Clinical Study Protocol	
Investigational Product	ZYN Moist
Sponsor study code	SM 19-01
Protocol Version and Date	Final v 3.0; 01JUL2020

STUDY TITLE

Nicotine plasma concentrations and pharmacokinetics of single doses of non-tobacco-based nicotine pouches (ZYN Moist and ZYN Dry Mini) and conventional, tobacco-based US moist snuff pouches among current, daily snus users.

Test product and dose	ZYN Moist Smooth containing 7 mg nicotine per portion ZYN Moist Smooth containing 9 mg nicotine per portion ZYN Moist Smooth containing 11 mg nicotine per portion ZYN Dry Mini Smooth containing 3 mg nicotine per portion ZYN Dry Mini Smooth containing 6 mg nicotine per portion
Comparator product and dose	Longhorn Pouch Natural containing 18 mg nicotine per portion
Sponsor signatory	[redacted] Swedish Match SE-Box 17037 104 62 Stockholm Sweden Maria Skolgata 83 SE-118 85 Stockholm Sweden [redacted]
Coordinating Investigator	Folke Sjöberg, MD, PhD, Professor CTC Clinical Trial Consultants AB Brigadgatan 26 SE-587 58 Linköping, Sweden

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 CTC Clinical Trial Consultants AB Brigadgatan 26 SE-587 58 Linköping, Sweden

1 STUDY SYNOPSIS

Study title Nicotine plasma concentrations and pharmacokinetics of single doses of non-tobacco-based nicotine pouches (ZYN Moist and ZYN Dry Mini) and conventional, tobacco-based US moist snuff pouches among current, daily snus users.	
Study code SM 19-01	
Planned study period Q3-Q4 2020	
Principal Investigator Folke Sjöberg, MD, PhD, Professor	
Study design This is an open, randomized, six-way cross-over, single dose administration study designed to assess the pharmacokinetic profile of non-tobacco-based nicotine pouches and tobacco-based US moist snuff pouches.	
Objectives <u>Primary objective</u> The primary objective of the study is to compare the exposure of nicotine after administration of a single dose of ZYN Moist 7 mg and a single dose of Longhorn 18 mg. <u>Secondary objectives</u> 1. To compare the pharmacokinetic profile of each of the non-tobacco-based nicotine pouches and Longhorn 18 mg. 2. To compare the estimated in vivo extracted amount (mg/unit) and extracted fraction (%) of nicotine from each product. 3. To correlate the estimates of pharmacokinetic (PK) parameters and the total amount of nicotine extracted from each product. 4. To evaluate the subjective effect on urge to snus for all products <u>Exploratory objectives</u> 1. To compare pharmacodynamic effects of nicotine by measuring pulse rate. 2. To compare the Cmax and AUCinf between plasma samples and Dried Blood Spot (DBS) samples for ZYN Moist 7 mg, ZYN Dry Mini 6 mg and Longhorn 18 mg. 3. To evaluate the early nicotine exposure for each product.	
Endpoints <u>Primary endpoints</u>	

Pharmacokinetics of nicotine in plasma: The difference in AUC_{inf} based on plasma concentrations of nicotine after administration of a single dose of ZYN Moist 7 mg and a single dose of Longhorn 18 mg.

Secondary endpoints

1. Pharmacokinetics of nicotine in plasma: The difference in T_{max}, C_{max}, AUC_{inf}, $AUC_{0\text{-}1.5h}$ and terminal elimination half-life of the non-tobacco-based nicotine ZYN Moist pouches, ZYN Dry Mini pouches and Longhorn 18 mg.
2. The difference in in vivo extracted amount of nicotine (mg/unit) and extracted fraction (%) from all products.
3. Correlation between total extracted amount of nicotine and C_{max} and AUC_{inf}.
4. The difference in the urge to snus, measured using a 100-mm visual analogue scale (VAS) anchored with ”not at all” to ”extremely” at pre-set time points up to 60 minutes after start of the investigational product (IP) administration will be compared among the products .

Exploratory endpoints

1. The difference in pulse rate measured using a pulse oximeter up to 2 hours after the start of the IP administration will be compared among the products.
2. The correlation for C_{max} and AUC_{inf} between DBS samples and plasma samples for ZYN Moist 7 mg, ZYN Dry Mini 6 mg and Longhorn 18 mg.
3. Pharmacokinetics of nicotine in plasma: $AUC_{0\text{-}30min}$ for each product.

Number of subjects planned

Approximately 42 subjects will be screened to achieve 36 randomized subjects and 32 fully evaluable subjects.

Diagnosis and main eligibility criteria

Healthy male or female snus users aged ≥19 years, who have used tobacco-based snus for ≥1 year, with a minimum weekly consumption of two or more snus cans, and are willing and able to usebrands 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.

Daily smokers, pregnant or breastfeeding female subjects, and subjects with a history or presence of 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 subjects will come for 6 treatment visits to the clinic, in addition to a visit for screening and a follow-up telephone visit. Screening (Visit 1) will take place from Day -28 to Day -1 and will include an eligibility check including evaluations of smoking and snus use, medical history. Between each treatment visit a wash-out period of at least 24 hours is required.

The treatments are administered as single doses in a pre-determined randomized order. The subject keeps the pouch still between the upper lip and 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 content.

Blood samples for assessment of plasma levels of nicotine will be collected at pre-defined time points from pre-dose to 6 hours after IP administration. In addition, urge to snus (using VAS) and pharmacodynamic effect of nicotine (by measuring pulse rate) will be determined.

