Clinical Study Protocol

Investigational Product: Oral nicotine products

Sponsor Protocol Code: BAT2119018

Protocol Version: 3.0

Date: 06 April 2020

STUDY TITLE

A multi-centre, randomised, cross-over, pharmacokinetic study of 8 oral nicotine products

Sponsor *British American Tobacco (Investments) Limited, Globe House, 4 Temple Place, London, WC2R 2PG, United Kingdom.*

Substantial amendment

Amendment No	Final version date
2.0	**17 Feb 2020**
3.0	**06 Apr 2020**

2 PROTOCOL SYNOPSIS

Study Title
A Multi-Centre, Randomised, Cross-over, Pharmacokinetic Study of 8 Oral Nicotine products

Sponsor Protocol Code: BAT2119018

Study period
Estimated date of first subject enrolled: May 2020

Estimated date of last subject completed: Aug 2020

Objectives
Primary objective(s)
To determine the kinetics of nicotine absorption into the blood of subjects using different variants of smokeless nicotine products and to compare the nicotine PK parameters between smokeless nicotine products.

Secondary objectives
To evaluate product subjective measures of the different smokeless nicotine products and to determine the amount of residual nicotine in the used pouches.

Endpoints
Primary endpoint
PK parameters C_{max} and $AUC_{0\text{-}6h}$ of nicotine.

Secondary endpoints
Scores on the product subjective measures questionnaires and the amount of residual nicotine in the used pouches.

Number of subjects planned
36 healthy volunteers will be randomised at two centres in competitive recruitment manner with a minimum of 20% female subjects.

Main eligibility criteria
Healthy daily user of smokeless snus or modern oral nicotine products aged 19-55 years.

Study design
Multi-centre, randomised, pharmacokinetic, cross-over study.

Methodology
36 healthy volunteers will after screening, and a familiarisation visit when the highest dose product will be tested for tolerance, be randomised to dosing and PK sampling with 8 oral nicotine products during two 4.5 days clinic admission periods or one 8.5 days clinic admission period. After the discharge from the second period a telephone follow-up will be done within a week.

Investigational product, dosage and mode of administration

8 oral nicotine products:
1) Swedish Snus (pouch) – Granit Vit Stark with 13 mg/pouch nicotine
2) Lyft (Commercial product), 4 mg/pouch
3) Lyft (Commercial product), 10 mg/pouch

4) Lyft non-commercial (alginate removed), 10 mg/pouch 5) Lyft non-commercial (benzoic acid added), 4 mg/pouch 6) Lyft non-commercial (benzoic acid added), 10 mg/pouch 7) Lyft non-commercial (citric acid added), 10 mg/pouch 8) Lyft non-commercial (benzoic acid added, sweet base), 10 mg/pouch
Duration of treatment Each of the study products will be used for 60 minutes for PK sampling.
Duration of subjects' involvement in the study The screening procedure will take place up to 28 days before the start of the one 8.5 days or two 4.5 days PK sampling admission periods followed by telephone follow-up within a week after discharge from the second session. The total duration for each subject is not expected to exceed 7 weeks.
Pharmacokinetic assessments Blood samples for pharmacokinetic parameters will be analysed at pre-dose, 5, 10, 20, 40, 50, 60, 65, 75, 90, 120, 240 and 360 minutes relative to the start of the 60 min product administration.
Safety assessments Safety assessments will include symptom-oriented physical examination, oral mucosa examination, vital signs, clinical laboratory tests, and AE monitoring.
Statistical methods A sample size of 32 subjects completing all PK sampling is calculated as sufficient. To achieve this, a total of 36 subject will be randomised to PK sampling.

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4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or term	Explanation
ADR	Adverse Drug Reaction
AE	Adverse event
BAT	British American Tobacco
BMI	Body mass index
CNS	Central nervous system
CRF	Case report form
CRO	Contract Research Organisation/Clinical Research Organisation
EC	Ethics Committee
ECG	Electro-cardiogram
EFV	Erythrocyte volume fraction
GCP	Good clinical practice
GMP	Good manufacturing practice
IB	Investigator's Brochure
ICH	International conference on harmonization
ICFIWRS	Informed Consent Form Interactive Web Response System
NSAID	Non-steroidal anti-inflammatory drug
PK	Pharmacokinetic
PRRP	Potentially Reduced Risk Products
SAE	Serious adverse event
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment emergent Adverse Event
UADR	Unexpected Adverse Drug Reaction

5 INTRODUCTION

Cigarette smoking is a leading cause of numerous human disorders including lung cancer, pulmonary disease and cardiovascular disease. Cigarette smoke is a complex and dynamic mixture of more than 6,500 identified chemical constituents, some of which have been identified as potential contributors to the disease-causing effects of cigarette smoke.

A number of companies, including British American Tobacco (BAT), are developing alternative tobacco and nicotine products that deliver nicotine to the user but do not burn tobacco. BAT use the term 'potentially reduced risk products' (PRRPs) to describe tobacco and nicotine products that, based on the available science, have been shown to be reduced-risk; are likely to be reduced-risk; or have the potential to be reduced-risk, in each case if switched to exclusively as compared to continuing to smoke cigarettes. PRRPs include the following categories: electronic cigarettes (e-cigarettes), tobacco heating products and smokeless oral products, such as snus.

Recently, oral nicotine products containing little or no tobacco (henceforth referred to as 'modern oral') have emerged on the market as potential alternatives to existing oral tobacco products. One such product is "Lyft", a smokeless, tobacco-free oral product which is white in colour and comes in pouches containing high-quality food-grade ingredients including naturally derived nicotine, water, eucalyptus and pine tree fibres, flavouring and sweeteners. Consumers place the pouch between their gum and upper lip, typically for up to 60 minutes. During use, nicotine and flavours are released and the nicotine is absorbed through the oral mucosa in the gum.

Chemical analysis and *in vitro* data conducted by the sponsor suggests that Lyft modern oral products demonstrate a lower toxicant profile and reduced biological response compared to traditional tobacco-containing snus products. Therefore, understanding the rate of nicotine uptake is key information required to further characterise these products as potential alternatives to cigarette smoking and traditional snus use.

BAT is currently developing non-tobacco containing smokeless products with nicotine and aim to understand how this category of products impact nicotine pharmacokinetics. Therefore, BAT would like to conduct a pharmacokinetic study, using smokeless products only to obtain human pharmacokinetic data to understand product efficacy at delivering nicotine, provide safety data, and inform product design.

The results of this study will answer a fundamental science question as to the nicotine pharmacokinetics of these modern oral products.

5.1 Rationale for study design

This study was designed to assess nicotine uptake for modern oral products in comparison to traditional tobacco containing Swedish snus to understand product efficacy at delivering nicotine, provide safety data and inform product design. A crossover design was chosen to minimise variability and the number of subjects needed for evaluation. Subjects will be randomised to study product sequences to minimise assignment bias. By necessity, the subjects will not be fully blinded due to the different visual appearances between the snus product and the seven oral nicotine products. This

is not anticipated to impact the outcome of the study endpoints. The bioanalytical laboratory will be blinded.

As the purpose of this study is to assess nicotine uptake for modern oral products in comparison to traditional snus, 8 smokeless nicotine pouch products will be used in this study. Smokeless pouch users or loose snus users as well as dual users (smokers or e-cigarette users and smokeless pouch or loose snus users) will be recruited.

To avoid any carry-over effect, a wash-out of 12 hours is planned between product administrations. Given the expected half-life of nicotine (about 2 hours), this wash-out period is judged to be sufficient.

5.2 Risk / benefit analysis

5.2.1 Risk Assessment

Smokeless pouch products, such as Swedish-type snus, have been used extensively as consumer products for decades. "Lyft", a smokeless, tobacco-free oral product comes in pouches containing high-quality food-grade ingredients including naturally derived nicotine, water, eucalyptus and pine tree fibres, flavouring and sweeteners. The sole pharmacologically active ingredient of the smokeless oral tobacco pouches is nicotine. Generally, such products are associated with minor and infrequent acute adverse effects, predominantly headaches, nausea, dizziness and palpitations. Human experience with this product category demonstrates an absence of significant acute adverse effects in humans, in line with the preclinical British American Tobacco Lyft non-tobacco containing smokeless pouch specific assessment (Unpublished data).

These non-tobacco containing smokeless pouches are oral products that consumers place between their gum and upper lip to release nicotine and flavours. It is widely acknowledged that most of the harm associated with conventional cigarettes is caused by the toxicants in the smoke produced by the burning of tobacco. Non-tobacco containing oral smokeless pouches deliver nicotine to the user through the oral mucosa in the absence of both tobacco and combustion and are therefore hypothesised to be substantially less toxic than cigarette smoke due to reduced exposure to chemical toxicants. Analytical analysis of modern oral products has shown that levels of chemical toxicants are reduced compared to cigarette smoke. A representative non-tobacco containing smokeless pouch product had either lower or no detectable levels of 11 harmful or potentially harmful constituents typically found in cigarette smoke (Unpublished data).

To date, no epidemiological studies have been performed with modern oral products. However, multiple studies have evaluated smokeless tobacco products, including pouched products similar in style to modern oral products except for their inclusion of tobacco. Multiple evaluations have concluded that risks of adverse health impacts from using snus are up to 90% lower than from using cigarettes (Lee, 2011; Lee, 2013; Levy et al., 2004; RCP, 2007; SCHNEIR, 2008). As these smokeless non-tobacco oral products are used in a similar way to Swedish-type snus, which contain tobacco, it is hypothesised that users of Swedish-type snus that switch exclusively to non-tobacco containing oral smokeless pouches would be exposed to less toxicants and therefore a similar if not lower risk than Swedish-type snus.

BAT tobacco and/or nicotine products are not suitable for use by pregnant or breastfeeding women. Therefore, females of childbearing potential may only be included in the present study if they consent to take appropriate measures to prevent pregnancy during the study.

Nicotine use can have side effects, but subjects included in the study will already be users of nicotine and tobacco products. During study product use, it is not expected that subjects would be exposed to nicotine levels higher than those they are usually exposed to during their daily consumption of nicotine and tobacco products. The duration of exposure for each product has been determined by the standard use of such products. Therefore, acute risks related to the product administration are anticipated to be low.

