Clinical Study Protocol	
Investigational Product	ZYN Moist
Sponsor study code	SM20-01
Protocol Version and Date	Final v1.0; 24JUN2020

STUDY TITLE

In vivo extraction of nicotine and flavor compounds from a single dose of non-tobacco-based nicotine pouches (ZYN Moist).

Test products and dose	ZYN Moist Wintergreen (1)* containing 9 mg nicotine/pouch ZYN Moist Wintergreen (2)* containing 9 mg nicotine/pouch ZYN Moist Chill containing 9 mg nicotine/pouch ZYN Moist Cool Mint containing 9 mg nicotine/pouch ZYN Moist Citrus containing 9 mg nicotine/pouch ZYN Moist Spearmint containing 9 mg nicotine/pouch ZYN Moist Deep Freeze containing 9 mg nicotine/pouch ZYN Moist Smooth containing 9 mg nicotine/pouch *ZYN Moist Wintergreen (1) and (2) contain different amounts of the flavor wintergreen
Sponsor signatory	[redacted] [redacted] Swedish Match SE-Box 17037 104 62 Stockholm Sweden Maria Skolgata 83 SE-118 85 Stockholm Sweden [redacted] [redacted] [redacted]
Principal Investigator	Johan Nilsson, MD, PhD CTC Clinical Trial Consultants AB
Clinical study conduct and management	CTC Clinical Trial Consultants AB Dag Hammarskjölds väg 10B SE-752 37 Uppsala, Sweden CTC Clinical Trial Consultants AB Uppsala University Hospital, Entrance 85, 2nd level SE-751 85 Uppsala, Sweden

1 STUDY SYNOPSIS

Study title In vivo extraction of nicotine and flavor compounds from a single dose of non-tobacco-based nicotine pouches (ZYN Moist).	
Study code SM20-01	
Planned study period Q3 2020 to Q4 2020	
Principal Investigator Johan Nilsson, MD, PhD CTC Clinical Trial Consultants AB	
Study design This is an open, randomized, nine-way cross-over, single dose administration study designed to assess in vivo extraction of nicotine and/or flavor compounds of non-tobacco-based nicotine pouches.	
Objectives <u>Primary objective</u> The primary objective of the study is to show equivalence of the estimated in vivo extracted fraction of nicotine between ZYN Wintergreen (1) and ZYN Smooth after administration of one single dose. <u>Secondary objectives</u> To compare the estimated in vivo extracted amount and fraction of nicotine from each product. To evaluate the estimated in vivo extracted amount and fraction of flavor compounds. To evaluate safety and tolerability of ZYN products.	
Endpoints <u>Primary endpoints</u> Estimated in vivo extracted fraction of nicotine. <u>Secondary endpoints</u> Estimated in vivo extracted amount and fraction of nicotine. Estimated in vivo extracted amount and fraction of flavor compounds. Frequency, intensity and seriousness of adverse events (AEs).	
Number of subjects planned 36 subjects will be included in the study to achieve 33 fully evaluable subjects. It is estimated that approximately 56 subjects will be screened.	
Diagnosis and main eligibility criteria Male or female subject who used oral tobacco/nicotine products for ≥1 year, with a minimum daily consumption of five or more snus pouches, and is willing and able to use brands with nicotine content ≥1%, and are willing to comply with study procedures and who have given written informed consent, are considered to be eligible for the study. Pregnant or breastfeeding female subjects, and subjects with a history or presence of untreated diagnosed hypertension or any cardiovascular disease or other medical condition that may interfere with the evaluation of the investigational product or may either put the subject at risk because of participation in the study, will not be included in the study.	
Methodology	

The study will include a screening visit, two treatment visits for administration of in total 9 doses of IP, and a follow-up (FU) telephone visit. Screening (Visit 1) will take place within 28 days prior to Visit 2 and will include an eligibility check including review of health status and evaluation of nicotine/tobacco use. The IPs are administered as single doses in a pre-determined randomized order with at least 60 minutes between doses (from end of administration to start of administration). 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. After 60 minutes the pouches are collected and frozen (-20°C) pending analysis of residual nicotine and flavor compound content.
Investigational Product (IP) and dosage ZYN Moist Wintergreen (1)* containing 9 mg nicotine/pouch ZYN Moist Wintergreen (2)* containing 9 mg nicotine/pouch ZYN Moist Chill containing 9 mg nicotine/pouch ZYN Moist Cool Mint containing 9 mg nicotine/pouch ZYN Moist Citrus containing 9 mg nicotine/pouch ZYN Moist Spearmint containing 9 mg nicotine/pouch ZYN Moist Deep Freeze containing 9 mg nicotine/pouch ZYN Moist Smooth containing 9 mg nicotine/pouch *ZYN Moist Wintergreen product (1) and (2) contains different amount of the flavor wintergreen
Duration of treatment The participating subjects will receive study product on 9 occasions divided into two treatment visits, in a cross-over fashion, with 60 minutes of treatment per occasion.
Duration of each subject's involvement in the study Each subject will participate in the study for a period of approximately 5 weeks (including a screening period of up to 4 weeks).
Nicotine and flavor compound extraction assessment Extracted amount (mg/unit) and fraction (%) of nicotine and flavor compound will be assessed.
Statistical methods Continuous data will be presented in terms of evaluable and missing observations, arithmetic mean, standard deviation (SD), median, minimum and maximum value. Categorical data will be presented as counts and percentages. When applicable, summary data will be presented by treatment, and by assessment time. Individual subject data will be listed by subject number, treatment, and, where applicable, by assessment time. All pairwise testing will use a significance level of 5%. The extracted fraction of nicotine for primary objective will be analyzed using the linear mixed-effects analysis of variance (ANOVA) model with fixed effects for product, and a random effect for subject with a confidence interval of 90%.
Study reporting After completion of the study, an International Council for Harmonisation (ICH) E3 compliant clinical study report (CSR) will be prepared.

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3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or term	Explanation
AE	Adverse event
ATC	Anatomical therapeutic chemical
BMI	Body mass index
CRF	Case report form
CSP	Clinical study protocol
CSR	Clinical study report
CTC	Clinical Trial Consultants AB
CV	Coefficient of variation
DMP	Data management plan
eCRF	Electronic case report form
EDC	Electronic data capture
EEA	European Economic Area
GCP	Good clinical practice
GDPR	General data protection regulation
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent ethics committee
IME	Important medical event
IP	Investigational product
ISF	Investigator site file
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
MedDRA	Medical dictionary for regulatory activities
NRT	Nicotine replacement therapies
PII	Personally Identifiable Information
PPS	Per protocol analysis set
PT	Preferred term
QC	Quality control
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDV	Source data verification
SOC	System organ class
SOP	Standard operating procedures
TMF	Trial master file
WHO	World Health Organisation
WOCBP	Women of childbearing potential

4 IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

4.1 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 described in Section 11.4.10.