Investigational Product (IP), dosage and mode of administration

1: ZYN Moist Smooth containing 7 mg nicotine per portion

2: ZYN Moist Smooth containing 9 mg nicotine per portion

3: ZYN Moist Smooth containing 11 mg nicotine per portion

4: ZYN Dry Mini Smooth containing 3 mg nicotine per portion

5: ZYN Dry Mini Smooth containing 6 mg nicotine per portion

Reference product

6: Longhorn Pouch Natural containing 18 mg nicotine per portion

Duration of treatment

The participating subjects will receive study product at 6 occasions, 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 6 weeks.

Pharmacokinetic (PK) assessments

Blood samples for analysis of PK parameters will be collected pre-dose, 5 min, 10 min, 15 min, 30 min, 45 min, 1h, 1h:15 min, 1h:30 min, 2h, 4h, 6h post-dose. The PK parameters in the study will include AUC_{inf}, AUC_{0-t}, C_{max}, T_{max}, and terminal half-life.

PK parameters (AUC_{inf} and C_{max}) calculated from plasma samples and dried blood spots (DBS) will be compared (reported separately).

Pharmacodynamic (PD) assessments

Continuous pulse rate

Pharmacodynamic effect of nicotine will be assessed by pulse rate measure.

Urge to snus

Urge to snus will be rated using VAS.

Nicotine extraction assessment

Extracted amount of nicotine (mg/unit) and extracted fraction (%) will be assessed

Statistical methods

No formal sample size calculation has been performed for this study. However, the proposed sample size is considered sufficient to provide adequate information for the study objectives.

Continuous data will be presented in terms of evaluable and missing observations, arithmetic mean, SD, median, minimum and maximum value, Q1-Q3 (interquartile range [IQR]). In addition, for the parameters AUC and C_{max} the geometric mean and coefficient of variation (CV) will be presented.

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). Baseline will be defined as the visit with last data collection point prior to the first administration of IP. All hypothesis testing will use a significance level of 5%. No imputation of missing data will be performed.
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
ADL	Activities of daily living
AE	Adverse event
ATC	Anatomical therapeutic chemical
AUC	Area under the curve
AUC_{inf}	Area under the curve from 0 to infinity
AUC_{0-t}	Area under the curve from 0 to the time t
C_{max}	Maximum observed concentration
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
DBS	Dried blood spot
DMP	Data management plan
eCRF	Electronic case report form
EDC	Electronic data capture
EEA	European Economic Area
FAS	Full analysis set
FU	Follow-up
GCP	Good clinical practice
GDPR	General data protection regulation
HIV	Human immunodeficiency virus
h	hour
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
IQR	Interquartile range

LLOQ	Lower limit of quantification
MedDRA	Medical dictionary for regulatory activities
min	minute
N	number
NCA	Non-compartmental analysis
NRT	Nicotine replacement therapies
PII	Personally Identifiable Information
PK	Pharmacokinetic
PKAS	PK analysis set
PT	Preferred term
PV	Pharmacovigilance
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
T_{max}	Time of occurrence of C_{max}
$T_{½}$	Terminal elimination half-life
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 11.6.9.

In the case of a medical emergency, the Investigator may contact the Medically Responsible Person at Sponsor.

[redacted]

5 INVESTIGATOR AND STUDY ADMINISTRATIVE STRUCTURE

Sponsor
Swedish Match
Maria Skolgata 83, 1 tr
SE-11885 Stockholm
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[redacted]

Clinical conduct
CTC Clinical Trial Consultants AB
Brigadgatan 26
SE-587 58 Linköping, Sweden

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SE-751 85 Uppsala, Sweden

And/or

CTC
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SE-752 37 Uppsala, Sweden

Study management
CTC
Dag Hammarskjölds väg 10B
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[redacted]

Signatures are provided in Section 19.

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, a novel, non-tobacco-based nicotine product (ZYN) has been developed and is now commercially available. It has 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 ZYN is comparable to that in snus and many other oral tobacco products that are currently common on the market in Scandinavia and the U.S.

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.

Commercially available oral tobacco products in the Scandinavian and U.S market have a nicotine content ranging between 3 mg/unit and more than 20 mg/unit.

Previous studies [2], have indicated that on average about 15-20% of the total nicotine content is extracted and absorbed, although with large interindividual variation. Recent in-house data (Swedish Match) shows an extracted fraction of about 20 - 30% following a 1-hour exposure. Extraction is generally not linear with pouch size: it is larger with small compared to larger pouches, which suggests that surface area, saliva penetration and diffusion factors may be more important determinants of nicotine uptake than pouch weight.

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.

A previous in vivo nicotine extraction study compared the ZYN Dry 3 and ZYN Dry 6 mg products to a conventional snus product (1.0-gram pouch) with 8 mg of nicotine. Nicotine extraction was measured after 15 and 60 minutes. The study showed that the extracted amount of nicotine increased in the order ZYN Dry 3 mg < General 8 mg < ZYN Dry 6 mg product. The same trend was observed for nicotine uptake. In a second uptake study, including ZYN Dry 8 mg and higher nicotine content reference products General Snus 8 mg *2 and Longhorn moist snuff 18 mg, the pharmacokinetics showed that the ZYN Dry 8 mg product delivered significantly less nicotine compared to General 8 mg*2 and similar levels compared to Longhorn moist snuff 18 mg.

The ZYN Dry products (3 mg, 6 mg and 8 mg) utilize a different matrix compared to the ZYN Moist products (7 mg, 9 mg and 11 mg). The nicotine uptake may differ as a consequence of different pouch geometry, water content, particle size etc. The ZYN Dry Mini (3 and 6 mg) product utilizing similar matrix as the previously tested ZYN Dry products, but with a higher nicotine concentration and different pouch geometry which may impact the nicotine uptake as well. Therefore, the current study will investigate the nicotine delivery and uptake profile of the ZYN Moist 7 mg, 9 mg and 11 mg products and the ZYN Dry Mini 3 mg and 6 mg products in comparison with a relevant oral tobacco product currently on the market – the US moist snuff Longhorn Pouch Natural 18 mg.