The best way to avoid the risks associated with tobacco products is not to use them at all.

Each nicotine product will meet the required quality standard applicable to marketed tobacco or nicotine products (as relevant).

The dose of nicotine administered in this study is not anticipated to induce any additional potential risk to the subjects who are already users of nicotine and tobacco products. The safety monitoring practices employed by this protocol (i.e. symptom-oriented physical examination, oral mucosa examination, vital signs, clinical laboratory assessments, and AE questioning) are adequate to protect the subjects' safety and should detect all expected treatment-emergent AEs (TEAEs).

5.2.2 Benefit Assessment

There will be no medical advantages as a result of using the study products. However, the subjects will undergo a medical examination, which may provide them with information on their state of health.

Subjects will be able to ask for advice to stop using tobacco / nicotine products and any subjects who are smokers will be provided with a smoking cessation helpline number and/or web address, e.g. https://www.slutarokalinjen.se/.

Understanding the rate of nicotine uptake is key information required to further characterise these products as potential alternatives to cigarette smoking and traditional snus use.

To date, there are no published data on the delivery of nicotine to human subjects from modern oral products. Therefore, the results of this study will answer a fundamental science question as to the nicotine pharmacokinetics of these modern oral products.

6 INVESTIGATOR(S) AND STUDY ADMINISTRATIVE STRUCTURE

The study will take place at two study centres, 1) CTC Clinical Trial Consultants AB, Dag Hammarskjöldsväg 10b, 752 37 Uppsala, Sweden and 2) The Skåne University Hospital, Clinical Studies Sweden – Forum South, Clinical Trial Unit, Lund, Sweden. The Country Coordinating Investigator is Dr. Johan Nilsson at the CTC Unit.

A total of 36 subjects will be selected to participate in the study to complete with at least 32 subjects.

The CRO company IRW Consulting will provide Project Management, Data Management, Pharmacovigilance, Clinical Monitoring, Biostatistics and Medical Writing Services.

7 STUDY OBJECTIVES AND ENDPOINTS

7.1 Primary objective(s)

The primary objective of this study is to determine the kinetics of nicotine absorption into the blood of subjects using different variants of smokeless nicotine products and to compare the nicotine PK parameters between smokeless nicotine products.

7.2 Primary endpoint(s)

The primary study endpoints are the PK parameters C_{max} and AUC_{0-6h} of nicotine.

7.3 Secondary objectives and endpoints

The secondary objectives of this study are to evaluate product subjective measures of the different smokeless nicotine products and to determine the amount of residual nicotine in the used pouches.

Secondary endpoints are the scores on the product subjective measures questionnaires and the amount of residual nicotine in the used pouches.

7.4 Safety endpoints

The safety endpoints are the incidence of AEs/SAEs, vital sign abnormality assessments, clinical laboratory abnormality assessments, and symptom-oriented physical examination findings.

8 INVESTIGATIONAL PLAN

8.1 Overall study design and schedule of events

This is a two centre, randomised, non-blinded, 8-product, 8-period crossover, single dose pharmacokinetic study, in which 36 healthy male or female adult users of smokeless nicotine products (subjects who use pouched snus should regularly use pouch weights of 0.6 g and above, and at least 7.5 mg nicotine/pouch) will be randomised in competitive recruitment manner to receive one of the study products during each study period. The 8 periods of product use and sampling will be scheduled during two admission periods of 4.5 days each. There is also option for subjects to perform the product use and sampling in one 8.5 days admission period. For subjects choosing the one 8.5 admission option, they will come to the clinic on day 1 and will then receive the 8 products and undergo PK sampling on days 2-9 after which the subject is discharged. For subjects choosing the two admission periods of 4.5 days, they will come to the clinic on day 1 and will then receive 4 of the 8 products and undergo PK sampling on days 2-5 after which the subject is

discharged. Subjects will return for a second admission on day 8 with PK dosing and PK sampling of the remaining 4 products on days 9-12.

To minimise the risk of dropouts during the study, it will be accepted for subjects to be discharged during the 8.5-day admission period, or one or both of the planned 4.5-day admission periods, to return for re-admission and the remaining dosing and sampling at a later date. This option will only be used if absolutely necessary to avoid subjects to drop-out of the study.

Subjects will be aged 19-55 inclusive and judged to be healthy by pre-study screening. Subjects must have been using smokeless oral nicotine products daily for at least 6 months and must not be trying to quit or planning on quitting during the study period. Product use status will be confirmed with a urinary cotinine level of ≥100 ng/ml at screening.

Subject eligibility for this study will be determined at the screening visit and eligible subjects will be admitted to the clinical research unit (CRU) at least 13 hours prior to the first product administration. The screening visit will take place up to 28 days prior to the first admission for product administration and PK sampling.

During or after the screening visit but prior to admission for the confinement period, the subjects will attend the clinic for a familiarisation session in which they will be given the highest nicotine strength product (Granit Vit Stark 13 mg/pouch). The purpose of this familiarisation session is to ensure the subject tolerates the product with the highest nicotine strength to avoid dropouts due to product intolerance during the PK sampling period. The subject will use the product in the same way they would normally use a smokeless snus product. There will be a 20 minutes duration of use of the product (from the time the subject places the product in their mouth until the time the subject removes the product from their mouth). Subjects who successfully complete this familiarisation session, i.e., those who are willing to use and show no intolerance to the test product, will be allowed to continue in the study. Subjects who already use Granit Vit Stark (13 mg nicotine/pouch) or snus of 13 mg nicotine/pouch or above do not need to attend the familiarisation session.

For each study period, subjects will abstain from all tobacco and nicotine usage for 12 hours prior to product administration. In addition, subjects will fast overnight (no food or drink except water), for a minimum of 8 hours prior to each product administration. In the morning of each study session, Subjects will receive a standardised light breakfast which will be consumed at least one hour before product administration. Subjects will then receive a single product for a fixed period of 60 minutes and undergo a 6-hour PK blood sample collection. For each study period, a total of 13 blood samples (4 mL per sample) will be collected for PK assessments. PK blood samples will be collected prior to product administration (-5 mins) and at 5, 10, 20, 40, 50, 60, 65, 75, 90, 120, 240 and 360 minutes following product administration.

Subjects are to be discharged from the clinic after the final 6-hour post-administration PK sample collection in each admission period following medical approval. However, they may be advised to stay at the clinical site for safety reasons, if judged necessary by the physician in charge. End of study procedures will be performed prior to discharge from the clinical site.

The duration of the clinical portion of this study per subject (excluding the screening period) is expected to be 10 days. The actual overall study duration may vary.

No later than one week after the last clinic visit a post-study follow-up will be performed, which will be conducted via a telephone call with the subjects. The follow-up call will

collect information on the status of any ongoing AEs at discharge and any new AEs experienced after discharge.

The schema of a typical study day is presented in Figure 1.

The schedule of events of the study is described in Table 1.