In the case of a medical emergency, the Investigator may contact the Medically Responsible Person at Sponsor (Table 4-1).

Table 4-1 Medical emergencies contact

Name	Function in the study	Telephone number and e-mail
[redacted]	[redacted]	[redacted]

5 INVESTIGATOR AND STUDY ADMINISTRATIVE STRUCTURE

Sponsor

Swedish Match
Maria Skolgata 83, 1 tr
SE-11885 Stockholm
Sweden

[redacted]

Clinical conduct

CTC Clinical Trial Consultants AB (CTC)
Uppsala University Hospital,
Entrance 85, 2nd level
SE-751 85 Uppsala, Sweden

And/or

CTC
Dag Hammarskjölds väg 10B
SE-752 37 Uppsala, Sweden

[redacted]

Study management

CTC
Dag Hammarskjölds väg 10B
SE-752 37 Uppsala, Sweden

[redacted]

Signatures are provided in Section 18.

6 INTRODUCTION

6.1 Background

Sweden has the lowest prevalence of smoking in Europe, particularly among males. It is widely accepted that one contributory factor to this trend is that snus has replaced cigarettes as the tobacco product of choice among many male and some female smokers.
Oral tobacco, like snus, is capable of rapidly delivering nicotine to the venous bloodstream through diffusion over the oral mucosa [1]. It may therefore be more satisfactory to smokers than currently available pharmaceutical nicotine replacement therapies (NRT). However, orally administered nicotine, whether in the form of snus or NRT, can never achieve the rapid and very high nicotine levels in the arterial blood to the brain that is typically associated with pulmonary delivery resulting from inhalation of tobacco smoke.
Use of smokeless tobacco is by definition unassociated with exposure to the many thousands of combustion compounds found in tobacco smoke (many of which are highly carcinogenic and may induce a state of systemic, chronic inflammation), or chronic irritation in the upper and lower airways resulting from the inhalation of tobacco smoke. Therefore, it is generally accepted that use of smokeless tobacco products has substantially lower health risks than cigarette smoking. However, smokeless tobacco typically entails a systemic exposure to nicotine that is comparable to that among cigarette smokers.
Nicotine is the substance that is thought to contribute the most to the addictive properties of using any type of tobacco product, and nicotine exposure may contribute to adverse pregnancy outcomes. In addition, oral tobacco products typically contain low levels of unwanted substances (including nitrosamines and polycyclic hydrocarbons) that have been classified as human carcinogens. So, although the health effects are substantially smaller for oral tobacco compared to cigarette smoking, some adverse effects cannot be ruled out, in particular not effects related to the nicotine exposure.
Traditionally there has been no non-tobacco-based nicotine product intended for recreational use. Despite the vast risk differential between snus and cigarettes in terms of adverse long-term health effects, snus remains a controversial product as it contains tobacco, is intended for recreational use, and is potentially addictive. The tobacco component of snus explains why it contains measurable amounts of unwanted, potentially carcinogenic constituents, albeit at very low concentrations. Recently non-tobacco-based oral nicotine products have been developed and are now commercially available. They have some features that are similar to snus since it comes in pouches that are intended to be placed under the upper lip. However, in contrast to snus, the product contains no nitrosamines or polycyclic hydrocarbons which are the two main classes of unwanted substances in snus. The nicotine content in Swedish Match nicotine pouches ZYN (3 – 13 mg/unit) is comparable to commercially available oral tobacco products in the Scandinavian and US market, which have nicotine contents ranging from 3 mg/unit to more than 20 mg/unit.
The nicotine delivery profile of a product is probably one main determinant of its efficacy to decrease nicotine craving and, thus, its ability to function as an alternative to cigarettes among current smokers. At the same time, it probably also helps to explain the product's addictive properties.
When comparing the nicotine content of different nicotine-delivery products it is important to consider that the nicotine extraction and uptake varies considerably depending on product type (tobacco versus a non-tobacco-based matrix) and product formulation (pouch geometry, water content, particle size, pH, etc). In addition, there is a substantial inter-individual variation in uptake with products used orally which is probably related to constitutional

differences in saliva production and results in a wide variation in nicotine extraction from the product.
It has been postulated that some flavors could enhance nicotine uptake. A previous in vivo nicotine extraction study compared ZYN Dry products with and without flavor components. Nicotine extraction was measured after 15 and 60 minutes. The study showed no statistically significant difference of extracted amount of nicotine between flavored and unflavored products, including Wintergreen. The nicotine uptake of different concentrations of ZYN Dry have also been explored in a second study and the pharmacokinetics showed no difference in nicotine delivery profile between products with respect to Wintergreen flavor content.
Addition of flavors to tobacco products and e-cigarettes have been discussed by regulatory agencies during the last years. The WHO seventh report on the scientific basis of tobacco product regulation included a chapter on flavors [2], although focusing on inhaled products, they highlighted that the actual levels of flavor compounds and potential metabolites delivered to the consumer is key for health risk assessment.
The ZYN Dry products utilize a different matrix compared to the ZYN Moist products included in the current study. The nicotine extraction may differ as a consequence of different pouch geometry, water content, particle size etc. Therefore, the current study will investigate the nicotine and/or flavor extraction of ZYN Moist 9 mg products, utilizing different flavor contents, compared to an unflavored ZYN Moist product.

6.2 Study rationale

The overarching aim of the study is to evaluate if the different flavor components have an impact on the nicotine extraction from a ZYN Moist 9 mg product compared to an unflavored ZYN Moist 9 mg product. In addition, the extraction of selected flavor components will be determined.

6.3 Risk/benefit assessment

It may be considered problematic to expose research subjects to a novel nicotine delivery product with properties of which are not yet fully known. However, all research subjects are required to be daily users of oral tobacco/nicotine products since at least one year (with an average or above snus consumption) so the participants are well acquainted with, and used to, the effects of nicotine.
Aside from the nicotine, all ingredients used in the test products are food-approved (similar to ingredients in conventional snus). ZYN Moist is commercially available on the Swedish market. The nicotine in ZYN Moist is of pharmaceutical grade, 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 products apart from mild effects likely to be related to the nicotine exposure (such as salivation, nausea, and dyspepsia).
Pregnant and breastfeeding 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 are likely to be minor and/or clinically insignificant, and are from a research ethics perspective, counterbalanced by the potential positive effects of the novel nicotine pouch as a reduced toxicity alternative to conventional oral tobacco. The evidence on the health effects of nicotine exposure is based on existing tobacco products.
All subjects are required to provide informed consent prior to any study procedures.