6.2 Study rationale

The overarching aim of the study is to ensure that the ZYN products do not entail a higher nicotine exposure than commercially available oral tobacco-based products that are currently common on the US-market.

6.3 Risk/benefit assessment

It may be considered problematic to expose research subjects to a novel nicotine delivery product with properties that 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 average snus consumption) so the participants are well acquainted with and used to the effects of nicotine.

Preliminary extraction data (data on file) indicate that the amount of nicotine extracted from the test articles are comparable to that from oral tobacco-based products. In addition, data from four clinical studies (unpublished) with ZYN Dry suggests that severe 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 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 events have been reported in the four clinical trials with a similar product type (ZYN Dry) 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 oral tobacco. 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.

Overdosing is not likely to occur since all IPs will be administered by site personnel and the subjects are daily snus users experienced in nicotine exposure.

Besides risks related to the IPs, there may also be risks related to the medical devices used in the study e.g. indwelling venous catheters. However, these are devices that are used in routine medical care and the risk associated with their use is considered low and ethically justifiable. Study specific evaluations and sampling procedures, such as frequent blood-sampling, may cause transient discomfort but the risk is deemed to be low and ethically justifiable.

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

7.1 Primary objective

The primary objective of the study is to compare the exposure of nicotine after administration of a single dose of ZYN Moist 7 mg and a single dose of Longhorn 18 mg.

7.1.1 *Primary endpoint*

Pharmacokinetics of nicotine in plasma: The difference in AUC_{inf} based on plasma concentrations of nicotine after administration of a single dose of ZYN Moist 7 mg and a single dose of Longhorn 18 mg.

7.2 Secondary objectives

The secondary objectives are:

1. To compare the pharmacokinetic profile of each of the non-tobacco-based nicotine pouches and Longhorn 18 mg.
2. To compare the estimated in vivo extracted amount (mg/unit) and extracted fraction (%) of nicotine from each product.
3. To correlate the estimates of pharmacokinetic (PK) parameters and the total amount of nicotine extracted from each product.
4. To evaluate the subjective effect on urge to snus for all products

7.2.1 *Secondary endpoints*

The secondary endpoints are:

1. Pharmacokinetics of nicotine in plasma: The difference in T_{max}, C_{max}, AUC_{inf}, $AUC_{01.5h}$ and terminal elimination half-life of the non-tobacco-based nicotine ZYN Moist pouches, ZYN Dry Mini pouches and Longhorn 18 mg.
2. The difference in in vivo extracted amount of nicotine (mg/unit) and extracted fraction (%) from all products.
3. Correlation between total extracted amount of nicotine and C_{max} and AUC_{inf}.
4. The difference in the urge to snus, measured using a 100-mm visual analogue scale (VAS) anchored with ”not at all” to ”extremely” at pre-set time points up to 60 minutes after start of the investigational product (IP) administration will be compared among the products.

7.3 Exploratory objectives

The exploratory objectives are:

1. To compare pharmacodynamic effects of nicotine by measuring pulse rate.
2. To compare the C_{max} and AUC_{inf} between plasma samples and Dried Blood Spot (DBS) samples for ZYN Moist 7 mg, ZYN Dry Mini 6 mg and Longhorn 18 mg.
3. To evaluate the early nicotine exposure for each product.

7.3.1 *Exploratory endpoints*

The exploratory endpoints are:

1. The difference in pulse rate measured using a pulse oximeter up to 2 hours after the start of the IP administration will be compared among the products.
2. The correlation for C_{max} and AUC_{inf} between DBS samples and plasma samples for ZYN Moist 7 mg, ZYN Dry Mini 6 mg and Longhorn 18 mg.

3. Pharmacokinetics of nicotine in plasma: $AUC_{0\text{-}30min}$ for each product.

8 STUDY DESIGN

8.1 Overall study design and schedule of events

This is an open, randomized, six-way cross-over, single dose administration study designed to assess the pharmacokinetic profile of non-tobacco-based nicotine pouches and tobacco-based US moist snuff pouches. The study will include 36 subjects.

The subjects will come for 6 treatment visits to the clinic, in addition to a visit for screening and a follow-up (FU) telephone visit. Screening (Visit 1) will take place from Day -28 to Day -1 and will include an eligibility check including evaluations of smoking and snus use, medical history and collection of height and weight, see Table 8.1-1 for details. Between each treatment visit a wash-out period of at least 24 hours is required.

Subjects shall be abstinent from snus and all other nicotine containing products for at least 12 hours before treatment and are instructed to abstain from snus or other nicotine delivery products as from 8.00 p.m. the evening before and to refrain from smoking 24 hours before each treatment visit. All IP administrations are performed during the morning hours to facilitate abstinence. The subjects should certify abstinence before each treatment is started.

The IPs 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 the IP, during application of the IP and 30 minutes after the IP has been taken out [3].

After 60 minutes the pouches are collected and frozen (-20°C) pending analysis of residual nicotine content.

Blood samples for assessment of plasma levels of nicotine will be collected at pre-defined time points from pre-dose to 6 hours after IP administration, see Table 8.1-2 for detailed sampling schedule. In addition, urge to snus (using VAS) and pharmacodynamic effect of nicotine (by measuring pulse rate) will be determined, see Table 8.1-2.

Study assessments are described in Section 11.

