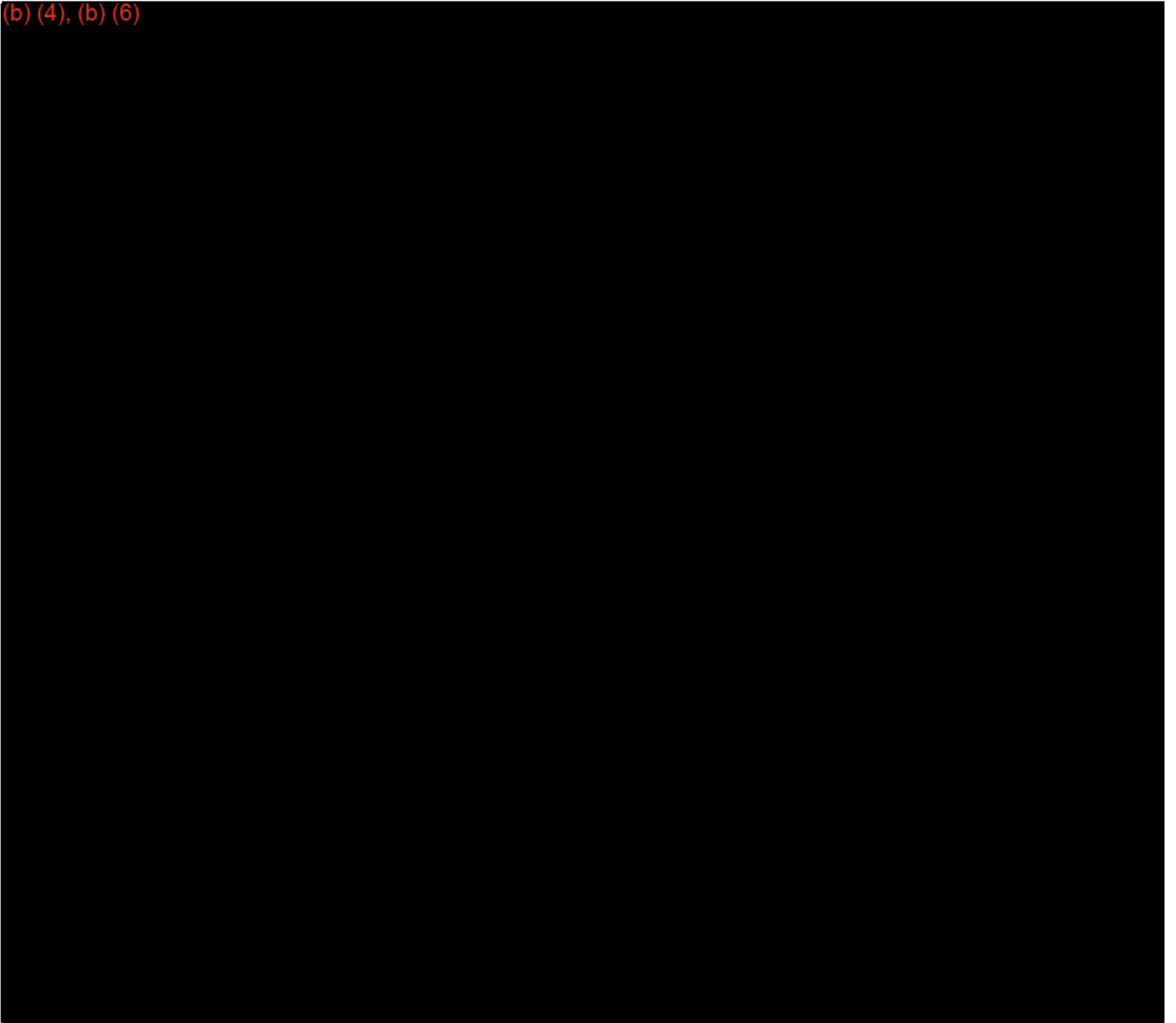
Jan Erik Berglund
Senior Consultant, MD, PhD