Risk assessment with regards to the COVID-19 pandemic:
Current recommendations from the authorities will be considered on a day-to-day basis. On-going risk evaluation, assessment sessions with Sponsors, Investigators, CRO/vendor representative members to align on local restrictions, impact assessment, contingency plans and study-specific risk mitigation strategies will be made to safeguard the study conduct and the safety of the study subjects. This study is a short-term study including a healthy population. Hence, study participation is not expected to confer increased risks to the study subjects in terms of COVID-19 exposure.

7 STUDY OBJECTIVES AND ENDPOINTS

Objectives and endpoints are summarized in Table 7-1.
Table 7-1 Objectives and endpoints

Primary objective	**Endpoint**	**Assessment(s)**
The primary objective of the study is to show equivalence of the estimated in vivo extracted fraction of nicotine between ZYN Wintergreen (1) and ZYN Smooth after administration of one single dose.	Estimated in vivo extracted fraction of nicotine.	Collection of used snus pouches
Secondary objective	**Endpoint**	**Assessment(s)**
To compare the estimated in vivo extracted amount and fraction of nicotine from each product*.	Estimated in vivo extracted amount and fraction of nicotine.	Collection of used snus pouches
To evaluate the estimated in vivo extracted amount and fraction of flavor compounds*.	Estimated in vivo extracted amount and fraction of flavor compounds.	Collection of used snus pouches
To evaluate safety and tolerability of ZYN products.	Frequency, intensity and seriousness of adverse events (AEs).	Collection of AEs

*See section 9.9 for included products

8 STUDY DESIGN

8.1 Overall study design and schedule of events

This is an open, randomized, nine-way cross-over, single dose administration study designed to assess in vivo extraction of nicotine and/or flavor compounds of non-tobacco-based nicotine pouches. The study will include 36 subjects.
The study will include a screening visit, two treatment visits for administration of in total 9 doses of IP, and a follow-up (FU) telephone visit.
Screening (Visit 1) will take place within 28 days prior to Visit 2 and will include an eligibility check including review of health status and evaluation of nicotine/tobacco use, see Table 8-1 for details.
Subjects shall be abstinent from snus and all other nicotine containing products for at least 12 hours before each treatment visit and are instructed to abstain from snus, cigarettes, or other nicotine delivery products as from 8.00 p.m. the evening before each treatment visit. The subjects should certify abstinence at the beginning of each treatment visit. The two treatment visits start with administration of one IP dose for the primary objective and are performed during the morning hours to facilitate abstinence. The subjects are instructed not to eat, drink, chew chewing gum, use nicotine free pouches or brush teeth from 30 minutes before and during

application of the IP [3]. Following administration of 3 or 4 doses of IP, according to a pre-determined randomized order, with at least 60 minutes between doses (from end of administration to start of administration).
The IPs are administered as single doses and 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. After 60 minutes the pouches are collected and frozen (-20°C) pending analysis of residual nicotine and flavor compound content.

Table 8-1 Schedule of events

		Screening	Treatment visits		Follow up
Visit	**Refer to CSP section:**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4 (Phone call)**
Assessment / Study days		Day -28 to Day 1	Day 1	≥1 day after Day 1	5 days (-3/+3) after last dose[1]
Informed Consent	13.3	X			
Inclusion/exclusion criteria	9.4, 9.5	X			
Demographics	11.2	X			
Medical/surgical history	11.2.4	X			
History of nicotine use	11.2.5	X			
Weight/height (BMI)	11.2.6	X			
Physical Examination	11.2.7	X			
Alcohol test[2]	11.2.8	X	X		
Urine Drug Screen[2]	11.2.9	X	X		
Pregnancy Test[3]	11.2.10	X	X		
Randomization	9.9		X		
IP treatment[4]	10.5		X[5]	X[5]	
Baseline symptoms	11.2.11	X	X[6]		
Adverse events	11.4		X[7]		
Prior and concomitant medications[8]	11.2.12	X			

BMI = Body mass index, WOCBP = women of childbearing potential

1. Or after early withdrawal.
2. Alcohol and Drug tests may also be performed at additional random occasions during the study.
3. WOCBP only. Urine dipstick.
4. The subject uses the pouch for 60 minutes after which it is collected and frozen.
5. Depending on randomization allocation, 4 or 5 doses are administered with at least 60 minutes between each administration (from end of administration to start of administration).
6. Baseline symptoms will be recorded up until first use of IP.
7. AEs will be recorded from first administration of IP.
8. For definitions of prior and concomitant medications, see Section 11.2.12.

8.2 Rationale for study design

A crossover design was chosen to yield a more efficient comparison of treatments than a parallel study design, i.e., fewer subjects are required since each subject will serve as its own control.
Randomization will be used to minimize bias in the assignment of subjects to a treatment sequence and to increase the likelihood that known and unknown subject attributes (e.g., demographic and baseline characteristics) are evenly balanced across treatment groups.

9 STUDY POPULATION

Prospective approval of protocol deviations from eligibility criteria, also known as protocol waivers or exemptions, is not permitted.

9.1 Recruitment

The subjects will be recruited from CTC's database of healthy volunteers and from advertising in media (including social media).

9.2 Screening and enrollment log

Investigators must keep a record of all screened subjects even if they were not subsequently included in the study. This information is necessary to verify that subjects were selected without bias. The reason for screen failure should be stated for all subjects screened but not included. The reason for withdrawal should be stated for all subjects included but not completed.
A screening number will be allocated to each subject in connection to the informed consent process at the Screening visit. The screening number is generated automatically in the electronic case report Form (eCRF). The screening number will allow identification of subjects irrespective of their possible eligibility for the study.
Subjects included and randomized will be assigned a randomization number (101, 102 and so on).
If a subject cannot receive the planned dose of IP within 28 days after screening (*i.e.*, the time interval between signing informed consent until dose administration) the subject should be re-screened before proceeding in the study.

9.3 Number of subjects

36 subjects will be included in the study to achieve 33 fully evaluable subjects. It is estimated that approximately 56 subjects will be screened.
For replacements of subjects who discontinue from the study, see Section 9.8.

9.4 Inclusion criteria

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

1. Willing and able to give written informed consent for participation in the study.
2. Male or female subject aged ≥19 years.

3. Subject who has used oral tobacco/nicotine products for ≥1 year, with a minimum daily consumption of five or more snus pouches, and is willing and able to use brands with nicotine content ≥1%.
4. Women of child bearing potential (WOCBP) must be willing to use a sufficient contraceptive method for the duration of the study, this includes mechanical barrier (e.g., a male condom or a female diaphragm), combined [oestrogen and progestogen containing] hormonal contraception associated with inhibition of ovulation [oral, intravaginal, transdermal], progestogen-only hormonal anticonception associated with inhibition of ovulation [oral, injectable, implantable], IUD or IUS. Sexual abstinence is allowed when this is the preferred and usual lifestyle of the subject.