Table 8.1-1 Schedule of events

Visit	Visit 1 Screening	Visit 2-7 (Cross-over)	Visit 8 Telephone FU
Assessments / Study days	*-28 to -1*		*7 days (-3/+7) after last dose*
Informed consent	X		
Demographics	X		
Medical/surgical history	X		
History of nicotine use	X		
Inclusion/exclusion criteria	X	X[1]	
Physical examination	X		
Weight, height	X		
HIV, Hepatitis B and C	X		
Pregnancy test[2]	X	X	
Urine drug screen	X	X[3]	
Alcohol screen	X	X[3]	
Randomization		X[4]	
IP (pouch) administration		X[5]	
PK blood sampling (plasma)		X[5]	
PK blood sampling (Dried Blood Spots)[6]		X[5]	
Urge to snus (VAS)		X[5]	
Pulse rate		X[5]	
IP (pouch) collection		X[5]	
Baseline symptoms	X	X[7]	
Adverse Events		X[8]	
Prior and concomitant medications[9]	X		

[1] Confirmation of eligibility, at visit 2 only

[2]Only women of child bearing potential (WOCBP)

[3]Random drug and alcohol tests may be performed during the treatment period

[4]At visit 2 only

[5]Timing of assessments is outlined in Table 8.1-2

[6]Performed for18 consecutive subjects when receiving ZYN Moist 7 mg, ZYN Dry Mini 6 mg and Longhorn 18 mg

[7]Until administration of IP at Visit 2

[8]From first administration of IP

[9]For definitions of prior and concomitant medication, see Section 11.2.13.

Table 8.1-2 Detailed schedule of events

Visit	Visit 2 to 7																	
Assessment/time-point	**Admission**	**Pre-dose**	**-00:10**	**-00:01**	**00:00**	**00:02**	**00:05**	**00:10**	**00:15**	**00:20**	**00:25**	**00:30**	**00:45**	**01:00**	**01:15**	**01:30**	**02:00**	**04:00**	**06:00**
Inclusion/exclusion criteria	X[1]																		
Urine drug screen	X[2]																		
Alcohol screen	X[2]																		
Pregnancy test[3]	X																		
Randomization		X[4]																	
IP (pouch) administration					X														
IP (pouch) collection														X					
PK blood sampling (plasma)		X[5]					X	X	X			X	X	X	X	X	X	X	X
PK blood sampling (DBS)[6]		X[5]					X	X	X			X	X	X	X	X	X	X	X
Urge to snus (VAS)			X	X		X	X	X	X	X	X	X	X	X					
Pulse rate		X[7]					X	X	X			X		X			X		
Baseline Events		X[4]																	
Adverse Events		X[8]										X							
Prior and concomitant medications									X										

[1] Confirmation of eligibility criteria, at visit 2 only

[2] Random drug and alcohol tests may be performed during the treatment period

[3] Only women of child bearing potential (WOCBP)

[4] At visit 2 only

[5] Pre-dose PK-sample taken within 15 min prior to dose

[6] Performed for 18 consecutive subjects when receiving ZYN Moist 7 mg, ZYN Dry Mini 6 mg, and Longhorn 18 mg

[7] Pre-dose pulse measure within 15 min prior to dose

[8] At visits 3-7 only

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. To avoid carryover effects, a wash-out period of at least 24 hours has been incorporated between administrations.

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 to 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 enrolment log

Investigator 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 etc.).

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 rescreened before proceeding in the study.

9.3 Number of subjects

36 subjects will be included in the study. Approximately 42 subjects will be screened to achieve 36 randomized subjects and 32 fully evaluable subjects.

For replacements of subjects who discontinue from the study, see Section 9.8.

9.4 Inclusion criteria

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

1. Willing and able to give written informed consent for participation in the study.

2. Snus user who has used tobacco-based snus for ≥1 year, with a minimum weekly consumption of two or more snus cans, and is willing and able to use brands with nicotine content ≥1%.
3. Healthy male or female subject aged ≥19 years.
4. Women of child bearing potential (WOCBP) must be willing to use a sufficient contaceptive 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 be excluded from the study if any of the following exclusion criteria are fulfilled:

1. Daily smoker, defined as smoking during the last 24 hours according to self-report.
2. A history or presence of diagnosed hypertension or any cardiovascular disease.
3. Any surgical or medical condition, or history thereof, which, in the judgment of the investigator, might interfere with the absorption, distribution, metabolism or excretion of the investigational product 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.
4. Female subject currently breast feeding, pregnant or planning to get pregnant during the study.
5. Any positive result on screening for serum hepatitis B surface antigen, hepatitis C antibody and Human Immunodeficiency Virus (HIV).
6. Positive screen for drugs of abuse or alcohol at screening or on admission to the unit prior to first administration of the IP.
7. Current or history of alcohol abuse and/or use of anabolic steroids or drugs of abuse, as judged by the investigator.
8. Plasma donation within one month of screening or blood donation (or corresponding blood loss) during the three months prior to screening.
9. 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*

- Subjects shall abstain from snus and all other nicotine containing products from 8.00 pm the night before the visit and during the visits (except the IP treatment).

- Subjects shall abstain from smoking the last 24 hours before each visit (from 8.00 am day before visit).
- Subjects are not allowed to eat or drink or conduct any other mouth related procedure (e.g. tooth brushing) 30 minutes before dose administration, during application of IP and 30 minutes after the IP have been taken out.
- Subjects shall abstain from drugs of abuse from Screening to the Follow-up visit.
- Subjects shall abstain from alcohol the last 12 hours before each visit (from 8.00 pm the night before visit).
- Subject must not donate blood or plasma during the study until three months after the Follow-up 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 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) 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 if any of the following were reasons for screening failure or non-randomization (as judged by the Investigator):

- Practical reasons.
- No significant medical conditions (e.g. influenza, nasopharyngitis).
- Reserve subject in previous cohort.
- Plasma or blood donation outside allowed time windows.

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:

- Severe non-compliance to study protocol procedures, as judged by the Investigator and/or Sponsor.
- Subject is lost to follow-up. A subject will be considered lost to follow-up if he/she fails to come for consecutive scheduled visits and if he/she is not possible to contact by site staff despite several attempts.
- Significant adverse event (AE) posing a risk for the subject, as judged by the Investigator and/or Sponsor.
- Pregnancy.