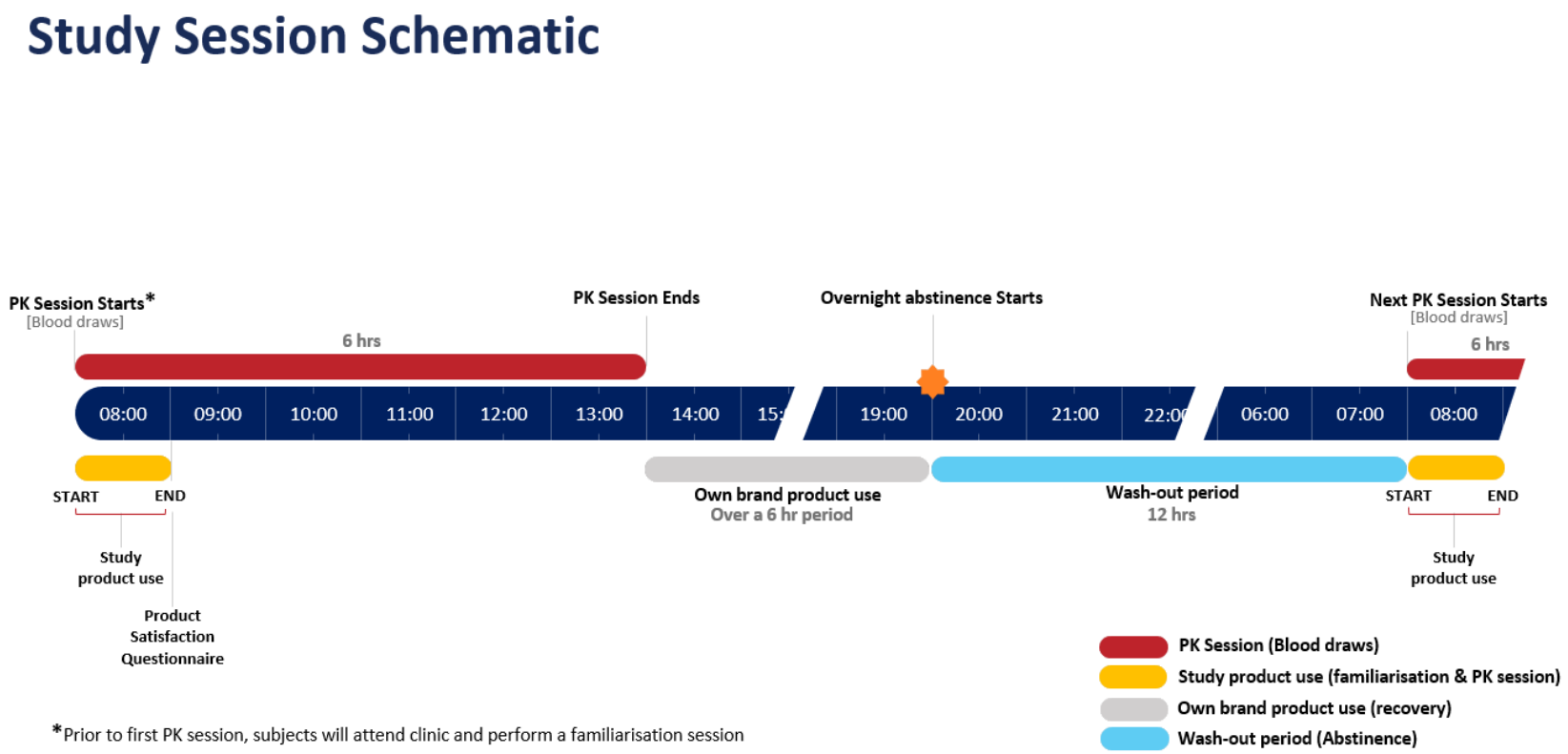

Figure 1 – Study Session Schematic

Table 1 Schedule of events

Event	**Screening**	**Familiarisation**	**Admission 1**	**PK Day 1**	**PK Day 2**	**PK Day 3**	**PK Day 4**	**Admission 2**	**PK Day 5**	**PK Day 6**	**PK Day 7**	**PK Day 8[4]**	**Post-study telephone f/u**
Informed consent	x												
Demographics	x												
Medical history	x												
Smokeless product use history	x												
Physical examination[1]	x		x				x	x				x	
Oral mucosa examination	x		x	x	x	x	x	x	x	x	x	x	
Vital signs	x		x	x	x	x	x	x	x	x	x	x	
ECG	x												
Prev. and concom. medication	x		x	x	x	x	x	x	x	x	x	x	x
Eligibility	x		x										
Product Familiarisation		x											
Randomisation			x										
Study Product administration				x	x	x	x		x	x	x	x	
PK Blood sampling,				x	x	x	x		x	x	x	x	
Blood sampling, safety	x[2]		x[3]				x[3]	x[3]				x[3]	
Compliance and product accountability check		x		x	x	x	x	x	x	x	x	x	
Adverse Events		x	x	x	x	x	x	x	x	x	x	x	x
Pregnancy test (female subjects)	x[5]		x					x				x[5]	

Event	Screening	Familiarisation	Admission 1	PK Day 1	PK Day 2	PK Day 3	PK Day 4	Admission 2	PK Day 5	PK Day 6	PK Day 7	PK Day 8[4]	Post-study telephone f/u
Urine sampling with Drug Screening, including cotinine	x		x					x					
Alcohol screen	x		x					x					
Product subjective measures Questionnaires				x	x	x	x		x	x	x	x	

[1] A full physical examination will be performed at screening by a medically qualified and licensed individual. At admission to the site and at discharge, symptom-oriented physical examinations will be performed, if needed

[2] All laboratory tests specified in appendix 19.2

[3] Full Blood Count, Sodium, potassium, glucose, creatinine, bilirubin total, alanine aminotransferase and albumin.

[4] In the event of early termination of a subject from the study, the tests scheduled on Day 8 will be performed if possible.

[5] A serum pregnancy test will be collected at screening. In the event of a positive or unclear result from a urine pregnancy test, a serum pregnancy test will also be performed to confirm the result.

8.2 Selection of study population

Subjects who meet all the inclusion criteria and none of the exclusion criteria at the screening visit may be eligible for participation in this study. Continued eligibility will be assessed upon admission to the clinical site, prior to randomisation and the first study product administration.

Screening failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to the study intervention or entered in the study.

This study will aim to recruit an equal split of males and females. A minimum of 20% females (6 out of 32) will be recruited. This is deemed acceptable based on the Sponsor's demographic data of 2991 Swedish snus users surveyed in 2019, where 81% were male and 19% were female.

A subject who withdraws or is withdrawn during the pre-study evaluations but before receiving the study product will not be considered as a drop-out and will not be included in the final database.

Standbys should be recruited and available to replace any subject who withdraws prior to the first product administration.

8.2.1 Inclusion criteria

1. Provision of signed and dated informed consent form (ICF)
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Healthy adult male or female
4. If female, meets one of the following criteria:
   a) Is of childbearing potential and agrees to use two of the accepted contraceptive regimens from at least 28 days prior to the first study product administration through to at least 30 days after the last administration of the study product. An acceptable method of contraception includes one of the following:
      - Systemic contraceptives (combined birth control pills, injectable/implant/insertable hormonal birth control products, transdermal patch)
      - Intrauterine device (with or without hormones)
      - Barrier methods of contraception (male condom with spermicide, female condom, cervical cap, diaphragm, contraceptive sponge)
      - Male partner vasectomised at least 6 months prior to the first study product administration

   Or

   b) Is of childbearing potential and agrees to abide by true abstinence from heterosexual intercourse, when this is in line with the preferred and usual lifestyle (not periodic abstinence)

   Or

c) Male partner has had a vasectomy less than 6 months prior to product administration, and agrees to use an additional acceptable contraceptive method from the first study product administration through to at least 30 days after the last administration of the study product

Or

d) Is of non-childbearing potential, defined as surgically sterile (i.e. has undergone complete hysterectomy, bilateral oophorectomy, or tubal ligation) or is in a postmenopausal state (i.e. at least 1 year without menses without an alternative medical condition prior to the first study product administration)

5. Aged at least 19 years but not older than 55 years
6. Body mass index (BMI) within 18.5 kg/m^2 to 30.0 kg/m^2, inclusively
7. Minimal body weight of 52 kg (males) or 45 kg (females)
8. Daily user of smokeless snus or modern oral nicotine products for at least 6 months and who use the products under their upper lip. Subjects who use pouched snus should regularly use pouch weights of 0.6 g and above, and at least 7.5 mg nicotine/pouch.
9. Stated willingness to abstain from nicotine and tobacco products (except for the study products provided) from 12 hours prior to each study product administration until the end of the study
10. Positive urine cotinine test (≥100 ng/mL) at screening and prior to the first and second study product administration period.
11. Successful completion of the product familiarisation session for study product use prior to the first study product administration (subject is able to follow the instructions and shows no intolerance to the test product during the training session)
12. Clinical laboratory values within the laboratory's stated normal range; if not within this range, they must be without clinical significance, as determined by an investigator
13. Have no clinically significant diseases captured in the medical history or evidence of clinically significant findings on the physical examination (including oral mucosa examination and vital signs) and/or ECG, as determined by an investigator

8.2.2 Exclusion criteria

1. Female who is lactating at screening
2. Female who is pregnant according to the pregnancy test at screening or prior to the first study product administration
3. Presence of braces, partials, dentures or any dental work that could, in the opinion of an investigator, affect the conduct of the study (including missing molars)
4. Presence or history of significant form of oral and/or pharyngeal inflammation, oral lesions and/or gum disease or temporomandibular joint dysfunction
5. History of significant hypersensitivity to any excipients of the formulations as well as severe hypersensitivity reactions (like angioedema) to any drugs
6. Presence or history of significant gastrointestinal, liver or kidney disease, or surgery that may affect nicotine bioavailability
7. History of significant cardiovascular, pulmonary, hematologic, neurological, psychiatric, endocrine, immunologic or dermatologic disease
8. Presence of clinically significant ECG abnormalities at the screening visit, as defined by medical judgment

9. Maintenance therapy with any drug (with the exception of hormonal contraceptives or hormone replacement therapy) or significant history of drug dependency or alcohol abuse (> 3 units of alcohol per day, intake of excessive alcohol, acute or chronic)
10. Any clinically significant illness in the 28 days prior to the first study product administration
11. Use of any prescription drugs (with the exception of hormonal contraceptives or hormone replacement therapy) in the 28 days prior to the first study product administration, that in the opinion of an investigator would put into question the status of the participant as healthy
12. Use of any medication or substance that aids in smoking cessation, including but not limited to any nicotine replacement therapy (e.g., nicotine gum, lozenge, patch), varenicline (Champix®), bupropion (Wellbutrin®, Zyban®), or Lobelia extract in the 28 days prior to the first study product administration.
13. Any history of tuberculosis
14. Positive test result for alcohol and/or drugs of abuse at screening or prior to the first product administration
15. Positive screening results to HIV Ag/Ab Combo, Hepatitis B surface Antigen (HBsAG (B) (hepatitis B)) or Hepatitis C Virus (HCV (C)) tests
16. Previous inclusion in this clinical study
17. Intake of an Investigational Product (IP) in any other clinical study in the 28 days prior to the first study product administration
18. Subjects who have donated:
    a. ≥400 mL of blood within 90 days prior to admission
    b. Plasma in the 7 days prior to admission
    c. Platelets in the 6 weeks prior to administration
19. Postponement of a decision to quit using tobacco- or nicotine-containing products in order to participate in this study
20. Previously attempted to quit using tobacco- or nicotine-containing products in the 28 days prior to the first study product administration.
21. Employees or immediate relatives of the tobacco industry or the clinical site.

8.2.3 Restrictions

8.2.3.1 Lifestyle and/or Dietary Requirements

- Subjects will be prohibited from consuming alcohol for 48 hours prior to the two periods of confinement for PK sampling.
- Subjects will be prohibited from consuming food or beverages containing xanthines (i.e. tea, coffee, cola drinks, energy drinks or chocolate) during the nicotine washout periods and PK

sampling sessions during confinement. Consumption is allowed during the 6h period between PK sampling and the next 12h pre-product administration abstinence period.

- Subjects will be advised that they must not eat food containing poppy seeds for 3 days before screening and prior to admission for each of the two confinement periods, as consumption of poppy seeds can lead to a positive opiate result in the drugs of abuse test.
- Subjects will eat only the food provided by the study site during confinement at the clinic.
- Subjects will abstain from nicotine and tobacco products (except for the study products provided) for 12 hours prior to each study product administration.
- Female subjects of childbearing potential will have to take appropriate measures to prevent pregnancy for at least 28 days prior to the first study product administration, during the study and for at least 30 days after the last study product administration. It is the participant's responsibility to notify the Investigator if a pregnancy occurs from the end of their study participation until 30 days after the last study product administration.
- Subjects will not have access to their personal belongings from admission prior to the product administration until the end of the confinement period with the exception of decontaminated personal belongings that are mandatory to the subject, e.g. computers, phone books, toilet articles and similar items.

8.2.3.2 Concomitant Treatment

In addition to the drugs prohibited as per the exclusion criteria (section 8.2.2), subjects will also be prohibited from taking any over-the-counter products for 2 days prior to study product administration and until discharge, unless approved by the investigator.