9.5 Exclusion criteria

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

1. Any surgical or medical condition including abnormal salivation (also pharmaceutically induced), or history thereof, which, in the judgment of the Investigator, might interfere with the absorption of the IP or may either put the subject at risk because of participation in the study, influence the results, or the subject's ability to participate in the study.
2. Any clinically significant illness in the 28 days prior to the first IP administration.
3. A history or presence of untreated diagnosed hypertension or any cardiovascular disease.
4. Female subject currently breast feeding, pregnant or planning to get pregnant during the study.
5. Positive screen for drugs of abuse or alcohol at screening or on admission to the unit prior to first administration of the IP.
6. Current or history of alcohol abuse and/or use of anabolic steroids or drugs of abuse, as judged by the Investigator.
7. Investigator considers the subject unlikely to comply with study procedures, restrictions and requirements.

9.6 Restrictions during the study

The subjects must be willing to comply to the following restrictions during the entire study duration *i.e.*, from screening to the end-of-study visit.

9.6.1 *General restrictions*

- Contraception Requirements:
  All females of child-bearing potential must use effective contraception (defined in inclusion criterion No 4) or practice abstinence during the study.
- Subjects shall abstain from snus and all other nicotine containing products from 8.00 pm the night before treatment visits and during the visits (except for the IP treatment).
- Subjects are not allowed to eat or drink or conduct any other mouth related procedure (e.g. tooth brushing) 30 minutes before dose administration and during application of IP.
- Subjects shall abstain from drugs of abuse from Screening to the Follow-up visit.
- Subjects shall abstain from alcohol the last 24 hours before each visit (from 8.00 am the day before visit).

- Subjects are not allowed to participate in any other clinical study during the study period i.e. screening to follow up.

9.6.2 *Prior and concomitant therapy*

No restrictions concerning concomitant medications or therapies.

9.7 Screen failures

Screen failures are defined as subjects who consent to participate in the clinical study but do not fulfil all eligibility criteria and are not subsequently randomized in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects. Minimal information includes documentation of signed and dated informed consent form (ICF), demographics, and reason(s) for screening failure.
Subjects who do not meet the criteria for participation in this study may be rescreened. Re-screening can be performed once if any of the following were reasons for screening failure or non-randomization (as judged by the Investigator):

- Practical reasons.
- Non-significant medical conditions (e.g. influenza, nasopharyngitis).

For subjects who are re-screened, a new screening number will be assigned and a new, signed ICF will be collected.

9.8 Subject withdrawal

9.8.1 *General withdrawal criteria*

Subjects are free to discontinue their participation in the study at any time and for whatever reason without affecting their right to an appropriate follow-up investigation or their future care. If possible, the reason for withdrawal of consent should be documented.
Subjects may be discontinued from the study at any time at the discretion of the Investigator. Reasons for discontinuation include:

- Subject decision
- Severe non-compliance to study protocol procedures, as judged by the Investigator and/or Sponsor
- Subject is lost to follow-up.
- Significant AEs posing a risk for the subject, as judged by the Investigator and/or Sponsor
- Pregnancy
- Death

9.8.2 *Procedures for discontinuation of a subject from the study*

A subject who prematurely discontinues participation in the study will always be asked about the reason(s) for discontinuation and the presence of any AEs. If a subject withdraws consent, the Investigator must ask the subject if he/she is willing, as soon as possible, to be assessed according to the procedures scheduled for the end-of-study visit. Any ongoing AEs will be followed as described in Section 11.4.11.

The primary reason for discontinuation/early withdrawal must be specified in the eCRF and final IP accountability must be performed.

9.8.3 *Subject replacement*

Subjects who are prematurely withdrawn from the study may be replaced at the Sponsor's discretion after consultation with the Investigator.

9.9 Randomization

On Visit 2, the subjects will be randomized to a treatment sequence consiting of the nine IP doses, see Table 9-1. The randomized treatment sequence at Visit 2 and 3 will start with either of treatment A or treatment B (to facilitate abstinence for the primary objective, see Section 8.1). A computer-generated randomization list will be created using SAS Proc Plan, SAS Version 9.4. The randomization list will contain subject number, treatment sequence, period, and treatment. As this is an open study, the treatment seqence to which each subject is allocated will be recorded in the eCRF.
The randomization list will be generated by CTC or delegate and provided to the packing company. The original randomization list will be kept by the randomizer. A copy of the randomization list will be provided to the clinic.

Table 9-1 IP treatments and type of extraction

Label	Treatment (type of extraction)
A	ZYN Moist Wintergreen (1) (nicotine extraction)*
B	ZYN Moist Smooth (nicotine extraction)
C	ZYN Moist Wintergreen (1) (flavor extraction)*
D	ZYN Moist Wintergreen (2) (flavor extraction)*
E	ZYN Moist Chill (flavor and nicotine extraction)
F	ZYN Moist Cool Mint (flavor extraction)*
G	ZYN Moist Citrus (flavor and nicotine extraction)
H	ZYN Moist Spearmint (flavor and nicotine extraction)
I	ZYN Moist Deep Freeze (flavor and nicotine extraction)

*Combined analysis of nicotine and flavor compound is not possible

9.10 Blinding

This is an open-label study, i.e. the Investigator, study staff and subjects will know the type of treatment to be received.

10 TREATMENTS

The IPs are supplied by Swedish Match North Europe.

10.1 Identity of investigational products

ZYN Moist Wintergreen (1)* containing 9 mg nicotine/pouch
ZYN Moist Wintergreen (2)* containing 9 mg nicotine/pouch
ZYN Moist Chill containing 9 mg nicotine/pouch
ZYN Moist Cool Mint containing 9 mg nicotine/pouch
ZYN Moist Citrus containing 9 mg nicotine/pouch
ZYN Moist Spearmint containing 9 mg nicotine/pouch
ZYN Moist Deep Freeze containing 9 mg nicotine/pouch
ZYN Moist Smooth containing 9 mg nicotine/pouch
*ZYN Moist Wintergreen product (1) and (2) contains different amount of the flavor wintergreen

10.2 Manufacturing, packaging and labelling

The IP will be manufactured and packaged in compliance with the Swedish law on food production.
The IP will be transferred from the original container, weighed and individually packaged in identical sealed food approved test containers at the Swedish Match analytical lab.
The containers will be labelled with unique identification numbers by Swedish Match in accordance with the randomization list.

10.3 Conditions for storage

The IP will be stored in an access-controlled storage area at CTC, at refrigerated temperature (4-8°C).
The temperature is recorded continuously by an automatic temperature control system.