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

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. 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. Any ongoing AEs will be followed as described in Section 11.6.10.

The primary reason for discontinuation/early withdrawal must be specified in the eCRF.

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. As this is an open study, the treatment sequence to which each subject is allocated for will be recorded in the eCRF. 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.

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. A coded copy of the randomization list will be generated, i.e. a list where the treatment is blinded, and this coded list will be provided to the bioanalytical laboratory and to the pharmacokineticist.

10 TREATMENTS

The IPs, both test- and reference products are supplied by Swedish Match AB.

10.1 Identity of investigational products

1: ZYN Moist Smooth containing 7 mg nicotine per portion

2: ZYN Moist Smooth containing 9 mg nicotine per portion

3: ZYN Moist Smooth containing 11 mg nicotine per portion

4: ZYN Dry Mini Smooth containing 3 mg nicotine per portion

5: ZYN Dry Mini Smooth containing 6 mg nicotine per portion

10.2 Identity of reference product

6: Longhorn Pouch Natural containing 18 mg nicotine per portion

10.3 Manufacturing, packaging and labelling

The production sites and batch ID for the IP and reference product will be documented in trial master file.

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.

10.4 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.

10.5 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 study IP received, prepared for and used by each subject and study medication 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.

10.6 Treatment administration

A single dose will be given in the morning of each treatment visit.

10.7 Treatment compliance

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

10.8 Return and destruction of investigational medicinal products

Any unused study IP 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 8.1-1 and Table 8.1-2, Section 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/she ensures the accuracy, completeness, legibility, and timeliness of the data reported to Sponsor in the eCRF and in all required reports.

It is important that PK blood sampling occurs as close as possible to scheduled time. In order to achieve this, the timing priority order at a particular time point is:

1. IP pouch collection
2. Blood samples for PK
3. Blood samples for DBS PK
4. Urge to snus (VAS)
5. Pulse rate measure

Time points for PK blood sampling and VAS are outlined in Table 8.1-2.

See Section 11.3.1 for allowed deviation of actual time for PK sampling.

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 14.3.

11.2.2 *Demographic information*

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

11.2.3 *Medical/surgical history*

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

11.2.4 *History of nicotine use*

History of snus use in terms of brand of snus, 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.

11.2.5 *Eligibility criteria*

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

11.2.6 *Physical examination*

A complete physical examination will include assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular, abdomen (liver and spleen), lymph nodes and extremities.

11.2.7 *Weight and height*

Weight and height will be measured without shoes.

11.2.8 *HIV and Hepatitis B/C*

Subjects will be tested for HIV and hepatitis B/C prior to inclusion into the study. Any positive result will exclude the subject from participating in the study.

11.2.9 *Pregnancy test*

All females of child bearing potential will do a urine pregnancy test at screening as well as at all treatment visits.

11.2.10 *Urine drug screen*

Urine will be screened for drugs of abuse at time points outlined in the schedule of events (Table 8.1-1) using the Alere™ Drug Screen Test Panel. Additional random tests can be performed during the study period.

11.2.11 *Alcohol breath test*

An alcohol breath test will be performed at time points outlined in the schedule of events (Table 8.1-1). Additional random tests can be performed during the study period.

11.2.12 *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.

11.2.13*Prior and concomitant medication*

Prior and concomitant medications taken within 2 weeks prior to screening will be obtained by subject interview for documentation of the subject´s status regarding current medications.

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 Day 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, unit, 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 endpoints

11.3.1 *Pharmacokinetic sampling and analysis*

Venous blood samples (approximately 5 mL) for the determination of plasma concentrations of nicotine after administration of the IP, will be collected through an indwelling venous catheter at pre-specified time-points; pre-dose (within 15 min prior to dose), 5 min, 10 min, 15 min, 30 min, 45 min, 1h, 1h:15 min, 1h:30 min, 2h, 4h, 6h post-dose, see Table 8.1-2. Actual time for blood PK sampling must not deviate from the planned time more than:

± 2 minute for time-points up to 30 minutes post-dose.

± 5 minutes for time-points up to 90 minutes post-dose.

± 10 minutes for time-points up to 6 hours post-dose.

Pre-dose sampling may be performed within 15 minutes prior to dosing.

The date and time of collection of each sample will be recorded in the eCRF.

The blood samples will be collected in pre-labelled tubes. All the collected blood samples will be centrifuged to separate plasma. The separated plasma from each blood sample will be divided into 2 aliquots in pre-labelled cryotubes and frozen at -20°C.

For further details see lab manual.

Plasma samples for determination of plasma concentrations of nicotine will be analyzed by Lablytica by means of a validated using LC-MS/MS method. Samples from all evaluable subjects will be analyzed.

11.4 Assessments related to secondary endpoints

11.4.1 *Nicotine extraction from pouches*

Used pouches will be collected after 60 minutes (+/- 1 minute) of use for the determination of residual nicotine in the IPs.

All the collected pouches will be frozen immediately at -20°C. Pouches for extraction of nicotine will be analyzed by Swedish Match.

11.4.2 *Urge to snus*

Urge to snus will be rated using VAS, anchored with "not at all" to "extremely" as answer to the question "Right now, how strong is your urge for snus?" at pre-set time points up to 60 minutes (-10 min pre-dose, -1 min pre-dose, 2 min, 5 min, 10 min, 15 min, 20 min, 25 min, 30 min, 45 min, and 60 min after each dose, see Table 8.1-2).

11.5 Assessments related to exploratory endpoints

11.5.1 *Pharmacodynamic effect of nicotine - pulse rate*

The pharmacodynamic effect of nicotine will be assessed by measuring the pulse rate at pre-specified timepoints; pre-dose (within 15 min prior to dose), and 5 min, 10 min, 15 min, 30 min, 1h, and 2 hours post-dose using pulse oximeter, see Table 8.1-2.

