INFORMATION TO CLINICAL RESEARCH PATIENTS

CLINICAL TRIAL CONSULTANTS AB

Study: 407-129_2021_BAT_AL

Screening number: _____

Study title

A single dose, randomised, crossover study to assess the nicotine pharmacokinetics and product subjective effects of oral nicotine products in healthy adult users of cigarettes and smokeless pouch products.

Introduction

We ask you if you want to participate in a clinical research study. In this document you will find information about the study and what it means to participate. It is important that you understand why the research is done and what will happen to you during the study. Take your time to carefully read the information and do not hesitate to ask questions. You can bring a copy of the information home if you want to further discuss with friends, relatives, or your general physician before you decide to participate in the study.

If you decide to participate in the study, you must sign and date this consent. No study-related procedures will be done before you have read, fully understood, and signed and dated this consent. You will receive a copy of the signed and dated consent.

What is the study about and why do you want me to participate?

The study is performed on behalf of the company British American Tobacco (BAT) called Sponsor, and performed at CTC Clinical Trial Consultants AB, Uppsala in Sweden. Entity responsible for the research is CTC Clinical Trial Consultants AB.

BAT is currently developing tobacco-free products (VELO) containing high-quality food-grade ingredients including naturally derived nicotine, water, eucalyptus, and pine tree fibres, flavouring and sweeteners. The only pharmacologically active ingredient in the tobacco-free nicotine products is the nicotine. BAT would like to conduct an abuse liability and pharmacokinetic study to obtain data to understand addictive effects of the modern tobacco-free nicotine products in comparison with products with high and low addictive effects, such as cigarettes and nicotine shewing gum (Nicorette 4 mg).

The results of this study will answer fundamental science questions as to the abuse liability of these nicotine products.

The main purpose of this study is to evaluate the subjective effects on product liking during and after product use. It will be investigated whether your heart rate changes when using the study products. The heart rate will therefore be measured during and after using products. Another purpose of the study is to determine the level of nicotine absorbed to the body when using different strength nicotine products, as well as to determine the time it takes for the nicotine to disappear from the body. This will be evaluated through blood samples taken during the study. A further purpose of the study is to evaluate the safety and tolerability after use of each tobacco-free nicotine product.

The subjective experience of using the study products, your general thoughts, smoke craving, product effect and the intention to use the product again will be examined by using questionnaires to be completed by the subjects.

The study is approved by the Swedish Ethics Review Authority (Etikprövningsmyndigheten) and the Swedish Medical Agency (Läkemedelsverket).

You are asked to participate in this study because you:

- are between 19–55 years old
- have either registered interest to CTC's database to participate in clinical studies or registered interest after CTC announced in the media regarding this study
- are a smoker of commercially available cigarettes, smoking 5 cigarettes or more on average per week and has smoked for at least 1 year
- use nicotine products, such as snus or other types of tobacco-free products placed under the lip
- have used this type of products, daily during at least one year

Study overview

If you decide to participate in the study, you need to sign and date this consent. The study investigator will check that you can participate in the study.

Visit/time required	Visit content
Visit 1. (Approximately 3 h) Day -28 - 1	• Written and oral information about the study and subject consent to participate • Check of criteria to participate in the study Health examination including: • Demographics (gender, age, ethnicity, nicotine- and alcohol habits) • Physical examination • Height and weight • Vital signs (blood pressure and pulse) • ECG measurement • Blood and urine sample collection (including, alcohol test and drug test, HIV- and hepatitis B and C) • Pregnancy test (women of childbearing potential) blood sample • Medical and surgical history • Prior and concomitant medication • Product familiarisation session – use of highest nicotine strength oral tobacco-free nicotine product (one of the study products)
Visit 2, Day -1 (Approximately1 h)	• You will come to the clinic on the evening before starting the use of oral tobacco-free nicotine product (study product) • Check of criteria to participate in the study • Blood and urine sample collection • Pregnancy test (women of childbearing potential) urine dip stick • Coffee or tea and sandwich are served in the evening
Visit 2, Day 1-4 (Overnight stay at site)	• Vital signs (blood pressure and pulse) • Randomization (selected by chance) to study arm/section (in the morning on Day 1) • Use of oral tobacco-free nicotine product (study product) • Use of sensor-vest • Collection of oral tobacco-free nicotine product (study product) after use • Repeated blood samples taken to evaluate the study product nicotine concentration (pharmacokinetic) • Repeated rating of your subjective effects on overall product liking, product effect and smoke craving by completing questionnaires • Repeated rating of your intention to use the study product again by completing a visual analyse scale (100 mm long horizontal scale) • Current medications • Control and follow-up of adverse events (side effects) • Meals are served during all days

Visit 2, Day 5 (Overnight stay - Product use/sample collection/questionnaire approximately 4 h)	Health examination including: • Physical examination • Vital signs (blood pressure and pulse) • ECG measurement • Use of oral tobacco-free nicotine product (study product) • Use of sensor-vest • Collection of oral tobacco-free nicotine product (study product) after use • Repeated blood samples taken to evaluate the study product nicotine concentration (pharmacokinetic) • Repeated rating of your subjective effects on overall product liking, product effect and smoke craving by completing questionnaires • Repeated rating of your intention to use the study product again by completing a visual analyse scale (100 mm long horizontal scale) • Safety blood sample collection • Pregnancy test (women of childbearing potential) urine dip stick • Current medications • Control and follow-up of adverse events (side effects) • Meals are served • You will be discharged from the site and get a scheduled time follow-up by telephone call
Visit 3. Follow-up Telephone call (30 min)	• You will be asked if you have taken any new medications since last visit • Control and follow-up of adverse events (side effects)