10.4 Preparation and accountability

The IP will be dispensed according to the randomization list by the site personnel. Before administration to the subjects, the IP should be placed in room temperature for at least 30 minutes to allow the IP to adapt to room temperature.
The Investigator will maintain a Storage and Accountability Log as well as a Dispensing Log detailing the dates and quantities of IP received, prepared for, and used by each subject and study product returned or destroyed at the end of the study. Any discrepancies between prepared and returned IP must be explained and documented. Products deliberately and/or accidentally destroyed by the site or the subject must be accounted for.

10.5 Treatment administration

A single dose of each IP will be given in accordance with the randomization list. The pouch will be placed between the upper lip and gum, and kept still there for 60 minutes. The subject is instructed to not manipulate the pouch with the tongue.

10.6 Treatment compliance

All IP will be administered at the research clinic under medical supervision to ensure compliance.

10.7 Return and destruction of investigational medicinal products

Any unused study medication and all empty containers will be destructed at the site upon confirmation from the Sponsor. The Monitor will perform final IP accountability reconciliation at the study end to verify that all unused IP is adequately destroyed and documented.

11 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 8-1).

11.1 Recording of data

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

11.2 Demographics and other baseline characteristics

11.2.1 *Informed consent*

Signed informed consent must be obtained before any screening procedures are initiated. The informed consent procedure is further described in Section 13.3.

11.2.2 *Eligibility criteria*

Eligibility criteria should be checked during screening and verified before randomization/IP administration. The criteria are specified in Sections 9.4 and 9.5.

11.2.3 *Demographic information*

The following demographic data will be recorded: gender, age, ethnicity and race.

11.2.4 *Medical/surgical history*

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

11.2.5 *History of nicotine use*

History of snus or oral nicotine product use in terms of brand of product, average consumption per day (last month), and duration of use (years) as well as history of smoking in terms of number of cigarettes per day (the last month) will be obtained by subject interview.

11.2.6 *Weight and height*

Weight and height will be measured without shoes. BMI will be calculated, with one decimal, from the height and weight recorded.

11.2.7 *Physical examination*

A brief physical examination will include assessments of lungs, cardiovascular, abdomen (liver and spleen), and extremities.
Any abnormalities will be specified and documented as clinically significant (CS) or not clinically significant (NCS).

11.2.8 *Alcohol test*
An alcohol test will be performed at time points outlined in the schedule of events (Table 8-1). Additional random tests can be performed during the study period.

11.2.9 *Urine drug screen*
Urine will be screened for drugs of abuse at time points outlined in the schedule of events (Table 8-1) using the Alere™ Drug Screen Test Panel. Additional random tests can be performed during the study period.

11.2.10 *Pregnancy test*
All females of childbearing potential will do a pregnancy test (urine dipstick) at time points outlined in the schedule of events (Table 8-1).

11.2.11 *Baseline symptoms*
A baseline symptom is defined as an event that occurs between the subject's signing of the ICF until the first administration of IP (i.e. an event that occurs during the screening period). Such events are not AEs and will be recorded as baseline symptoms in the Medical History Log in the eCRF.

11.2.12 *Prior and concomitant medication*
Prior and concomitant medications taken within 2 weeks prior to screening will be obtained by subject interview in order for documentation of the subject´s status regarding current medications (see also Section 9.6.2).
Medications are classified as prior if the stop date was before or on the day of the first dose administration (pre-dose) and as concomitant if ongoing on the day of the first dose administration, stopped after the first dose administration or started after the first dose administration. To distinguish between prior and concomitant medications on Visit 1 (i.e. the first dosing day), the start time of any newly introduced medication or the stop time of any previously ongoing medication must be recorded in the eCRF.
Any use of concomitant medication from screening until the last end-of-study visit must be documented appropriately in the subject's eCRF. Relevant information (*i.e.* name of medication, dose, dose form, unit, route, frequency, start and stop dates, reason for use) must be recorded. All changes in medication should be noted in the eCRF.

11.3 Assessments related to primary and secondary endpoints

11.3.1 *Nicotine and flavor compounds extraction from pouches*
Used pouches will be collected after 60 minutes (+/- 1 minute) of use for the determination of residual nicotine and flavor compunds in the IPs.
All the collected pouches will be frozen immediately at -20°C. Pouches for extraction of nicotine and flavor compounds will be analyzed by Swedish Match and Eurofins Food & Feed Testing Sweden.

11.4 Adverse events

In this study, the IP is a nicotine product and not an investigational medicinal product. However, the procedures for monitoring, collecting, and reporting of AEs will be the same as for an investigational medicinal product, as far as possible. The Principal Investigator is

responsible for ensuring that all medical staff involved in the study are familiar with the content of this section and the content of the CTC standard operating procedures (SOPs) regarding emergencies and Phase I studies.

11.4.1 *Definition of adverse event*

An AE is defined as any untoward medical occurrence in a subject administered an IP and which does not necessarily have a causal relationship with this IP. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an IP, whether or not considered related to the IP.

11.4.2 *Definition of serious adverse event*

An SAE is any AE which:

- results in death
- is life-threatening (this refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might had led to death if the reaction was more severe)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (IME) (this refers to a reaction that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent any of the other outcomes defined above)

Examples of IMEs are intensive treatment in an emergency room for allergic bronchospasm or blood dyscrasias, convulsions that do not result in hospitalization, development of drug dependency, and drug abuse.
Planned hospitalizations or surgical interventions for a condition that existed before the subject signed the ICF and that did not change in intensity are not SAEs.
If there is any doubt as to whether an AE meets the definition of an SAE, a conservative viewpoint must be taken, and the AE must be reported as an SAE.

11.4.3 *Time period and frequency for collecting adverse events*

All AEs (including SAEs) will be collected from the start of IP use until the end-of-study visit.
Any AE with start date on the day of the first IP use must be recorded with start time.
At the end-of-study visit, information on new AEs or SAEs, if any, and stop dates for ongoing events must be recorded as applicable.
Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

11.4.4 *Assessment of severity*

The severity of each AE is to be graded by the Investigator. The severity grades are defined as follows:

Mild	The event is usually transient and requires minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	The event is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant of permanent risk or harm to the subject.
Severe	The event interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

11.4.5 *Assessment of causal relationship*

The Investigator must assess the causal relationship between an AE and the IP using the definitions below and record it the AE Log of the eCRF:

Probable	The event has a strong temporal relationship to the IP or recurs on re-challenge, and another etiology is unlikely or significantly less likely.
Possible	The event has a suggestive temporal relationship to the IP, and an alternative etiology is equally or less likely.
Unlikely	The event has no temporal relationship to the IP or is due to underlying/concurrent illness or effect of another drug (that is, there is no causal relationship between the IP and the event).