11.5.2 *Pharmacokinetic sampling using Dried Blood Spot technique*

Blood samples for determination of concentrations of nicotine after administration of ZYN Moist 7 mg, ZYN Dry Mini 6 mg and Longhorn 18 mg will be collected using DBS for 18 consecutive subjects at pre-specified time-points; pre-dose (within 15 min prior to dose), and 5 min, 10 min, 15 min, 30 min, 45 min, 1h, 1h:15 min, 1h:30 min, 2h, 4h, 6h post-dose, see Table 8.1-2.

Following finger prick procedure with a lancet, the entire circle on the collection card should be uniformly saturated for each sampling timepoint. The card should be fully air-dried-horizontally at room temperature and stored away from direct sunlight.

For further details see lab manual.

DBS for determination of concentrations of nicotine will be analyzed by Department of Chemistry, Uppsala University.

The collection of whole blood samples on paper is known as DBS. DBS offers a number of advantages over conventional blood collection. As a less invasive sampling method, DBS offers simpler sample collection and storage and easier transport, with reduced infection risk of various pathogens, and requires only a few drops of blood. The DBS blood collection platform is rapidly becoming an important basis for quantitative analysis of biomarkers.

11.6 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) regarding emergencies.

11.6.1 *Definition of adverse event*

An AE is defined as any untoward medical occurrence in a subject administered a medicinal product (in this case an investigational product) and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the investigational product.

11.6.2 *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.

11.6.3 *Time period and frequency for collecting adverse events*

All AEs (including SAEs) will be collected from the start of IP administration until the end-of-study visit.

Any AE with start date on the day of IP administration 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 during 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.

11.6.4 *Assessment of intensity*

The grading of the intensity of AEs will follow the CTCAE v5.0 [4]. 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 intensity of an AE using the following definitions, and record it on the AE Log in the eCRF:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.

Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	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.*

11.6.5 *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 aetiology is unlikely or significantly less likely.
Possible	The event has a suggestive temporal relationship to the IP, and an alternative aetiology 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 when the causality assessment is probable or possible.

11.6.6 *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	

11.6.7 *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

11.6.8 *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; intensity; causal relationship to IP; action taken, and outcome.

If the AE is serious, this must be indicated in the eCRF.

AEs 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.

11.6.9 *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]

The SAE report is reviewed by a designated person at CTC's Pharmacovigilance (CTC PV) department to ensure that the report is valid and correct. For fatal or life-threatening SAEs where important or relevant information is missing, immediate follow-up is undertaken and queries to the site are raised. Investigators or other site personnel should inform CTC PV of any follow-up information on a previously reported SAE immediately but no later than the end of the next business day of when he or she becomes aware of it.

If the SAE report in the eCRF is updated, a new e-mail alert will be sent.

If any additional documentation is required (e.g. autopsy report), CTC PV will request this information from the study site.

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.

11.6.10 *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.

11.6.11 *Procedures in case of pregnancy*

In case of pregnancy or suspicion of possible pregnancy of any female, 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 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.

11.6.12 *Treatment of 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 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.

11.7 Appropriateness of measurements

All methods used for safety assessments are commonly used in standard medical care and in Phase I clinical studies. Non-compartmental analysis of PK parameters is standard for Phase I clinical studies.

12 PROCEDURES FOR BIOLOGICAL SAMPLES

12.1 Sample collection

The sample collection procedure for PK analysis is described in Section 11.3.1.

12.2 Volume of blood

The anticipated volume of blood samples collected during the study from each subject will be approximately 380 mL (i.e., less than the volume drawn during a regular blood donation).

12.3 Handling, storage and destruction of laboratory samples

The plasma samples and DBS samples for analysis of PK parameters will be registered in a biobank at CTC (893).

Any remains from the safety laboratory samples will be disposed of after analyses.

The plasma samples for analysis of PK parameters will be stored at <-20°C until analyzed. DBS samples will be stored at room temperature until analyzed. The samples will be disposed of after the clinical study report (CSR) has been finalized respectively the DBS results have been reported.

12.4 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

CTC keeps full traceability of collected biological samples from the subjects while in storage at the research clinic until shipment and keeps documentation of receipt of arrival.

The sample receiver (the analytical laboratory) keeps full traceability of the samples while in their storage and during use until used or disposed of.

The Sponsor keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

12.5 Withdrawal of informed consent for donated biological samples

If a subject withdraws consent to the use of biological samples donated, the samples will be disposed of /destroyed, if not already analyzed and documented.

The Principal Investigator will ensure that:

- Subject withdrawal of informed consent is notified immediately to Sponsor.
- Biological samples from the subject, if stored at the research clinic, are immediately identified, disposed of/destroyed and the action is documented.

The Sponsor has to ensure that the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed or returned to the research clinic and the action is documented.

13 QUALITY MANAGEMENT, QUALITY ASSURANCE AND QUALITY CONTROL

13.1 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 Harmonisation (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.

13.2 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.

14 ETHICAL AND REGULATORY REQUIREMENTS

14.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki [5] and are consistent with ICH/Good Clinical Practice (GCP) E6 (R2), EU Clinical Trials Directive, and applicable local regulatory requirements.

14.2 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 independent ethics committee (IEC) before the first subject can be recruited.

The Sponsor will provide the IEC and Principal Investigators with safety updates/reports according to local requirements.

14.3 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 CRF. 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.

14.4 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 and the concerned IEC 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 14.3.

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 CRF 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 Swedish Match AB 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.

14.5 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 before implementation according to applicable regulations.