CTC CLINICAL TRIAL CONSULTANTS AB

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

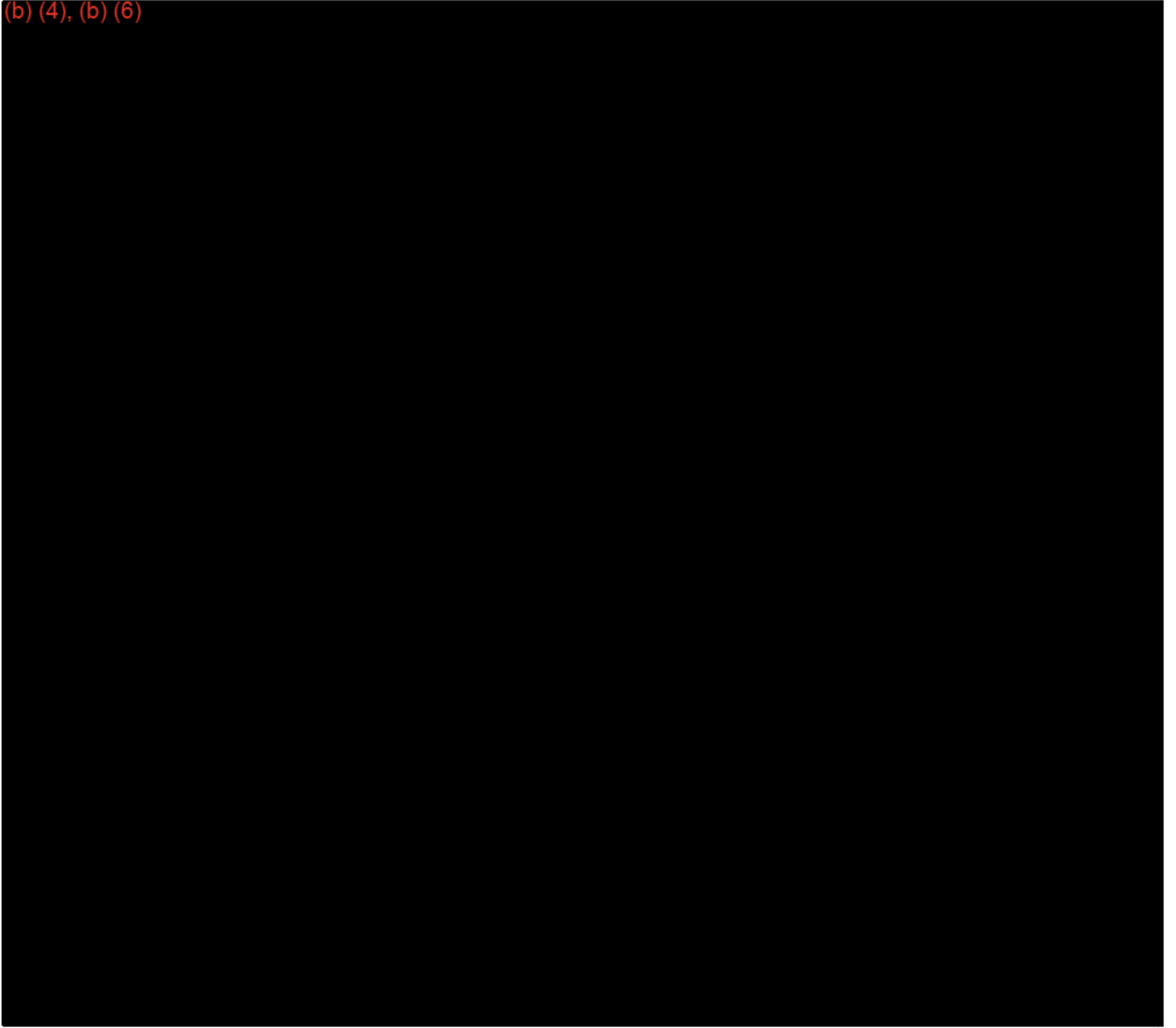


(b) (4), (b) (6)



16.1.5 Signatures of Sponsor, Statistician and Principal Investigator

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



**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)

[Randomisation SM 1703 Final 06NOV2017](#)

(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



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(b) (4)



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(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



(b) (4)



16.1.8 Audit Certificates (If Available)

Not applicable.