An AE is considered causally related to the use of the IP (ZYN Moist) when the causality assessment is probable or possible.

11.4.6 *Assessment of outcome*

The Investigator must assess the outcome of an AE using the definitions below and record it on the AE Log of the eCRF:

Recovered/resolved	The subject has recovered completely, and no symptoms remain.
Recovering/resolving	The subject's condition is improving, but symptoms still remain.
Recovered/resolved 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/not resolved	The subject's condition has not improved and the symptoms are unchanged (for example, an atrial fibrillation has become chronic).
Fatal	
Unknown	

11.4.7 *Reporting of action taken with study product*

The Investigator must report the action taken with study product using the definitions below and record it on the AE Log of the eCRF:

Study product dose not changed
Study product interrupted
Study product withdrawn
Not applicable
Unknown

11.4.8 *Collecting adverse events*

AEs 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

11.4.9 *Recording adverse events*

AEs must be recorded in the AE Log of the eCRF. The Investigator must provide information on the AE, preferably with a diagnosis or at least with signs and symptoms; start and stop dates, start and stop time; severity/intensity; causal relationship to IP; action taken, and outcome.
If the AE is serious, this must be indicated in the eCRF.
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.
In case of subject's pre-existing condition deteriorating at any time during the study, it will be recorded as an AE.

11.4.10 *Reporting of serious adverse events*

SAE reporting should be performed by the Investigator within 24 hours of awareness via the eCRF. All available information regarding the SAE should be entered in the AE Log for the specific subject. By saving the event as "serious" in the eCRF and once the Investigator has signed-off of the event, an e-mail alert is automatically sent to predefined recipients to highlight that an SAE has been registered. The same information is automatically sent to [redacted]
If the SAE report in the eCRF is updated, a new e-mail alert will be sent.
In case the eCRF cannot be accessed, the SAE should be reported by manual completion of the paper SAE Form, provided in the Investigator Site File (ISF). The completed, signed and dated paper SAE Form should, within 24 hours, be scanned and e-mailed to:
[redacted]
A copy of the paper SAE form must also be e-mailed to CTC [redacted]
The study site should notify the site Monitor via phone or e-mail about the submission of the SAE report. As soon as the site personnel have access to the eCRF, the SAE should be reported electronically as well.

11.4.11 *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 to the end-of-study visit, whichever comes first. At the end-of-study visit, information on new AEs, if any, and stop dates for previously reported AEs must be recorded (if known). AEs assessed as stable by the Investigator at the end-of-study 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.

11.4.12 *Procedures in case of pregnancy*

In case of pregnancy or suspicion of possible pregnancy of any female subjects, the use of IP 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 the IP 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.

11.4.13 *Treatment of overdose*

An overdose is a dose in excess of the dose specified for each product in this CSP.

Over-dosing is not likely to occur in this study since all IP will be administered by site personnel under medical surveillance. In cases of accidental overdose, standard supportive measures should be adopted as required.

An overdose should be documented as follows:

- An overdose with associated AE is recorded as the AE diagnosis/symptoms in the AE Log of the eCRF.
- An overdose without associated symptoms is only reported in the subject's medical records.

11.5 Appropriateness of measurements

All methods used for safety assessments are commonly used in standard medical care and in Phase I clinical studies.

12 QUALITY MANAGEMENT, QUALITY ASSURANCE AND QUALITY CONTROL

12.1 Quality management: critical process, system and data identification

During CSP development, the Sponsor will identify those processes, systems (facilities, computerized systems) and data that are critical to ensure human subject protection and the reliability of trial results according to applicable SOPs and International Council for Harmonization (ICH) E6 (R2).
Identified risks, including risks associated with the COVID-19 (Coronavirus) pandemic, will be categorized separately from the CSP.
Sponsor oversight responsibilities, such as monitoring, adverse event reporting, safety monitoring, changes in investigators and key study team staff and quality assurance activities may need to be reassessed in relation to the COVID-19 pandemic and temporary, alternative proportionate mechanisms of oversight may be required.

12.2 Quality assurance and quality control

The Sponsor is responsible for implementing and maintaining quality assurance (QA) and quality control (QC) systems with written SOPs with regards to management of identified risks, CSP compliance, good clinical practice (GCP) compliance and applicable regulatory requirements.
The Sponsor is responsible for securing agreements with involved subcontractors and to perform regular subcontractor oversight to ensure CSP compliance, GCP compliance and compliance with applicable regulatory requirements.
The Sponsor is responsible for implementing a risk-based validated electronic data capture system and maintain SOPs for the whole life cycle of the system.
QC should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.
The Sponsor has delegated the responsibilities outlined above to CTC whilst maintaining overall study oversight.

13 ETHICAL AND REGULATORY REQUIREMENTS

13.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki [4] and are consistent with ICH/Good Clinical Practice (GCP) E6 (R2), EU Clinical Trials Directive, and applicable local regulatory requirements.

13.2 Ethics and regulatory review

The Principal Investigator is responsible for submission of the CSP, the subject information and ICF, any other written information to be provided to the subjects and any advertisements used for recruitment of subjects to applicable IEC for approval.
Approval must be obtained in writing from IEC before the first subject can be recruited.
The Sponsor will provide the IEC and Principal Investigator with safety updates/reports according to local requirements.

13.3 Subject information and consent

It is the responsibility of the Investigator or an authorized associate to give each potential study subject adequate verbal and written information before any study specific assessments are performed.
The information will include the objectives and the procedures of the study as well as any risks or inconvenience involved. It will be emphasized that participation in the study is voluntary and that the subject may withdraw from participation at any time and for any reason, without any prejudice. All subjects will be given the opportunity to ask questions about the study and will be given sufficient time to consider participation before signing the ICF.
Before performing any study-related procedures the ICF must be signed and personally dated by the subject and by the Investigator. A copy of the subject information including the signed ICF will be provided to the subject.
Documentation of the discussion and the date of informed consent must be recorded in the source documentation and in the eCRF. The subject information sheet and the signed ICF should be filed by the Investigator for possible future audits and/or inspections.