Except for medication which may be required to treat AEs, no other treatment or medication will be allowed from the first product administration until all study activities and evaluations have been completed. Occasionally paracetamol and NSAID will be allowed during the study days.

Systemic contraceptives and hormone replacement therapy are permitted for female subjects.

Subjects will be instructed to notify the study site about any new medications taken after the start of the study. All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject has received the study treatment must be listed in the subject case report form (CRF). The drug name and dose taken will be noted. An investigator or delegate and/or the sponsor will decide whether the subject will be permitted to remain in the study, depending on the drug used, the time of drug intake, etc.

8.2.4 Removal of subjects from therapy or assessment

8.2.4.1 Before First Product Administration

Before the first product administration inclusion/exclusion criteria will govern the subjects to continue to the PK confinement phase. Subjects withdrawn before the first product administration will not be followed up and will not undergo early termination assessments. Other safety assessments may be performed if required.

Subjects are free to withdraw their consent to participate in the study at any time, without prejudice. The reason for their withdrawal or for deciding to end their participation (if the subject agrees to give the reason) will be documented.

All subjects will be informed that they are free to quit smoking and to withdraw from the study at any time.

8.2.4.2 After First Product Administration

Subjects may, at any time, voluntarily withdraw from the study or be removed from the study at the discretion of an investigator or Sponsor. An investigator may withdraw a subject at any time if it is determined that continuing the study would result in a significant safety risk to the subject or if their behavior is deleterious to the study environment.

Following the first product administration, participation in the clinical study may be discontinued by the physician in charge of the study or by the sponsor for any of the following reasons, but not limited to:

- Subject experiencing emesis following product administration may be removed from the study period.
- AEs (including if a subject develops any significant illness or needs to undergo any major surgery during course of the study)
- Difficulties with blood collection
- New information becomes available which makes the subject noneligible according to the inclusion (section 8.2.1) and exclusion (section 8.2.2) criteria.
- Subject non-compliance (including any violation of protocol requirements which may affect the study outcome)

If such withdrawal occurs, an investigator should determine the primary reason for a subject's premature withdrawal from the study and record the reason in the subject's study documents.

An investigator may remove a subject from the study on the recommendation of the PK facility and/or sponsor due to an unanticipated event that could result in an inadequately characterised PK profile, such as a missed blood draw, an AE, meal deviation or concomitant medication intake.

Attempts should be made to have such subjects complete the early termination assessments. Early termination assessments should be performed as soon as possible after the last study treatment administration.

Details of reasons for removal of subjects will be recorded, reported to the sponsor and documented in the clinical study report.

For subjects who are lost to follow-up (i.e. those subjects whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), study staff should show "due diligence" by documenting in the source documents the dates of attempted phone calls and/or e-mails sent.

8.2.5 Screening and enrolment log

Each clinic will keep a log of all subjects screened and included. 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.

8.3 Treatments

8.3.1 Identity of Study Products

The following products will be administered in the study as 60 minute single product administrations.

1) Swedish Snus (pouch) – Granit Vit Stark with 13 mg/pouch nicotine
2) Lyft (Commercial product), 4 mg/pouch
3) Lyft (Commercial product), 10 mg/pouch
4) Lyft non-commercial (alginate removed), 10 mg/pouch
5) Lyft non-commercial (benzoic acid added), 4 mg/pouch
6) Lyft non-commercial (benzoic acid added), 10 mg/pouch
7) Lyft non-commercial (citric acid added), 10 mg/pouch
8) Lyft non-commercial (benzoic acid added, sweet base), 10 mg/pouch

All products will be provided by the sponsor.

8.3.2 Packaging, labelling and storage of study products

The study products provided by BAT will be packaged and labelled for this clinical study according to the principles of GMP. Packaging and labelling will be performed by suitably qualified personnel in Sweden and the supplies will then be shipped to directly to the study sites.

The 8 products will be labelled with sequential numbers (1/8 – 8/8) for the study period in which each product is to be administered. The order of administration of the products will be randomised. The products will be labelled in a blinded manner only providing a unique number for each series of 8 treatments and the study period for each treatment. The product containing Swedish snus will not be fully blinded due to the nature of the product. All other products will not be possible to distinguish from each other based on appearance.

Please also refer to Appendix 19.5 Labelling of Trial Medication which includes the label texts.
Product administration and treatment regimens

8.3.2.1 Administration of Study Product, Meals and Fluids

During the confinement period all meals will be provided by the site. Subjects will fast overnight (no food or drink except water), for a minimum of 8 hours with a standardised light breakfast which will be consumed at least one hour before product administration. Fasting will continue for the initial 4 hours of the PK session following each product administration. 4 hours after product administration, subjects will be offered a light snack. Following the 6 hour PK session a standardised lunch will be served. A supper and a light snack will be served at appropriate times thereafter and there are no restrictions on food and drink intake and snacks in between until the start of the next fasting period 8 hours prior to next product administration. Water will be provided as required until 1 hour pre-product administration. No water will be consumed during product use. Water will be allowed beginning 1 hour after the administration of the product, following removal of the product.

Study product will be administered in the morning. The date and time of each product administration will be recorded. For each subject, all scheduled post-product administration activities and assessments will be performed relative to the time of study product administration.

The time of study product administration will be noted as the time when the product is placed in the mouth.

In the morning, prior to each product administration, subjects will be re-instructed on how to use the assigned product.

Administration of the Test products

Subjects will use test products as they typically use their own snus products. Subjects will be instructed to "park" the pouch between their top lip and their gum for 60 minutes. Subjects will be asked to swallow their saliva as needed during this period. At the end of the 60-minute period, the subject will remove the pouch from their mouth. The pouch must not be swallowed whole, chewed or broken. The elapsed time between when the pouch is placed in the mouth and when the pouch is removed will be recorded for each subject.

The used pouches will be placed in individual containers. Each container will be labelled with the study number, subject's screening number and the period of administration (PK-sampling day and date). The containers will be stored in a fridge or freezer until analysis of the residual nicotine content at a facility designated by the Sponsor.

8.3.2.2 Other Protocol Restrictions

Subjects will remain seated or kept in minimal ambulatory movement for the first 6 hours following each product administration, avoiding both vigorous exertion and complete rest. However, should AEs occur at any time, subjects may be placed in an appropriate position. During this interval subjects will be permitted, under supervision, to get up (e.g. to use the washroom facilities). Subjects will not engage in strenuous activity at any time during the confinement periods

8.3.3 Product accountability

The study products will be released to the study site(s) after approvals of the study protocol have been received from the IEC.

The Investigator is responsible for keeping detailed records, which show the quantity of study product that is stored, delivered to and taken out from the place of storage. Any discrepancies between dispensed and returned study product must be explained and documented.

Products deliberately and/or accidentally destroyed by the Investigator/Hospital Pharmacy or the subject must also be accounted for.

The Monitor will perform study product accountability and make sure that all unused study product is adequately destroyed/returned and documented.

Complete and accurate inventory records of all study products will be kept. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), subject dispensing records, and returned or destroyed study product.

At the conclusion of the study, all unused study products and all study product containers will be returned to the sponsor unless the sponsor has approved other arrangements. Product accountability will be performed at the completion of the study.

8.3.4 Method of assigning subjects to treatment groups

The order of administration of each of the 8 products will be randomised. The randomisation will occur through IWRS.

Subjects who sign the informed consent form and are randomised but do not receive the study treatment of period 1 may be replaced. Subjects, who sign the informed consent form, are randomised and receive the study treatment of period 1, and subsequently withdraw, or are withdrawn or discontinued from the study, may be replaced by an equal number of newly enrolled subjects.

8.3.5 Blinding

The study products which will be distributed in a randomised order, will be packaged and labelled to make the products' appearance as similar as possible between products. The study product containing Swedish snus will be possible to identify based on its smell and appearance. The other 7 products will be similar in their general characteristics and appearance. The study consequently is not fully blinded for subjects and investigators. The bioanalytical laboratory will be fully blinded.

The randomisation code will not be available to study staff, subjects, the Sponsor, bioanalytical laboratory or CRO staff until after clean file and database lock.

Study participants will be aware they will receive different products of nicotine.

8.3.6 Emergency decoding of blinded treatment

In case of emergency and a medical need to know the identity of the administered product the randomisation code can be broken by Investigators and/or the Sponsor or CRO. The method of unblinding will be defined and instructions provided.

Breaking the code must only be done in emergency situations and should only be used when knowledge of the treatment is necessary for the proper management of the subject. If the code is broken, the reason and the date should be recorded by the Investigator. Decoding of the blinded treatment must be reported to IRW and the Sponsor.

8.3.7 Continuation of treatment and provision of additional care

The participants in this study are healthy volunteers and as such there are no special requirements on post-study care. If subjects express a wish to reduce or stop their use of nicotine containing products advice on how to obtain help with this will be provided by the study staff.

8.3.8 Treatment compliance

The study products will be dispensed only to eligible subjects and administered under the supervision of study personnel. Treatment compliance will be verified and documented according to the sites' standard procedures and will be subject to review by the CRO.

8.4 Study assessments

Unless otherwise stated in this protocol, the standard routines and procedures of the study facilities, which are available for all activities relevant to the quality of the study, will be followed during this study.

An overview of the study activities for each participant is detailed in Table 1.

PK blood sampling is to be prioritised when clinical activities are scheduled to occur at the same time.

Subjects will be admitted to the clinical site no later than 13 hours prior to each product administration. Subjects may temporarily leave the clinical site following the last PK sample and following medical approval. However, they may be advised to stay at the clinical site for safety reasons, if judged necessary by the physician in charge.

Any deviation from protocol procedures should be noted in the eCRF and compiled for reporting in the Clinical Study Report.

8.4.1 Demographics and other baseline characteristics

8.4.1.1 Medical History

The medical history at screening will include all queries by the medical and clinical staff related to the subject's well-being and history of relevant past medical events/experiences. Medical history will include all demographic data (age, gender, race, body weight, height, and BMI) and baseline characteristics. Alcohol and smoking habits will also be recorded.

8.4.2 Clinical efficacy assessments

This is a pharmacokinetic study and the only assessment of clinical efficacy of the products is the subjects' subjective experience of each product as measured by Product Subjective Measures Questionnaires (Appendix 19.3).