16.1.9 Documentation of Statistical Methods

[Statistical Analysis Plan SM1703 12MAR2018 final](#)

CONFIDENTIAL

Statistical Analysis Plan (SAP)

Sponsor:	Swedish Match AB
Study code:	SM 17-03
Study title:	Nicotine pharmacokinetics and subjective effects of a single dose of a non-tobacco-based nicotine pouch (ZYN®) compared with conventional, tobacco-based Swedish snus among current, daily snus users.
Date:	12MAR2018 – FINAL

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1 LIST OF ABBREVIATIONS

AE – Adverse Event

ATC – Anatomical-Therapeutic-Chemical

CF – Clean File

CRF – Case Report Form

CSP – Clinical study protocol

FAS – Full Analysis Set

MedDRA – Medical Dictionary for Regulatory Affairs

PPS – Per Protocol Set

SAE – Serious Adverse Event

SAP – Statistical Analysis Plan

SAS – Statistical Analysis System

SD – Standard Deviation

2 INTRODUCTION

This Statistical Analysis Plan (SAP) gives details regarding the statistical analyses and data presentation outlined in the final Clinical study protocol (CSP) for the study *SM 17-03 Protocol_Final_1.0_05Oct2017*. Any changes from the final CSP are given in Section 8.

3 CLINICAL STUDY DETAILS

3.1 Clinical Study Objectives

3.1.1 Primary objective

To compare each subject's AUC_{inf} based on plasma concentrations of nicotine after administration of one single dose of a novel, non-tobacco-based nicotine pouch containing 3 and 6 mg of nicotine, to that of one single dose from a 1 g Swedish snus pouch containing 8 mg of nicotine.

3.1.2 Primary endpoint

AUC_{inf} based on plasma concentrations of nicotine after administration of one single dose of a novel, non-tobacco-based nicotine pouch containing 3 and 6 mg of nicotine, to that of one single dose from a 1 g Swedish snus pouch containing 8 mg of nicotine.

3.1.3 Secondary objectives

1. To compare AUC_{60min} , C_{max} , T_{max} , AUC_{Co-t} and terminal half-life of a novel, non-tobacco-based nicotine pouch to that of a Swedish snus pouch.
2. To compare the estimated *in-vivo* extracted amount of nicotine from a novel, non-tobacco-based nicotine pouch containing 3 and 6 mg of nicotine, respectively, with that from a 1 g Swedish snus pouch containing 8 mg of nicotine.
3. Comparison of pulse rate and subjective effects ("head buzz") after study product administration (proxy for *in vivo* nicotine uptake).
4. Adverse events

3.1.4 Secondary endpoints

1. AUC_{60min} , C_{max} , T_{max} , AUC_{Co-t} and terminal half-life of a novel, non-tobacco-based nicotine pouch to that of a Swedish snus pouch.
2. *In-vivo* extracted amount of nicotine
3. To assess the correlation between the estimates of AUC_{inf} and the total amount of nicotine extracted from the ZYN® pouches.
4. Pulse rate and VAS for measure "head buzz" (head rush, "hit", feeling alert, overall "product strength"), using a 100-mm visual analogue scale (VAS) anchored with "not at all" to "extremely" at preset time points up to 60 minutes (predose, + 5min, +10 min, + 15 min, +30 min, +60 min after each dose), respectively, after study product administration (proxy for systemic uptake).
5. Collection of adverse events

3.2 Clinical Study Design

The study will be conducted as an open, randomized, five-way cross-over, single dose administration. The study will include 18 subjects.

The subjects included will be healthy males and females 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 $\leq 1\%$) or two or more cans (brands with nicotine content $> 1\%$). Subjects who are pregnant or who have a history of hypertension or any cardiovascular disease are excluded. Subjects shall be abstinent from snus and all other nicotine containing products from 8.00 p.m. the night before each trial day.

Before entry to the study subjects undergo screening evaluations including smoking and snus use, medical history and pulse rate measurements before/after application of their usual brand of snus. The pulse rate assessment will be made in abstinent condition from 8 p.m. the night before.

A pulse rate increase of ≥ 10 beats/min in the morning before use of any nicotine containing product will classify the subject as eligible for participation in the study.

Subjects report to the clinic on separate days for the 5 experimental sessions. The subjects are instructed to abstain from snus, cigarettes or other nicotine delivery products as from 8 pm the evening before. All sessions are performed during the morning hours to facilitate abstinence. The subjects should certify abstinence before each treatment is started.

The treatments are administered as single doses in a pre-determined randomized order. The subject keeps the pouch still between the upper lip and the gum for 60 minutes and are instructed not to manipulate the pouch with the tongue or lips. The subjects are instructed not to eat, drink, chew chewing gum or brush teeth from 30 minutes before application of treatment, during application of investigational products and 30 minutes after the investigational product has been taken out.