14.6 Audits and inspections

Authorized representatives of Sponsor may perform audits at the research clinic, including source data verification (SDV). The purpose of an audit 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

Subjects will be covered under Swedish Match AB´s liability insurance policy through IF insurances. 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.

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 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 key staff to whom study-specific duties are delegated.

15.2 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.
- ensure that withdrawal of informed consent to the use of the subject's biological samples will be reported and biological samples are identified and disposed of/destructed accordingly, and that this action is documented and reported to the subject.
- 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.

15.3 Source data documents

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

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.

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 timetable 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 visit 8, telephone follow-up.

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

15.6 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.

15.7 Reporting and publication

15.7.1 *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.

Results for the exploratory comparison of sampling technique between plasma sampling and DBS for nicotine concentrations will be reported separately.

15.7.2 *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.

15.7.3 *Publication*

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

15.8 Archiving

The Principal Investigator is responsible for maintaining essential documents, (as defined in ICH E6 GCP, Section 8) for 10 years after finalisation 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 finalisation of the CSR.

The completed eCRF 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.

16 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 offline 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).

16.1 The web-based eCRF

Clinical data will be entered into a 21 CFR Part 11-compliant eCRF (Viedoc™) provided by PCG Solutions 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 15.3).

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.

16.2 The entering of data into the eCRF

All entries, corrections, and alterations in the eCRF are to be made by the Investigator or designated site personnel. Neither the Monitor nor any other study team member besides site personnel may 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. 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 must verify that all data entries in the eCRFs are accurate and correct and will be required to electronically sign off the clinical data. This will be performed by means of the Investigator's unique UserID and password; date and time stamps will be added automatically at the time of electronic signature.

16.3 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.

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.

16.4 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.

16.5 External data

External data consists of data that are not recorded in the eCRF. Data may be received in electronic format. Key variables are defined in order to uniquely identify each sample record. File and data formats are agreed with the external data provider.

16.6 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.

16.7 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.

17 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.

17.1 General

Continuous data will be presented with descriptive statistics in terms of evaluable and missing observations, arithmetic mean, standard deviation (SD), median, minimum and maximum value, Q1-Q3 (interquartile range [IQR]). In addition, for the parameters AUC and C_{max} the geometric mean and coefficient of variation (CV) will be presented.

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).

Baseline will be defined as the visit with last data collection point prior to the first administration of IP.

All hypothesis testing will use a significance level of 5%.

No imputation of missing data will be performed.

17.2 Determination of sample size

No formal sample size calculation has been performed for this study. However, the proposed sample size is considered sufficient to provide adequate information for the study objectives.

The sample size of 32 evaluable subjects is assumed to be enough to address the hypothesis.

Approximately 42 subjects will be screened to achieve 36 randomized subjects and 32 fully evaluable subjects (assuming a drop-out rate of 10%).

17.3 Analysis data sets

17.3.1 *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.

17.3.2 *PK analysis set*

The PK analysis set (PKAS) will consist of all subjects who received at least one dose of study IP and provided at least one full set of PK plasma sampling and no major deviation judged to compromize the PK analysis. Individual PK values and/or full profiles for explicit IPs may be excluded from the analysis as specified in the SAP.

17.3.3 *Additional analysis datasets*

Additional datasets may be created as needed for exploratory analyses.

17.4 Description of study population

17.4.1 *Demographics and baseline characteristics*

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

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

Medical/surgical history will be presented by treatment by system organ classes (SOC) and preferred term (PT) and Prior/concomitant medications will be presented by treatment by ATC level 1, 3 and 5 through descriptive statistics and listings.

17.4.3 *History of nicotine use*

History of snus use and smoking will be presented through descriptive statistics.

17.4.4 *Treatment compliance*

The number of subjects treated with each treatment will be presented through descriptive statistics and listings.

17.4.5 *Physical examination*

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

17.5 Analysis of primary endpoints

17.5.1 *Comparison of nicotine exposure after administration of ZYN Moist 7 mg and Longhorn 18 mg*

The PK analysis will be based on the PK analysis set and performed by CTC. The PK parameter will be calculated by non-compartmental analysis (NCA) using the software Phoenix WinNonlin® version 8.1 or later (Certara Inc, Princeton, New Jersey, U.S.A.).

AUC_{inf} based on plasma concentrations of nicotine after administration of one single dose of ZYN Moist 7 mg of nicotine will be compared to that of a single dose of Longhorn 18 mg and be described using summary statistics Student´s t-test for between treatment difference. For details on calculation of AUC_{inf}, see Section 17.6.1.

17.6 Analysis of secondary endpoints

17.6.1 *Analysis of pharmacokinetics*

The PK analysis will be based on the PK analysis set and performed by CTC. The PK parameters will be calculated by NCA using the software Phoenix WinNonlin® version 8.1 or later (Certara Inc, Princeton, New Jersey, U.S.A.).

The following non-compartmental PK parameters will be determined for each IP treatment:

- T_{max} (sampling time at which C_{max} occurred)
- C_{max} (maximum observed concentration)
- AUC_{inf} (area under the plasma concentration-time curve from time 0 to infinity)
- $AUC_{0\text{-}1.5h}$ (area under the plasma concentration-time curve from time 0 to 1.5 hours)
- $T_{½}$ (terminal elimination half-life)

C_{max} and T_{max} will be derived from the observed plasma concentration data. The AUC will be calculated using log-linear trapezoidal interpolation. Calculations will be based on the actual sampling times recorded during the study. Concentrations below Lower limit of quantification (LLOQ) occurring before C_{max} will be treated as zero. Concentrations below LLOQ occurring after C_{max} will be omitted from the analysis. $AUC_{inf,}$ $AUC_{0\text{-}1.5h,}$ and C_{max} will be corrected for nicotine baseline concentrations.