Subjects will answer short questionnaires on their liking of the product and their overall intent to use the product again following the end of use of each study product (i.e., 60 ±5 minutes) in periods 1 to 8.

8.4.3 Product Familiarisation session

A familiarisation session will be conducted with the highest nicotine strength product (Granit Vit Stark 13 mg/pouch) at a site visit during screening or between screening and the first admission.

Widespread experience in BAT shows that snus users are able to judge the effects of nicotine and whether they can tolerate it within 20 minutes of use. Subjects will use the Granit Vit Stark product for 20 minutes (from the time the subject places the product in their mouth until the time the subject removes the product from their mouth).

Subjects will not be required to fast prior to this training session. Subjects who successfully complete this familiarisation session will be allowed to continue in the study.

Subjects who already use Granit Vit Stark (13 mg nicotine/pouch) or snus of 13 mg nicotine/pouch or above do not need to attend the familiarisation session.

Used pouches from the familiarisation session will not be retained for residual nicotine analysis and should be destroyed according to local regulations, after product accountability has been performed and documented.

8.4.4 Own brand product use

Between PK sessions, subjects are allowed to use their own brand nicotine products after completion of each PK sampling and until 12 hours prior to the next PK session.

The subjects will be asked to bring their own product to the screening visit and report their daily use. A photo of the subject's own product may be taken as reference in order to identify the product before recording in the eCRF. Use of subjects' own products during the study will be reported in the eCRF.

8.4.5 Blood Volume Collected

The total volume of blood withdrawn will be up to 466 mL. A catheter will be used for PK sampling. The total blood collection may be higher if repeat blood samples are required for safety assessments.

A detailed breakdown of the approximated blood volume to be collected per subject is presented in Table 2.

Table 2. Blood Volume Breakdown

	Male subject	Female subject
Screening clinical laboratory tests	14 mL	14 mL
Pre-PK period 1 serum pregnancy test:	-	3.5 mL
PK blood samples:	416 mL (13 samples per period x 4 mL per sample x 8 periods)	416 mL (13 samples per period x 4 mL per sample x 8 periods)
Safety tests during study	36 mL (4 samples of 9 ml each)	36 mL (4 samples of 9 ml each)
Total blood collection:	**466 mL**	**466 mL**

8.4.6 Pharmacokinetic assessments

8.4.6.1 Sample collection and handling

A total of 13 blood samples will be collected (one tube of 4 mL each) in each study period for PK assessments as scheduled in Table 3.

Table 3. Pharmacokinetic Blood Sampling Schedule

Sample No	Nominal Time* (hours)
01	0.00**
02	0.08 (equivalent to 5 minutes)
03	0.17 (equivalent to 10 minutes)
04	0.33 (equivalent to 20 minutes)
05	0.67 (equivalent to 40 minutes)
06	0.83 (equivalent to 50 minutes)
07	1.00
08	1.08 (equivalent to 65 minutes)
09	1.25 (equivalent to 75 minutes)
10	1.50 (equivalent to 90 minutes)
11	2.00
12	4.00
13	6.00

* Nominal times listed are relative to the time of study product administration.
** Within 5 minutes prior to study product administration

Allowed time frames for sampling: +/- 2min for all timepoints up to and including 120 minutes. +/-5 minutes for the 240 minutes and 360 minutes samples.

Blood samples will be collected into a labeled tube containing the appropriate anticoagulant as specified by the bioanalytical facility. They will be collected from an indwelling cannula (stylet catheter that requires no flushing), which will be placed in the forearm vein of the subject. As an option to the subject, or if judged necessary by the clinical staff, direct venipuncture will be used.

The time of PK blood sample collection will be calculated relative to the time of treatment administration. The actual time of all PK blood draws will be recorded and reported for all subjects. The actual start and end time of product use will also be recorded.

Urine samples will only be collected at screening and prior to the first and second product administration periods. A urine sample will also be collected from female subjects at PK sampling day 8 for a pregnancy test. Nicotine concentrations for PK assessments will be obtained through bioanalysis of the plasma derived from the blood samples drawn during this study, using a validated bioanalytical method.

8.4.6.2 Pharmacokinetic sample processing, storage and shipping

Blood samples for PK determination will be processed, split, stored, and shipped according to the sample processing instructions supplied by the bioanalytical facility.

8.4.7 Laboratory assessments

Laboratory evaluations will be performed as scheduled in Table 1.

The laboratory evaluations to be conducted for this study are presented in Appendix 19.2 Clinical Laboratory Evaluations.

The physician in charge or delegate will assess each abnormal value to determine if it is clinically significant. Post-product administration clinically significant laboratory values will be reported as AEs, if applicable, as judged by the physician in charge or delegate. Verification of collection for all laboratory test panels will be collected in the clinical database.

8.4.8 Clinical safety assessments

Safety assessments will include symptom-oriented physical examination, oral mucosa examination, vital signs, clinical laboratory tests, and AE monitoring. Additional safety measurements may be performed at the discretion of an investigator for reasons related to subject safety.

The physician in charge will be present or available by phone at the clinical site for at least the first 4 hours following each product administration and will remain available at all times throughout the study.

8.4.8.1 Physical Examination

A physical examination will be performed by a medically qualified and licensed individual as scheduled in Table 1.

The physical examination will include a general review of the following body systems (at minimum): head and neck, cardiovascular, respiratory, abdomen, brief neurological and general appearance, unless a symptom-oriented physical exam is indicated.

The physical examination performed at screening will also include a general mouth examination.

8.4.8.2 Vital Signs

Vital signs will be measured as scheduled in Table 1. Vital signs at screening, at admission to the clinical site and prior to each product administration will include blood pressure, pulse rate and body temperature. Vital signs following each product administration will include blood pressure and pulse rate.

8.4.8.3 12-Lead Electrocardiogram

A twelve-lead ECG will be performed at screening as scheduled in Table 1.

8.4.8.4 Oral Mucosa Examination

Examination of the oral mucosa (including local irritancy) will be performed at screening, at admission to the clinical site and during each study period as scheduled in Table 1. The mucosa examination should be performed before product administration and up to 2 hours after product removal as presented in Table 4.

Table 1. Oral Mucosa Examination Schedule

Oral Mucosa Examination - Scheduled Time Points
Prior to product administration
Up to 2 hours post-product removal

8.4.9 Adverse Events

8.4.9.1 Definitions

8.4.9.1.1 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical study subject related to the study product or not, 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 study product, whether or not related to the investigation product.

This includes events related to the study product or any comparator. This also includes events related to the procedures involved in the Clinical Study Protocol.

8.4.9.1.2 Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that at any dose

- Results in death
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
  Or
- Is regarded as medically important without meeting the above mentioned criteria.

The term life-threatening in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
Hospitalisation is defined as an unplanned overnight stay. Note however that the subject must be formally admitted. Waiting in outpatient clinic or emergency room would not count. A hospital stay planned prior signing the Patient Information Consent (PIC) does not count as SAE, nor does staying in hospital for social reasons (e.g. respite care, the fact that there is no-one at home to care for the patient), nor does planned hospital stay required by the study protocol.
Medically important, includes e.g. blood dyscrasias or convulsions that do not require hospitalisation or allergic bronchospasm requiring intensive treatment either at home or in an emergency room.

8.4.9.1.3 Adverse Reaction (AR) or Treatment Emergent AEs (TEAEs).

All noxious and unintended responses to a study product related to any dose administered. The definition also covers study product errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.

All adverse events judged by either the reporting Principal Investigator (PI) and/or the Sponsor as having a reasonable causal relationship to the study product qualify as adverse reactions or treatment emergent AEs.

8.4.9.1.4 Unexpected Adverse Drug Reaction (UADR)

An adverse reaction, where the nature, or severity is not consistent with the applicable product information i.e., Investigator's Brochure (IB)

8.4.9.1.5 Suspected unexpected serious adverse reaction (SUSAR)

Any adverse reaction that is classed as serious and is suspected to be caused by the study product that is not consistent with the information about the study product in the safety reference document (IB) i.e. it is suspected and unexpected. The clinical study protocol and/or IB should include when necessary a list of known side effects for both study product and comparator (if applicable). This list should be checked for each SAE that occurs in terms of expectedness. If the adverse reaction is not listed as expected or has occurred in a more serious form than anticipated, this SAE should be considered a SUSAR.

8.4.9.2 Methods for eliciting adverse events

Adverse Events will be collected based on the Investigators' and other study staff's reporting as well as adverse events spontaneously reported by Subjects verbally and/or in questionnaires.
All AEs, serious and non-serious, will be recorded in the eCRFs.
The following evaluations are to be done by the Investigator in connection with the AE:

- type of event
- seriousness
- degree of severity
- duration (start - end)
- action taken
- causality with investigational product
- outcome of the adverse event

For AE reporting purposes no distinction should be made between the study product and any reference/comparator product.

For the purposes of this study, the monitoring period for AEs extends from the signature of the ICF by the subject until the collection of the last blood sample of the study. From screening to the first product administration of the product familiarisation session, AEs will be recorded as screening events or as part of the medical history, as applicable. AEs occurring from the first product administration of the product familiarisation session to the product administration of period 1 will be recorded as product familiarisation session events. AEs occurring after the first product administration (i.e. after the familiarisation session) will be indicated as TEAEs in the clinical study report.

Subjects will be questioned on their health status at the beginning of each study period and before each departure from the clinical site. Open-ended questions will be asked.

During the study, all AEs spontaneously reported by the subject, observed by the clinical staff or elicited by general questioning will be recorded for all subjects and reported in the CRF.

If necessary, every effort will be made to obtain an adequate follow-up of the subjects. Should any subject choose to withdraw from the study, they will be advised of the safety precautions to be taken.

Any AE which remains unresolved as of the last visit will require an evaluation and follow-up until the AE has been resolved or a reasonable explanation for its persistence found or is deemed mild and safely resolving.

In the case of AEs deemed related to the product, every effort will be made to determine the final outcome.

8.4.9.3 Intensity/severity

It is an investigator's responsibility to ensure subjects experiencing AEs receive appropriate follow-up, treatment where required, and that every action is well documented.