Each used pouch is collected and frozen (-20°C) pending analyses of nicotine.

3.3 Number of Subjects

The study will include 18 subjects.

3.4 Methods of Assigning Subject to IMP

Subjects will be assigned to the treatments using a computer-generated randomization list.

3.5 Blinding

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

3.6 Treatments

Test articles:

- 1= ZYN Smooth containing 3 mg nicotine per portion
- 2= ZYN Smooth containing 6 mg nicotine per portion
- 3= ZYN Smooth containing 3 mg nicotine per portion (alternative manufacturing process)
- 4= ZYN Smooth containing 6 mg nicotine per portion (alternative manufacturing process)

Reference articles:

- 5= Swedish portion snus PSWL 1.0 g (8 mg nicotine/g)

4 STATISTICAL AND ANALYTICAL PLANS

4.1 Sample Size Justification

The primary endpoint is nicotine extraction. The study will include 18 subjects. A previous study [Lunell E & Curvall M 2011] has made the calculation of sample size possible. Nicotine extraction from a 1 g Swedish portion snus (PSWL) containing 8mg nicotine/pouch was estimated at 2.18 ± 0.92 mg per portion. Under the assumption of a complete dissolution and *in-vivo* extraction of the 3 and 6 mg ZYN® products, respectively, versus the 2.18 ± 0.92 mg nicotine, and a standard deviation of 5.0 the estimated sample size is 16 with a power of 80% and $\alpha=0.05$. The randomization will be performed using Latin Squares approach.

4.2 Definition of Analysis Sets

4.2.1 Full Analysis Set

The Full Analysis Set will consist of all subjects who have been randomized and received one dose of IP.

4.2.2 Per Protocol Analysis Set

The PPS population will consist of all subjects who have been randomized, completed the study period and without any major protocol violations. All violations will be presented and discussed at the clean file meeting.

The baseline and safety data will be presented using the FAS population. All data regarding extraction of nicotine and plasma concentration will use the PPS population.

4.3 Definition of Baseline

Baseline measurement is defined as the latest measurement prior to first dose of IMP.

4.4 Summary Statistics

Continuous data will be presented using summary statistics. Data will be presented in terms of number (N), arithmetic mean, standard deviation (SD), 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.

A significance level of 5% with two-sided tests will be used in all comparisons.

The test articles below will in all analyses be compared to the reference product.

4.5 Significance Level

All test will be performed using 5% significance level.

4.6 Multiple Comparisons/Multiplicity

The number of tests performed would suggest that all p-values should be adjusted according to Bonferroni-Holm adjustment. However, all statistical significance comparison must be judged from a medical perspective to decide the clinical relevance of such significance.

4.7 Handling of Drop-outs, Missing Data and Outliers

Outliers will be included in summary tables and listings, and will not be handled separately in any analyses. No imputation of data will be performed.

4.8 Adjustment for Covariates

No adjustments for covariates will be performed.

4.9 Multicenter Studies

Not applicable.

4.10 Examination of Subgroups

No examination of subgroups is planned.

4.11 Blind Review

Not applicable.

5 SUBJECTS**5.1 Subject Disposition**

The number of subjects that entered the study, withdrawn subjects, completed subjects and the number of subjects at each visit will be summarized by treatment.

5.2 Baseline Characteristics and Demographics

The following baseline characteristics will be given by treatment:

- Age
- Gender
- Ethnicity
- Medical/Surgical history
- Substance use
- Pulse rate
- Pregnancy test
- Abstinence result

6 TREATMENT INFORMATION AND EXTENT OF EXPOSURE**6.1 Active Treatment**

The number of subjects on each IP will be tabulated with start time, stop time and duration of application will be tabulated using listings and summary statistics. The abstinence result for each pouch will be presented using frequency tables.

6.2 Prior and Concomitant Medications

Prior and concomitant medication data will be listed only. Prior and concomitant medications will be coded according to the World Health Organization (WHO) Anatomic Therapeutic Chemical (ATC) classification system.

7 STATISTICAL METHODOLOGY

All parameters will be presented by treatment and visit using summary statistics. Additional statistical analyses are specified below.