Pharmacokinetic data will be summarized for each IP treatment using summary statistics. Data will be presented in terms of N, arithmetic mean, SD, minimum and maximum value. In addition, for the parameters AUC and C_{max} the geometric mean and CV will be presented. Between-treatment differences for all pairwise comparisons will be analyzed using signed Student´s t-test. Categorical data will be presented as counts and percentages as applicable.

17.6.2 *In vivo extracted amount 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 extraction 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 of nicotine in reference pouches and in used pouches will be presented through descriptive statistics.

17.6.3 *Extracted nicotine versus nicotine exposure*

Correlation between total extracted amount of nicotine and C_{max} and AUC_{inf} will be analyzed using correlation analysis as further described in the SAP.

17.6.4 *Urge to snus*

Subjective urge to snus measured through VAS will be summarized for each IP using summary statistics both as a total score and the min and max score during the IP administration phase. Further analyses will be described in the SAP.

17.7 Analysis of exploratory endpoints

17.7.1 *Pharmacodynamic effect of nicotine*

Analyses of pulse rate as measure of pharmacodynamic effect of nicotine will be further described in the SAP.

17.7.2 *Comparison of PK plasma samples versus DBS samples*

The correlation for C_{max} and AUC_{inf} between DBS samples and plasma samples for ZYN Moist 7 mg, ZYN Dry Mini 6 mg and Longhorn 18 mg will be analyzed with correlation analysis.

17.7.3 *Early nicotine exposure*

$AUC_{0\text{-}30min}$ will be analyzed as described in Section 17.6.1.

17.8 Analysis of Adverse events

An overview of all AEs, including SAEs, intensity, and deaths will be presented by SOC and PT.

Incidence of AEs and SAEs will be summarized by SOC and PT by treatment.

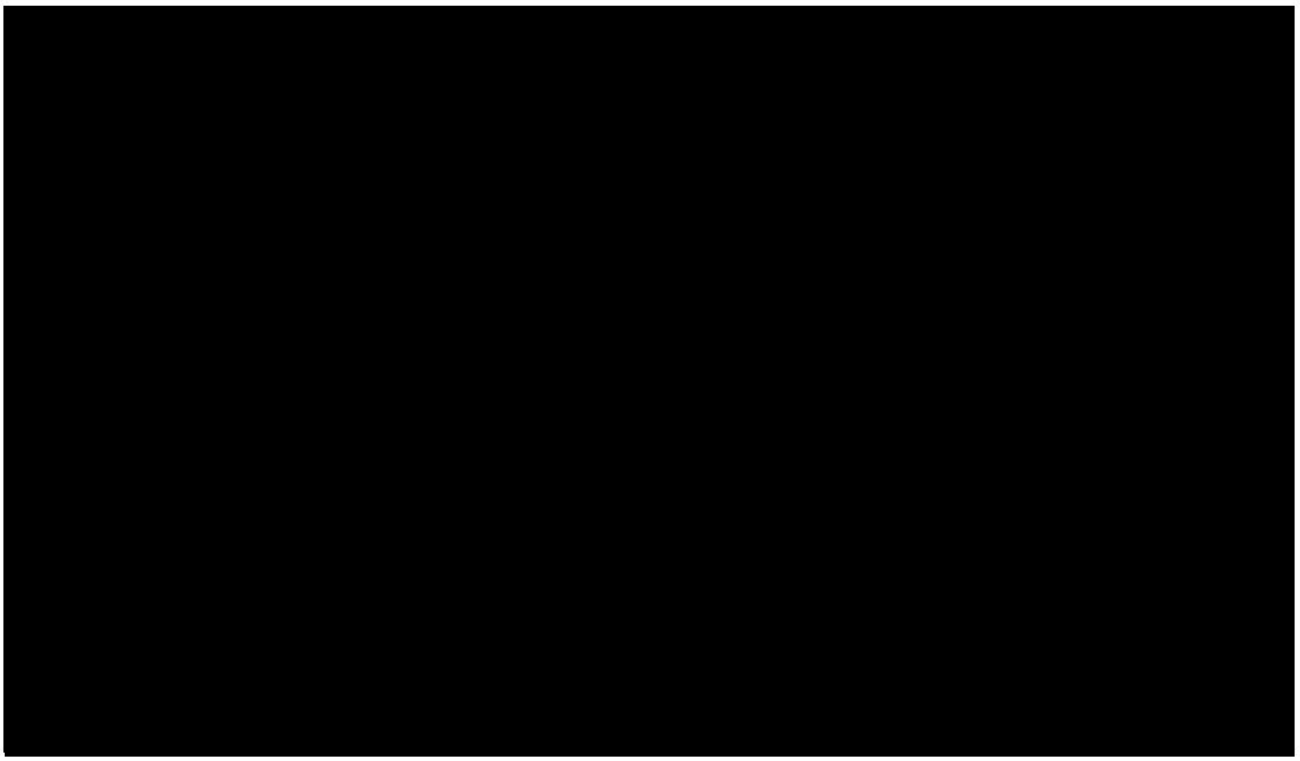
All AE data will be listed subject and treatment include the verbatim term entered by the Investigator.

18 REFERENCES

1. Fant RV, Henningfield JE, Nelson RA and Pickworth WB. Pharmacokinetics and pharmacodynamics of moist snuff in humans. Tob. Control, 8, 387-392 (1999).
2. 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, 13 (7), 573-578 (2011).
3. Henningfield et al. Drinking coffee and carbonated beverages blocks absorption of nicotine from nicotine polacrilex gum. JAMA, 264 (12), 1560-4 (1990).
4. National Cancer Institute Cancer Therapy Evaluation Program. Common terminology criteria for adverse events, CTCAE v5.0 (2017).
5. Declaration of Helsinki: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

19 SIGNATURES

19.2 Signature page (approval of the clinical study protocol)



19.2 Signature page (approval of the clinical study protocol)