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

13.4 Subject data protection

The ICF includes information that data will be recorded, collected and processed and may be transferred to European Economic Area (EEA) or non-EEA countries. In accordance with the European Union Data Protection Directive (95/46/EC) and General Data protection Regulation (GDPR), the data will not identify any persons taking part in the study.
The potential study subject should be informed that by signing the ICF he/she approves that authorized representatives from Sponsor and CTC, the concerned IEC and have direct access to his/her medical records for verification of clinical study procedures. For further details on the subject information and ICF process, refer to Section 13.3.
The subject has the right to request access to his/her personal data and the right to request rectification of any data that is not correct and/or complete in accordance with the European Union Data Protection Directive (95/46/EC) and the request will be raised to the Principal Investigator.
The Investigator must file a Subject Identification List which includes sufficient information to link records, i.e. the eCRF and clinical records. This list should be preserved for possible future inspections/audits but must not be made available to the Sponsor except for monitoring or auditing purposes.
Personal data that are collected in the study such as health information and ethnicity are considered as sensitive personal data. This data will be pseudoanonymized, i.e. personally identifiable information (PII) will be removed and replaced by a unique subject ID and will be processed by the Sponsor and other involved parties during the study. After the study end, only anonymized data, i.e. aggregated data sets, can be used.
For this study, the Sponsor is the data controller of all data processed during the study (e.g. Trial Master File [TMF], study reports) and CTC AB is the data processor. Any subcontractors used in the study, are also data processors.
For data that are processed at the clinic(s) (e.g. medical records and ISF), CTC AB is the data controller.

13.5 Changes to the approved clinical study protocol

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

13.6 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. The Investigator will contact the Sponsor immediately if contacted about an inspection at the site.

13.7 Insurance

Subjects will be covered under Swedish Match AB´s liability insurance policy through IF insurance. The certificate of insurance and an information leaflet containing essential information about the insurance coverage can be provided upon request. The participating subjects are also protected in accordance with national regulations, as applicable. CTC has a company insurance covering services performed by CTC.

14 STUDY MANAGEMENT

14.1 Training of study site personnel

Before enrollment 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 and have a detailed knowledge of and training in the procedures that are to be executed by them. Any new information of relevance to the performance of this study must be forwarded to the staff involved in a timely manner.
The Investigator will keep a list of all personnel involved in the study together with their function and study related duties delegated. A Curriculum Vitae will be available for all staff to whom study-specific duties are delegated.

14.2 Clinical monitoring

The Sponsor is responsible for securing agreement from all involved parties to ensure direct access to all study related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by domestic and foreign regulatory authorities.
As defined in the risk-based monitoring (RBM) plan, approved by the Sponsor and provided separately, the responsible Monitor will periodically visit the study site at times agreed upon by the Investigator and the Monitor. Adaptations related to the on-site monitoring plan, when it is impossible or inappropriate to follow due to the COVID-19 pandemic, may be required such as supplementation with (additional/increased) centralised monitoring and central review of data if considered possible and meaningful. Results of adjusted monitoring/review measures should be reported to the Sponsor in monitoring reports and in the CSR.
At the time of each monitoring visit, the role of the Monitor is (but not limited to) to:

- provide information and support to the investigational team.
- confirm that facilities and resources remain acceptable.
- confirm that the investigational team is adhering to the CSP, applicable SOPs, guidelines, manuals and regulatory requirements.
- verify that data are being accurately and timely recorded in the eCRFs and that IP accountability checks are being performed.
- verify that data in the eCRF are consistent with the clinical records (SDV) in accordance with the RBM plan.
- verify that the correct informed consent procedure has been adhered to for participating subjects.
- verify that AEs are recorded and reported in a timely manner and according to the CSP.

- raise and escalate any serious quality issues, serious GCP breach and any data privacy breach to the Sponsor.

Centralized monitoring will also be performed continuously by study team members at CTC in accordance with the RBM plan.
When the study has been completed and all queries have been resolved and the database has been locked, the Monitor will perform a close-out visit.

14.3 Source data documents

A separate Origin of Source Data List will be generated for each site before start of enrollment, specifying the location of the source of derived information appearing in the eCRF. This document must be signed by the Principal Investigator and the Monitor to confirm agreement before start of recruitment.
Source documents are all documents used by the Investigator or hospital that relate to the subject's medical history, that verifies the existence of the subject, the inclusion and exclusion criteria, and all records covering the subject's participation in the trial. They include laboratory notes, memoranda, material dispensing records, subject files, etc. The eCRF may constitute source data if clearly defined in the Origin of Source Data List.
The Investigator should guarantee access to source documents to the Monitor and the IECs, if required.

14.4 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.

14.5 Study time table and end of study

The study is expected to start in Q3 2020 and to be completed by Q4 2020.
A subject is considered to have completed the study if he/she has completed all visits in the study including the end-of-study telephone call (Visit 4).
The end of the clinical part of the study is defined as the last visit of the last subject participating in the study.

14.6 Termination of the study

The Sponsor reserves the right to terminate this study prematurely for any reasonable cause. Conditions that may warrant study termination include, but are not limited to:

- A decision by the Sponsor to suspend or discontinue development of the IP.

If the study is prematurely terminated or suspended for any reason, the Investigator should promptly inform the study subjects and should assure appropriate follow-up for the subjects.

14.7 Reporting and publication

14.7.1 *Clinical study report*

A clinical study report (CSR), in compliance with ICH-E3, describing the conduct of the study, any statistical analyses 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.

14.7.2 *Confidentiality and ownership of study data*

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

14.7.3 *Publication*

The results from this study may be submitted for publication and/or presented during conferences at the discretion of the Sponsor.

14.8 Archiving

The Principal Investigator is responsible for maintaining essential documents, (as defined in ICH E6 GCP, Section 8) for 10 years after finalization of the CSR. This includes any original source documents related to the study, the Subject Identification List (providing the sole link between named subject source records and anonymous eCRF data), the original signed ICFs and detailed records of disposition of IP.
It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.
The Sponsor will archive the TMF in accordance with ICH E6 GCP, Section 8 and applicable regulatory requirements.
The data from the eCRFs will be sent to the Sponsor and a copy will be sent to the clinic and filed in the Investigator Study File for archiving for 10 years after finalization of the CSR.
The completed eCRFs are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from the Sponsor.

15 DATA MANAGEMENT

The data management routines include procedures for handling of the eCRF, database set-up and management, data entry and verification, data validation, QC of the database, and documentation of the performed activities including information of discrepancies in the process. The database, data entry screens, and program will be designed in accordance with the CSP.
Data validation/data cleaning procedures are designed to assure validity and accuracy of clinical data. These procedures consist of computerized online edit checks identifying e.g. data values that are outside the allowed range and SAS-programmed batch checks on data exports. All study-specific and standard data validation programming will be tested in a separate testing environment prior to use on production data.
Detailed information on data management will be described in a study-specific Data Management Plan (DMP).

15.1 The web-based eCRF

Clinical data will be entered into a 21 CFR Part 11-compliant eCRF (Viedoc™) provided by Viedoc Technologies AB. The eCRF includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents or at bedside (if the eCRF data constitutes source data). Source data are to be defined at the site before inclusion of the first subject (Section 14.3).
Authorized site personnel designated by the Investigator will complete data collection. Appropriate training and security measures will be completed with the Investigator and all authorized trial site personnel prior to the trial being initiated and any data being entered into the system for any study subject.