- **Mild** means awareness of symptoms or signs, but easily tolerated (acceptable)
- **Moderate** means discomfort enough to interfere with usual activity (disturbing)

  Severe means incapacity to work or to do usual activity (unacceptable)

8.4.9.4 Causality

The causal relationship between an AE and the IP is defined as follows:

Not Related: The AE is definitely caused by the subject's clinical state or the study procedure/conditions.

Unlikely Related: The temporal association between the AE and the product is such that the product is not likely to have any reasonable association with the AE.

Possibly Related: The AE follows a reasonable temporal sequence from the time of product use but could have been produced by the subject's clinical state or the study procedures/conditions.

Related: The AE follows a reasonable temporal sequence from the time of product use, abates upon discontinuation of the product and reappears when the product is reintroduced.

8.4.9.5 Reporting of SAEs

All SAEs must be reported to IRW by the Investigator immediately and not later than within 24 hours of knowledge of the event regardless of the time that may have elapsed from the time the event occurred to when the Investigator first learns of it. The preferred method of reporting is through the eCRF, but paper versions of the SAE forms are always available on site if for any reason the eCRF cannot be accessed. The completed paper SAE form should be sent to IRW either via email or fax.

The Initial Report should contain as much information as possible, but a minimum the following information:

- subject identification
- treatment specification (blinded information, if code not broken)
- adverse event diagnosis
- time specification for the medical event
- name of the original reporter

A Serious Adverse Event Report Form must also be completed, signed by the Investigator and submitted to IRW no later than five calendar days after the initial information was received (preferably through the eCRF). Apart from the information above, this Follow-up Report should also contain the following information:

- assessment of severity
- assessment of causality

Investigator shall immediately inform IRW in writing if any of the below occurs (by email to: pv@irwcro.com):

(i) any serious adverse event (SAE),

(ii) any incident,

(iii) any investigational medical device deficiency that might have led to a SAE,

(iv) new findings/updates in relation to already reported events, and/or

(v) any corrective measure.

which occur during the study. When reporting any of the above, the investigator shall provide IRW with details of the product used, the nature of the event/reaction, anonymised patient details, and the details of the person reporting the event/reaction.

SAEs should be reported to IRW even after the study has been finished, if, in the judgment of the Investigator, there might be an association between the event and the previous use of the study product(s) or as a result of the study procedures. The minimum post-study observation period is 5 working days after the Post-study telephone follow-up, but this period can be extended in case the Investigator believe it is necessary.

Only SAEs that are both unexpected and related to the study product(s), Suspected Unexpected Serious Adverse Reactions (SUSARs), are subject to expedited reporting.

The Sponsor is responsible for informing all Investigators concerned of relevant information about SUSARs that could adversely affect the safety of subjects. The appropriate EC and CA, as per local requirements, should be informed by the Sponsor about SAEs associated with the use of the study product/device (SUSARs).

8.4.9.6 Expedited reporting of SUSARs

SUSARs are subject to expedited reporting to CA and EC as defined by local requirements. This includes reactions associated with the study product in the concerned study, or another study with the same study product by the same Sponsor in the EU or in a third country.
Other safety issues also qualify for expedited reporting where they might alter the current benefit-risk assessment of a study product or that would be sufficient to consider changes in the administration of the study product or in the overall conduct of the study.
All SUSARs, which are fatal or life-threatening, must be reported to the applicable CA and EC as quickly as possible but no later than 7 calendar days after the Sponsor/company first became aware of the AE. Additional information on such AE must be reported within 8 days from submission of the first notification.
SUSARs which are not life threatening or fatal must be reported to the applicable CA and EC as soon as possible but no later than 15 calendar days after the sponsor/company first became aware of the AE.

8.4.9.7 Follow-up period after an AE

If a clinical investigation Subject is withdrawn due to an AE, or if an AE persists at the end of the investigation treatment period, this should be followed up until the condition has ceased or until the subject is under professional medical care and a potential causality between the study product and the AE has been penetrated. An outcome assessment should be performed when an AE persists.

8.4.9.7.1 Procedures in case of pregnancy

All pregnancies (either through maternal exposure or transmission of a product via semen following parental exposure) shall be reported to IRW on a pregnancy notification form immediately and within 24 hours of the knowledge of its occurrence by an investigator or delegate (for pregnancies

occurring during the course of the study or immediately following the end of the study). Because of the possibility the fetus/embryo could have been exposed to the study product through the parent and for the subject's safety, the pregnancy will be followed up to determine its outcome, including spontaneous or voluntary termination, details of birth, presence or absence of any birth defects, congenital anomalies, or maternal and/or newborn complications.

The pregnancy will be recorded and reported by the clinical site to IRW, as Sponsor's representative. Pregnancy follow-up will also be properly recorded to ensure quality and completeness of the data belonging to the study product and will include an assessment of the possible causal relation between the study product and any pregnancy outcome.

8.4.9.8 Coding of AEs

Classification of AEs will be performed by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA), version 21.0 or higher.

8.4.9.9 Appropriateness of measurements

This study utilises standard PK assessments and safety assessments.

8.4.9.10 Periodic Safety Reporting

Not applicable in this clinical study

8.4.9.11 List of foreseeable adverse events and anticipated adverse device effects

Please see section/document for Risks and anticipated adverse device effects.

8.4.9.12 Contact details for reporting SAE/TESAE/Pregnancy/Overdose

IRW Pharmacovigilance Manager:
Marina Fredholm
Email: pv@irwcro.com
Fax: +46 8 758 90 56
Mobile: + 46 73 519 60 41
Phone: +46 8 791 66 40

8.5 Data quality assurance

Designated personnel from the BAT quality assurance unit(s) will be responsible for maintaining QA of the clinical, PK, statistical and bioanalytical facilities to ensure that the study is conducted and data are generated, documented and reported in compliance with the protocol, ICH Guideline E6 for GCP, applicable requirements as outlined in the FDA and Organization for Economic Co-operation and Development Principles of Good Laboratory Practice, and the *Reflection paper for laboratories that perform the analysis or evaluation of clinical trial samples* (EMA/INS/GCP/532137/2010).

Designated personnel from each corresponding operation unit (e.g. clinical, PK, statistical and bioanalytical facilities) will be responsible to maintain and assure the QC of all data generated and documented in compliance with the protocol.

8.5.1 Monitoring and auditing procedures

The Study site will be visited by the Monitor periodically at times agreed on by the Investigator and IRW and as defined in the study specific Monitoring Plan. It is the function of the Monitor to ascertain that all aspects of the Study Protocol are complied with and that the conduct of the study conforms to applicable regulatory requirements and established rules for GCP.

At the time of each monitoring visit, the Monitor will review the completed eCRFs to ascertain that all items have been completed and that the data provided are accurate and obtained in the manner specified in the protocol.

The Monitor will also check that the data in the eCRF are consistent with the clinical records (Source Data Verification) and that study results are recorded completely and correctly. The Monitor will check on the reporting of SAEs and the procedures for study product accountability and record keeping. For this purpose, the Monitor must be given direct access to clinical records, original laboratory data, etc., as far as these relate to the study and without jeopardising subject integrity. eCRFs for all included subjects must be made available to the Monitor for review.

The study site may also be subject to quality assurance audit by the Sponsor or someone appointed for this task by the Sponsor. A Competent Authority may request to make an inspection of the study site. The procedures of such a visit would be similar to those of a monitoring visit, and data already checked by the IRW Monitor may be checked again. The Investigator is required to inform IRW immediately of an inspection requested by a Competent Authority.

The sponsor or its representative may visit the study facilities at any time in order to maintain current and personal knowledge of the study through review of the records, comparison with source documents, observation and discussion of the conduct and progress of the study. The clinical site will permit study-related monitoring, audits, IEC review, and regulatory inspection(s) by providing direct access to source data/documents.

8.5.2 Case Report Forms (CRFs)

The data required by the protocol is obtained in two ways. Source Documents are used in the clinic as recording devices during procedures. The data is transcribed from source into an electronic data capture software and stored in the secure database for each subject included in a clinical study (i.e., who received a study product). Screen Failure data may be transcribed into the database at the discretion of the sponsor.

Data assembled outside the clinic source (e.g. safety lab data), will be received from a specified external vendor via an electronic data file. The file received encrypted (or posted to a secure File Transfer Protocol) and is stored in a secure folder on a server. The electronic data file(s) are independent of the Electronic Data Capture (EDC) data during the conduct of the study.

The EDC cleaned data will be reviewed, approved and electronically signed by the Principal Investigator or delegate. The EDC data will be output in a CRF format. The external data files will be output in SAS® datasets. All data will be included with the final report provided to the sponsor.

eCRFs of a design mutually agreed upon by the Sponsor and IRW will be supplied by IRW. A CRF must be completed and signed electronically for each included subject. All study team members will get formal training on the eCRF system, before the study starts and it will be documented. The Investigator or his delegate should only allow individuals with the required qualifications and training in eCRFs completion to take part in this task. Confirmation of this qualification or training should be available. CRFs should be completed only by authorised persons. This authorisation should be documented.

The CRF should be completed as soon as the data are available or during the subject's evaluation or follow-up visit.

The completed CRFs should be made available for checking of completeness and accuracy before collection by the Monitor as agreed in advance. The original CRFs are the sole property of the Sponsor and should not be copied or made available in any form to a third party, with the exception of authorised representatives of local Competent Authorities, without the written permission from the Sponsor

8.5.3 Source Data

Data recorded in the CRF should correspond to the data in the source documents, as applicable. Any discrepancies or notable omissions should be brought to the attention of the Investigator/ study staff. For protection of the confidentiality of subjects participating in the clinical study, only non-ambiguous subject identification numbers should be used for identification of all data reported in the CRF.

8.5.4 Training of study staff

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.

All Investigators and staff carrying out observations of primary or other major outcome variables involved in the study should provide a Curriculum Vitae (CV). The Investigator will keep a list of all personnel involved in the study together with their function and study related duties delegated. He/she will ensure that appropriate study related training is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

Before inclusion of subjects the Monitor and/or Project Manager will perform a Site Initiation Visit to inform and train relevant study staff.