7.1 Primary endpoint

AUC_{inf} based on plasma concentrations of nicotine after administration of one single dose of a novel, non-tobacco-based nicotine pouch containing 3 and 6 mg of nicotine, to that of one single dose from a 1 g Swedish snus pouch containing 8 mg of nicotine will be described using summary statistics and non-parametric signed Wilcoxon rank sum test for within subject difference between test and reference products.

7.2 Secondary endpoints

Graphs of extracted nicotine and AUC will be plotted with a regression fit.

7.2.1 Extracted dose of nicotine

The mean + SD extracted dose of nicotine from each pouch, will be calculated.

The extracted dose of nicotine will be compared between the different IP and analyzed using the signed Wilcoxon rank sum test and Students t-test for within subject difference.

The extracted dose of nicotine will be presented using summary statistics together with the p-values for both t-test and Wilcoxon signed rank sum test.

The correlation between the (AUC_{60min}, AUC_{0-t}) and the total amount of nicotine extracted from the pouch will be analyzed using Proc corr. in SAS.

7.2.2 Plasma concentration

The mean + SD plasma concentration from each pouch, will be calculated.

The plasma concentration will be compared between the different IP and analyzed using the signed Wilcoxon rank sum test and Students t-test for within subject difference.

The plasma concentration will be presented using summary statistics together with the p-values for both t-test and Wilcoxon signed rank sum test.

7.2.3 Pharmacokinetic outcome

The mean + SD of AUC_{inf} based on plasma concentrations of nicotine after administration of of each pouch, will be calculated. AUC_{60min}, C_{max}, T_{max}, AUC_{0-t} and terminal half-life will also be calculated.

AUC_{60min}, C_{max}, T_{max}, AUC_{0-t} and terminal half-life of a novel, non-tobacco-based nicotine pouch to that of a Swedish snus pouch will be described using summary statistics and analyzed using the Wilcoxon Rank Sum test.

7.2.4 Pulse rate

The difference in pulse between 60 minutes and pre-dose will be calculated for each IP and the change between reference products and test product using Students t-test and the Wilcoxon Rank sum test for within subject difference.

The pre-dose, 60 minutes, difference per IP and the within subject difference will be described using summary statistics together with p-values.

Summary statistics for all pulse rate measurement will be presented using summary statistics.

7.2.5 VAS scale

The difference in pulse between 60 minutes and pre-dose will be calculated for each IP and the change between reference products and test product using Students t-test and the Wilcoxon Rank sum test for within subject difference.

The pre-dose, 60 minutes, difference per IP and the within subject difference will be described using summary statistics together with p-values.

Summary statistics for all VAS measurement will be presented using summary statistics.

7.2.6 Adverse Events (AEs)

AEs and Serious Adverse Event (SAEs) will be recorded from start of IP administration. Medical events occurring between screening and first treatment with IP will be reported separately as

AEs verbatim terms will be encoded using the Medical Dictionary of Regulatory Activities (MedDRA), latest version available when approving the DMP.

AE/SAE:

The following summaries of AEs and SAEs will be given by treatment and in total:

- Total number of AEs
- Total number of unique AEs
- Total number of unique, related AEs
- Total number (%) of subjects with at least one AE
- Total number (%) of subjects with at least one related AE
- Unique AEs by MedDRA System Organ Class (SOC) and preferred term
- Number (%) of subjects with a least one AE by MedDRA
- Unique AEs by relation of study product and MedDRA SOC and preferred term.

Severity, action taken, concomitant therapy started and subject outcome of the AEs will be given in data listings only. AEs, which were reason for premature discontinuation of study product, will be listed separately.

The total number of SAEs and patients with a least one SAE will always be given. Further summaries of SAEs depending on the number of SAEs observed.

7.2.7 Discontinuation

Patients who discontinue from IP treatment will be tabulated. The reason for discontinuation will be given. For discontinuation due to AE, the AEs will be given.

7.3 Interim Analysis

Not applicable.

8 CHANGES FROM THE CSP

Pairwise comparisons between all test product will be added as exploratory analyses

9 STATISTICAL DELIVERABLES

The following documents will be delivered:

- SAP
- Statistical analyses and summary tables

10 SOFTWARE

All statistical analyses will be performed using SAS Version 9.4 (SAS institute, Cary, NC).

11 APPROVAL

(b) (4)



14-Mar-2018

Date (dd-Mmm-yyyy)

Approved by:

(b) (4)



14-Mar-2018

Date (dd-Mmm-yyyy)

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.