15.2 The entering of data into the eCRF

All entries, corrections, and alterations are to be made by the Investigator or designee. Neither the Monitor nor any other study team member besides site staff can enter data in the eCRF. All data should be entered in English. The eCRFs should be completed as soon as possible during or after the subject's visit. To avoid inter-observer variability, every effort should be made to ensure that preferably the same individual who made the initial baseline determinations completes all corresponding follow-up evaluations. The Investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available, not applicable, or unknown, the Investigator or assigned clinical staff should record such information in the eCRF. The Investigator will be required to electronically sign off the clinical data. This will be performed by means of the Investigator's unique User ID and password; date and time stamps will be added automatically at time of electronic signature.

15.3 The query process

The Monitor will review the eCRFs and evaluate them for completeness and consistency. Data in the eCRF will be compared with the respective source documents to ensure that there are no discrepancies for critical data as described in the RBM plan. All entries, corrections, and alterations are to be made by the Investigator or designee. Neither the Monitor nor any other study team member besides site staff can enter data in the eCRF.
If corrections are needed, queries will be raised within the eCRF, either as a result of built-in edit checks or manually raised by the monitor. An appropriate member of the site staff will answer the queries in the eCRF either by correcting the data or by entering a response to the query. The monitor will either approve the answer/correction or re-issue the query.

15.4 Audit trail

All entries in the eCRF will be fully recorded in a protected audit trail. Once clinical data have been saved, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who made the change, together with time and date will be logged.

15.5 External data

External data consists of data that are not recorded in the eCRF. Data may be received in electronic format or as a 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.

15.6 Medical coding

Medical coding will be performed by trained personnel at CTC. AEs and medical/surgical history verbatim terms will be coded using the Medical Dictionary of Regulatory Activities (MedDRA; latest version available at start of coding). Prior and concomitant medications will be coded according to the World Health Organisation (WHO) Anatomic Therapeutic Chemical (ATC) classification system. All coding will be approved by Sponsor prior to database lock.

15.7 Database lock

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

16 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The principal features of the statistical analysis to be performed are described in this section. A more technical and detailed elaboration of the principal features will be presented in a separate Statistical Analysis Plan (SAP), which will be signed and approved prior to database lock.
Analyses of the primary and secondary endpoints will be performed by CTC.

16.1 General

Continuous data will be presented in terms of evaluable and missing observations, arithmetic mean, standard deviation (SD), median, minimum and maximum value.
Categorical data will be presented as counts and percentages. When applicable, summary data will be presented by treatment, and by assessment time. Individual subject data will be listed by subject number, treatment, and, where applicable, by assessment time.
All descriptive summaries and statistical analyses will be performed using SAS Version 9.4 or later (SAS Institute, Inc., Cary, NC).
All pairwise testing will use a significance level of 5%.
No imputation of missing data will be performed.

16.2 Determination of sample size

The main hypothesis is to show that the fraction of extracted nicotine in ZYN Wintergreen is equivalent to that of Zyn Smooth.
Former studies (SM-17-03 and SM 18-01) has shown that the fraction of extracted nicotine has a mean CV of 31%, using a power of 80% and a 90% confidence interval (0.8-1.25) for the ratio will give a sample size of 33 subjects needed to show equivalence between the ZYN Wintergreen and ZYN Smooth (using Proc Power in SAS). In order for a small number of dropout will 36 subjects be included.

16.2.1 *Full analysis set*

The Full Analysis Set (FAS) will consist of all subjects who have been randomized and received at least one dose of IP and who has at least one post-baseline assessment of efficacy data. This population will be used as the Safety analysis set.

16.2.2 *Per protocol set*

The Per Protocol Set (PPS) will consist of all subjects who have been randomized and completed the study without any major protocol deviations that are judged to compromise the analysis of the data. All protocol violations will be judged as major or minor prior to database lock.

16.3 Description of study population

16.3.1 *Demographics and baseline characteristics*

Demographics, weight and height will be presented by treatment through descriptive statistics.

16.3.2 *Medical/surgical history and prior/concomitant medication*

Medical/surgical history will be presented by SOC and preferred term (PT). Prior/concomitant medications will be presented by ATC level 1, 3 and 5.
All data will be listed by subject.

16.3.3 *History of nicotine use*

History of nicotine use will be presented through descriptive statistics and listings.

16.3.4 *Treatment compliance*

The number of subjects treated with each treatment period will be listed.

16.3.5 *Physical examination*

Abnormal findings will be specified and presented by subject through descriptive statistics.

16.4 Analysis of primary endpoints

16.4.1 *In vivo extracted fraction of nicotine*

The data needed for the analysis of in vivo extracted amount of nicotine are the individual data of amount of nicotine for unused reference pouches and the amount of nicotine left in the study pouches. The difference between the nicotine content of the reference pouch and the study pouch will be used to calculate the extracted amount. The mean of extracted amount (mg/unit) and fraction (%) of nicotine for each IP pouch, will be calculated. The extracted fraction of nicotine will be analyzed using the linear mixed-effects analysis of variance (ANOVA) model with fixed effects for product, and a random effect for subject. A 90% confidence interval which lies between 0.8 to 1.25 will be judged as equivalent.
Amount and fraction of nicotine in reference pouches and in used pouches will be presented through descriptive statistics.

16.5 Analysis of secondary endpoints

16.5.1 *In vivo extracted amount and fraction of nicotine*

The data needed for the analysis of in vivo extracted amount of nicotine are the individual data of amount of nicotine for unused reference pouches and the amount of nicotine left in the study pouches. The difference between the nicotine content of the reference pouch and the study pouch will be used to calculate the extracted amount. The mean of extracted amount (mg/unit) and fraction (%) of nicotine for each IP pouch, will be calculated. The extracted dose of nicotine will be analyzed using the signed Wilcoxon rank sum test for within subject difference (i.e. between IPs).
Amount and fraction of nicotine in reference pouches and in used pouches will be presented through descriptive statistics.

16.5.2 *In vivo extracted amount and fraction of flavor compound*

The data needed for the analysis of in vivo extracted amount and fraction of flavor compound are the individual data of amount of flavor compound for unused reference pouches and the amount of flavor compound left in the study pouches. The difference between the flavor compound content of the reference pouch and the study pouch will be used to calculate the extracted amount (mg/unit) and fraction (%). The mean of extracted amount (mg/unit) of flavor compound for each IP pouch, will be calculated.
Amount and fraction of flavor compound in reference pouches and in used pouches will be presented through descriptive statistics.

16.5.3 *Analysis of Adverse events*

An overview of all AEs, including SAEs, intensity, and deaths will be presented by SOC and PT.
All AE data will be listed subject include the verbatim term entered by the Investigator.

17 REFERENCES

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18 SIGNATURES