Should an investigator delegate the supervision of the product administration to a designated person, this individual must have the appropriate professional-legal qualifications and certifications. An investigator should also ensure key staff personnel have the appropriate medical qualifications to effectively conduct or supervise any potential resuscitation procedures.

8.5.5 Adherence to Protocol

Excluding an emergency situation in which proper treatment is required for the protection, safety and well-being of the study subjects, the study will be conducted as described in the approved protocol and performed according to ICH/GCP and the applicable regulatory requirements. Any deviation from the protocol will be recorded and explained.

If amendments to the protocol and/or amendments or revisions to the ICF are required, the modifications will be documented and submitted to an IEC for approval.

8.6 Statistical methods and determination of sample size

8.6.1 Demographics and baseline data

Listings and descriptive summary statistics of demographic (age, height, weight and BMI) and baseline data will be presented.

8.6.2 Analysis of pharmacokinetic data

8.6.2.1 Subjects to be Analysed

Samples from all subjects who received at least one of the products will be assayed and nicotine plasma levels will be reported.

8.6.2.2 Bioanalytical Methods

Nicotine plasma concentrations will be measured according to a validated bioanalytical method.

8.6.2.3 Calculated parameters

$C_{max,}$ T_{max} and $AUC_{0\text{-}6h}$ will be calculated from the PK data. Methodology of AUC calculation will be described in the SAP.

8.6.3 Analysis of safety

8.6.3.1 Safety Endpoints

The safety endpoints are the incidence of AEs, vital sign abnormality assessments, clinical laboratory abnormality assessments, symptom-oriented physical examination findings, and oral mucosa examination findings.

8.6.3.2 Safety Analysis

The clinical laboratory tests, the symptom-oriented physical examination, oral mucosa examination and the measurements of vital signs will be used to perform the safety statistical analysis.

8.6.3.3 Safety Statistical Methodology

Descriptive statistics will be used to summarise AEs and safety results.

8.6.4 Statistical/analytical issues

8.6.4.1 Adjustments for covariates

Possible confounding factors are gender and age. SAP will describe the method of analysis in detail.

8.6.4.2 Handling of dropouts or missing data
Any missing PK data will not be replaced.

8.6.4.3 Multi-centre studies
Not applicable

8.6.4.4 Multiple comparison/multiplicity
Multiple comparisons adjustment must be used during the statistical analysis. Details of comparisons and adjustments will be presented in the SAP.

8.6.4.5 Examination of subgroups
Subgroups by age and gender will be analysed.

8.6.4.6 Interim analyses and data monitoring
No interim analyses planned.

8.6.5 Analysis data sets

8.6.5.1 Pharmacokinetic Population

The decision of which subjects will be included in the PK analysis is to be documented before the start of the sample analysis. Subjects who received at least one of the study products and are expected to provide evaluable PK data for at least one study product will be included in the PK analysis. Concentration data of any remaining subjects will be presented separately.

The PK population will be further described in the SAP.

Subjects who do not complete the sampling schedule of one or more study periods may be included in the PK analysis for only the PK parameters that are judged not to be affected by the missing sample(s).

8.6.5.2 Safety Population

The safety population will include all subjects who received at least one PK session product administration.

The number of subjects who were included, who discontinued, and who completed the study will be tabulated. The primary reasons for discontinuation will be provided.

8.6.6 Demographic Data and Other Baseline Characteristics

Listings and descriptive summary statistics of demographic (age, height, weight and BMI) and baseline data will be presented.

8.6.7 Pharmacokinetics

The PK analysis will be carried out according to CRO's SOPs. PK data handling and analysis will be further detailed in a SAP.

The PK parameters for nicotine (baseline unadjusted and baseline adjusted [if applicable]) are presented in Table 5.

Table 5. Pharmacokinetic Parameters

Parameter	Definition
C_{max}	Maximum observed concentration
T_{max}	Time of maximum observed concentration; if it occurs at more than one time point, T_{max} is defined as the first time point with this value
AUC_{0-6h}	Area under the concentration time curve from the time of product administration to T_{6h}

8.6.7.1 Pharmacokinetic Statistical Methodology

8.6.7.1.1 Descriptive Statistics

Individual raw PK concentration data and derived concentrations will be calculated with the build-in Phoenix® WinNonlin® platform and displayed with the same precision as received from the bioanalytical laboratory.

Descriptive statistics will be calculated for concentrations at each individual time point and for all PK parameters. Individual concentrations, actual sampling times, and PK parameters obtained from the Non-Compartmental Analyses (NCA) will be summarised per test product group using the following descriptive statistics: number of observations (N), minimum, arithmetic mean, geometric mean, median, maximum, standard deviation (SD), coefficient of variation (CV%).

8.6.7.1.2 Statistical Analysis

8.6.7.1.2.1 Study Product Comparisons

The study product comparisons of interest are presented in Table 6. There are seven primary comparisons for the primary PK parameters AUC_{0-6h} and C_{max}.

Table 6. Study Product Comparisons

Primary	Other
Effect of nicotine strength (3 vs 2)	All MOPs vs Swedish snus (2-8 vs 1)
Effect of alginate (4 vs 3)	
Effect of acid inclusion (3 vs 6; 3 vs 7; 2 vs 5)	
Effect of acid type (6 vs 7)	
Effect of sweet base (8 vs 6)	

Abbreviations: MOP=Modern oral product

Note: see Section 8.3.1 for product numbering

8.6.7.1.3 Primary Analysis

The geometric mean nicotine $AUC_{0\text{-}6h}$ and C_{max} between the study products will be compared using a mixed-effect ANOVA model with treatments, periods, sequences as fixed effects and subjects nested within sequences as random effects. Treatment comparisons will be conducted using the fitted model with adjusted significance level of 0.00714. Data will be analysed on the natural log (ln)-transformed scale.

The superiority hypothesis to be tested is:

H0: $\mu \leq 1$ vs. H1: $\mu > 1$

where μ is the ratio of primary PK parameter ($AUC_{0\text{-}6h}$ or C_{max}) between a pair of study products. Following the ln-transformation the interchangeable hypothesis will be:

H0: $\Delta \leq 0$ vs. H1: $\Delta > 0$

where Δ is the paired difference of primary PK parameter ($AUC_{0\text{-}6h}$ or C_{max}) between pair of study products.

Both comparisons ($AUC_{0\text{-}6h}$ and C_{max}) will need to be statistically significant at the one-sided Holm adjusted 0.05 level to show superiority for a primary comparison (3 vs 2, 4 vs 3, 3 vs 6, 3 vs 7, 2 vs 5, 6 vs 7 and 8 vs 6). For descriptive purposes, unadjusted p-values will be provided for other study product comparisons.

8.6.7.1.4 Secondary Analysis

Product satisfaction

Product satisfaction data will be listed by subject and summarised for each product using frequencies (n, %).

Residual nicotine in used pouches

Nicotine transfer levels will be listed by subject and summarised for each product using descriptive statistics.

The PK statistical analyses will be detailed in the SAP.

8.6.8 Determination of sample size

8.6.8.1 Primary Analysis

Seven one-sided primary superiority comparisons (products 3 vs 2, 4 vs 3, 3 vs 6, 3 vs 7, 2 vs 5, 6 vs 7 and 8 vs 6; see Section 8.3.1 for product numbering) will be performed in this study which utilises an 8-product and 8-sequence Williams crossover design. A minimum of 32 subjects (4 subjects per sequence) will be needed to achieve a balanced design and a power of 0.848 with an alpha level of 0.00714. This will enable detecting a difference of 25% in the log scale with a correlation of 0.3 and an intrasubject CV of 0.3. A total of 36 subjects will thus be needed to be included, if an overall drop-out rate of 10% is assumed in the study.

8.7 Data Management

Data Management develops documentation to define activities performed during the data management conduct of the study. An EDC is the tool used to conduct all data cleaning activities, monitoring activities and review/approval activities for clinic collected data and procedure data. Data Management activities are performed in accordance with the Data Management vendor SOPs.

In addition to the cleaning activities, data entered in EDC will be checked for accuracy through quality control (QC) assessments. When the database data is declared to be complete and accurate, the database will be locked, and user access removed.

8.8 Changes in the approved study protocol

Any proposed change to the approved Final Study Protocol (including appendices) will be documented in a written and numbered protocol amendment. All amendments including substantial changes to the protocol must be submitted to appropriate IEC for approval, according to applicable national regulations. A substantial protocol amendment should be signed and dated by the same parties who signed the Final Study Protocol, as applicable.

9 ETHICS

9.1 Ethical review

Necessary approvals of the Study Protocol, the Subject Information sheet and Informed Consent form must be obtained before enrolment of any Subject into the study. Furthermore, it is the responsibility of the Sponsor to keep the Independent Ethics Committee (IEC) informed of any Suspected Unexpected Serious Adverse Reactions (SUSARs) and any substantial amendments to the protocol during the study period. The written approval from the IEC, including a study identification and the date of review will be filed at IRW and at the study site(s) together with a list of the IEC members, their titles or occupation, and their institutional affiliations. All correspondence with the IEC should be filed both at IRW and at the study site(s).

9.2 Ethical conduct of the study

The study will be performed in accordance with current revision of ICH Guidelines for Good Clinical Practice (EMA/CPMP/ICH/135/1995) last updated 15 Dec 2016 and The Declaration of Helsinki-adopted in 1964 by the 18th World Medical Assembly, in Helsinki, Finland, with later revisions.

The Declaration of Helsinki is included as Appendix 19.4 to the Protocol. Current revision of ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) 15 Dec 2016 is referenced in Appendix 19.6.

9.3 Patient information and consent

It is the responsibility of the Investigator to give each potential study Subject adequate verbal and written information regarding the objectives and the procedures of the study as well as any risks or inconvenience involved before including the Subject in the study. The Subject must be informed about the right to withdraw from the study at any time. The Subject should be allowed sufficient time for consideration of the proposal.

Furthermore, it is the responsibility of the Investigator to obtain signed informed consent (or witnessed verbal consent, according to local regulations) from all Subjects before including them in the study. The Informed Consent form must be signed and dated before any study-specific procedures are performed, including screening procedures. The signed Informed Consent form should be filed by the Investigator for monitoring and possible future audits and/or inspections. The Investigator will confirm the receipt of the signed Informed Consent form for each Subject by documenting it to the Subject's medical chart and signing the appropriate part of the Subject's Case Report Form (CRF), if applicable.

The Final version of the Patient Information sheet and Informed Consent form is submitted to the IEC(s) and concerned Competent Authority(ie)s and must not be changed without permission from Sponsor and the local IEC.

9.4 Subject data protection

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 should not be made available to the Sponsor or IRW except for monitoring or auditing purposes.

The Subjects will be informed that the data will be stored and analysed using computer, according to the regulatory requirements and local legislation for handling patient information and that identification of individual subject data will only be possible for the Investigator.

The potential study subject should be informed that by signing the Informed Consent Form he/she approves that authorised representatives from the Sponsor and IRW, the IEC and the Competent Authorities have direct access to his/her medical records for verification of clinical study procedures.

Investigators and the sponsor will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP and local regulations. Subjects should be identified by a unique subject identifier** on all study documents provided to the sponsor.

10 EMERGENCY PROCEDURES

10.1 Emergency contacts

If an SAE/TESAE/Pregnancy/Overdose occurs during this study, IRW must be contacted:

IRW Pharmacovigilance Manager:
Marina Fredholm
Email: pv@irwcro.com
Fax: +46 8 758 90 56
Mobile: + 46 73 519 60 41
Phone: +46 8 791 66 40

If for any reason immediate medical advice is needed, site may approach the National Coordinating Investigator:

Name: Johan Nilsson
Qualifications: MD, PhD
Tel. (Working hours): +46 (0) 18-30 33 00
Tel. (nights, weekends, and holidays): +46 70-3303692

Email: johan.nilsson@ctc-ab.se

10.2 Procedures in case of medical emergency

The Investigator is responsible for ensuring that there are procedures and expertise available to cope with medical emergencies during the study.

10.3 Procedures in case of overdose

Due to the nature of this study, where all study product is administered at the sites, the risk of accidental or intentional overdose is highly unexpected, but in the unlikely event that an overdose event occurs, IRW should be informed immediately and no later than 24 hours of becoming aware of the event, via the same communication channel used in case of pregnancy.

11 STUDY TIMETABLE

The study is expected to start with the first screening visit in Q1 2020 and to be completed in Q2/Q3 2020.

12 DISCONTINUATION OF THE STUDY

The sponsor or its representative may terminate the study at any time for scientific or corporate reasons.

If the study is prematurely terminated or suspended for any reason, the clinical site or an investigator (or delegate) should promptly inform the study subjects, should assure appropriate therapy and follow-up for the subjects and should inform the IEC when required.

13 FINAL STUDY REPORT AND PUBLICATION OF STUDY RESULTS

The CRO will prepare a clinical study report (CSR). The report will be written in accordance with the International Conference on Harmonisation (ICH). Note for Guidance on Structure and content of CSRs.

The draft report may be submitted for Quality Assurance audit, the findings of which will be incorporated in the final version.

All data collected during the study will be the property of the Sponsor.

The publication policy for this study will be part of a separate agreement between the Investigator and the Sponsor.

14 RECORD RETENTION

The Investigator must arrange for retention at the investigational site of a list of the subjects and their identifying code, subject files and other study documents including all essential documents. The archiving period must be adapted to regulations in force and should not be shorter than ten years after the termination of the study and the presentation of the final report.

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

15 DISCLOSURE AND CONFIDENTIALITY

All unpublished information concerning the test product and research carried out by the Sponsor, including patent applications, manufacturing processes, basic scientific data, etc., is considered confidential and the sole property of the Sponsor. Any disclosure of Sponsor confidential information must have prior written approval from the Sponsor.

16 INSURANCE/INDEMNITY

The Investigator agrees to notify the Sponsor BAT and the CRO whenever he/she becomes aware of a claim or action, and to co-operate with and to authorise the Sponsor BAT to carry out sole management of such claim or action.

The Sponsor's responsibility there under is covered by insurance. The insurance also covers the Sponsor's liability under law and generally accepted liability standards within the pharmaceutical industry towards any third parties, including subjects, as Sponsor of the study.

It is the sponsor's responsibility to guarantee sufficient insurance coverage should any serious events or deaths result, either directly or indirectly, from the execution of the present protocol.

17 STUDY AGREEMENTS

The Principal Investigator at the investigational site must comply with all the terms, conditions, and obligations of the Clinical Trial Agreement (CTA) for this study.

A separate Financial Agreement between Sponsor and the Principal Investigator and/or institution will be filed in the Investigator Site File and the Trial Master File.

18 REFERENCES

1. Lee, P.N. (2011). Summary of the epidemiological evidence relating snus to health. Regul Toxicol Pharmacol. 59(2):197-214

2. Lee, P.N. 2013. The effect on health of switching from cigarettes to snus – A review. Regul. Toxicol. Pharmacol. 66, 1-5.

3. Levy D.T. et al., 2004. The relative risks of a low-nitrosamine smokeless tobacco product compared with smoking cigarettes: estimates of a panel of experts. Cancer Epidemiol Biomarks Prev 13(12):2035-2042.

4. Royal College of Physicians (RCP). Harm reduction in nicotine addiction: helping people who can't quit. A report by the Tobacco Advisory Group of the Royal College of Physicians. London: RCP, 2007. Accessed from https://hams.cc/tobacco1/tobacco.pdf

5. Scientific Committee on Emerging and Newly Identified Health Risks (SCHNEIR) 2008: https://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_013.pdf

19 APPENDICES

19.1 Signature pages

Investigator

	Clinical Study Protocol	
	EudraCT No.	N/A
	Investigational Product	Oral nicotine products
	Sponsor Protocol Code	BAT2119018
	Protocol Version:	3.0
	Date	06 April 2020

Study title:
A multi-centre, randomised, cross-over, pharmacokinetic study of 8 oral nicotine products

"I agree to the terms of this Study Protocol. I will conduct the trial in accordance with the procedures specified in the protocol, the ethical principles in the latest version of the Declaration of Helsinki, ICH Good Clinical Practice and applicable regulatory requirements".

Investigator Name	*Signature*	*Date*

Sponsor

EudraCT No.	N/A
Investigational Product	Oral nicotine
Sponsor Protocol Code	BAT2119018
Protocol Version	3.0
Date	06 April 2020

Study title:
A multi-centre, randomised, cross-over, pharmacokinetic study of 8 oral nicotine products

"I agree to the terms of this Study Protocol."

Sponsor signatory

George Hardie MSc RICR, Head of Clinical Research	*Signature*	*Date*

19.2 Clinical Laboratory Evaluations

Clinical Laboratory Panel	**Description**
General biochemistry:	Sodium, potassium, chloride, glucose, creatinine, bilirubin total, alkaline phosphatase, alanine aminotransferase and albumin
Hematology:	White cell count with differential (absolute values of neutrophil, lymphocyte, monocyte, eosinophil, and basophil), red cell count, hemoglobin, hematocrit, mean corpuscular volume, and platelet count
Serology:	Human immunodeficiency virus (HIV) Ag/Ab Combo, Hepatitis B (HBsAg (B)) and Hepatitis C (HCV (C))
Serum pregnancy test:	A Serum pregnancy test will be collected at screening. In the event case of a positive or unclear result from a urine pregnancy test, a serum pregnancy test will also be performed to confirm the result
Urinalysis:	Colour, clarity, specific gravity, pH, leukocyte, protein, glucose, ketones, bilirubin, blood, nitrite, urobilinogen. Microscopic examination will only be performed if the dipstick test is outside of the reference range for leukocyte, blood, nitrite or protein
Urine drug screen:	Amphetamines, barbiturates, cannabinoids, cocaine, cotinine, opiates and phencyclidine
Urine Pregnancy test:	To be performed for all female subjects
Alcohol screen:	Alcohol breathalyser screen

19.3 Product Subjective Measures Questionnaires

Subject number: _____

Date of completion: _____ / _____ / 20_____

Product: _____

Product Liking Questionnaire (PLQ)

At this moment, how much do you like the product?

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
Strongly dislike					Neither like nor dislike					Strongly like

Overall Intent to Use Again (OIUA) Questionnaire

Rate the degree to which you would like to use the product again.

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
Not at all										Very much

19.4 Declaration of Helsinki

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.
The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.
2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
5. Medical progress is based on research that ultimately must include studies involving human subjects.
6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.
8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.
9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.
11. Medical research should be conducted in a manner that minimises possible harm to the environment.
12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.
The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.
In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.
The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.
26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.
After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
All medical research subjects should be given the option of being informed about the general outcome and results of the study.
27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must

be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.
36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

19.5 Labelling of Study Products

General Case (containing 8 sequentially numbered pouches (1-8))
FOR CLINICAL TRIAL USE ONLY
KEEP OUT OF REACH OF CHILDREN
Sponsor: British American Tobacco
Contract Research Organisation: IRW Consulting AB Tel. No.: 08 791 66 40
Investigator: [Investigator name] **Tel No.**: [Investigator Tel No.]
Dosage form and directions for use: Nicotine containing pouch for oral user under the upper lip for 60 minutes
Quantity: 8 packages containing 1 pouch each
Treatment Sequence Code Number: [xx]
Trial Reference Code: BAT2119018
Subject Number: [*enter number*]
Storage conditions: Room temperature
Use before: MM/YY

Primary Package (containing one numbered pouch (1-8))
FOR CLINICAL TRIAL USE ONLY
KEEP OUT OF REACH OF CHILDREN
Sponsor: British American Tobacco
Contract Research Organisation: IRW Consulting AB Tel. No.: 08 791 66 40
Investigator: [Investigator name] **Tel No.**: [Investigator Tel No.]
Dosage form and directions for use: Nicotine containing pouch for oral user under the upper lip for 60 minutes
Quantity: 1 pouch
Treatment Sequence Code Number: [xx]
Treatment Number: [1-8]
Trial Reference Code: BAT2119018
Subject Number: [*enter number*]
Storage conditions: Room temperature
Use before: MM/YY

19.6 ICH Good Clinical Practice

This study will be conducted in accordance with the ICH: E6(R2) Guideline for good clinical practice EMA/CHMP/ICH/135/1995 last updated 15/12/2016