On the following sections you can read more about:
• Volunteering and consent
• How is the study conducted?
• Restrictions you need to consider during the study period
• Possible consequences and risks of participating in the study
• Possible benefits of participating in the study
• What happens to my personal data (EU Data Protection Regulation, GDPR)?
• What happens to my samples?
• How do I get information about the results of the study?
• Insurance and compensation
• Responsible for the study

Volunteering and consent

Your participation in this study is entirely voluntary and you can withdraw your consent for participation at any time. It is your choice whether to participate or not. If you choose not to

participate or if you change your mind later and stop participating even if you agreed earlier, you do not have to explain why, nor will it affect your future care or treatment. If you want to stop your participation, you should contact the responsible doctor for the study (see section Responsible for the study)

The responsible doctor may decide to cancel your participation in the study if it is deemed necessary for your safety or if you do not follow the restrictions required by the study. The study Sponsor can also decide to stop the study. If your participation in the study is cancelled, it is important that you come to the follow-up visit(s) that the study doctor considers necessary for your safety.

If any new information emerges during the study that might influence your decision to participate, you will be informed about it.

How is the study conducted?

The study will include a total of 45 healthy men and women aged 19-55 years who are a smoker of commercially available factory-made cigarettes and have used oral nicotine products, such as snus or other types of tobacco-free pouch products placed under the lip, daily during at least one year.

The study period is estimated to continue up to 40 days.

The study will be performed at one site in Sweden Sverige, CTC Dag Hammarskjölds väg 10B Uppsala.

The study includes two visits at the study site and one telephone follow-up at the end of the study. At visit 2, you will stay overnight at the study clinic for 5 days. You will arrive at the clinic on Day -1 and remain at the clinic until the afternoon of Day 5. Day -1, is the day before you start to use the study products. During your stay at the clinic, you will use the study products daily and assessments of the effect will be done every day (1 to 5). oral tobacco-free nicotine products, cigarettes, or nicotine chewing gum (study products) daily

Five nicotine products will be compared in the study: Three levels different strengths of nicotine pouches: 11 mg nicotine/pouch, 15 mg nicotine/pouch and 20 mg nicotine/pouch of “VELO”, an oral tobacco-free nicotine product, will be compared with conventional cigarettes of the brand you normally use and nicotine chewing gum.

The order in which you will use the different study products and strengths/concentration levels, is randomized to five sequences with 5 arms. Each study sequence for oral tobacco-free study product and duration of use are as follows:

Product No.	Test/ Comparator	Product Name	Format	Usage time

Product 1	Comparator	Subject's usual brand of choice	Commercially available, factory made, conventional cigarette	Up to 10 minutes
Product 2	Test	VELO Freeze 11 mg	Nicotine pouch (11 mg/pouch) pouch size: 0.7 g, concentration: 15.7 mg nicotine/g.	20 minutes
Product 3	Test	VELO Freeze 15 mg	Nicotine pouch (15 mg/pouch) pouch size: 1.0 g, concentration: 15 mg nicotine/g.	20 minutes
Product 4	Test	VELO Freeze 20 mg	Nicotine pouch (20 mg/pouch) pouch size: 1.3 g, concentration: 15.4 mg nicotine/g.	20 minutes
Product 5	Comparator	Nicorette® 4 mg	Nicotine mint flavour gum	30 minutes

You will be randomized to (a sequence) the order in which you will use the study products during the 5 days of use. The study will be open, meaning both you and the study staff will be aware of which study product and duration of use you will use at a certain time.

Further, during the 5 days you will repeatedly be asked to complete five questionnaires to assess your subjective experience of using the study products, your general thought, smoke craving, product effect and if you would intend to use them again.

Detailed information regarding the activities during the visits are described below.

<u>Visit 1 (approx. 3 hours): Health examination</u>
During this visit, you will be informed orally and in writing about the study. If you decide to participate, you will sign a consent form to participate. To ensure that you can be included in the study, your doctor will perform a health examination, including height, weight, heart rate, blood pressure and ECG (a record of the electrical activity in your heart). Blood and urine samples for health status (including HIV and hepatitis) will be taken as well as urine samples for drug- and alcohol testing. For women of childbearing potential, a pregnancy test will be done by taking blood sample. You will get questions about your medical history and current medications and asked about your snus and nicotine habits. If you intend to stop using nicotine, you will have an opportunity to ask for advice and receive contact information to where you can get help (if your intention is to stop using nicotine you should not participate in the study).

You will get acquainted with the oral tobacco-free nicotine products by using one of the products (20 mg nicotine) for 30 minutes (minimum), to ensure that you can accept and

tolerate the products. You should use the product in the same way as you normally use an oral tobacco-free product (under the upper lip).

If you are eligible to participate in the study, you will be invited to visit 2.

Visit 2 (Overnight stay at the clinic, product use and tests approx. 4 h Day -1 to Day 5):
You will arrive at the clinic on the evening before starting the use of the study products. A health examination is done to ensure that you are in good health condition and fulfil the criteria for study participation.
Your heart rate and blood pressure will be measured. Blood samples and urine tests for health status as well as for drug and alcohol will be taken. For women of childbearing potential, a pregnancy test will be done by taking urine sample. During the entire visit (Day -1 to Day 5), you are not allowed to use any nicotine products other than the study products 12 hours before to 4 hours after use of the study product.

You must bring enough of your own products (snus, cigarettes and tobacco-free nicotine products) to cover use during the study period at permitted times.

If you are considered suitable to participate in the study, you will be randomized (selected by chance) in the morning of Day 1, to the sequence in which you should use the study products. You should place the pouch under the upper lip as you normally do when using snus and tobacco-free nicotine products.

During visit 2 (Day 1 to Day 5), you will use a sensor-vest (Equivital LifeMonitor) that monitors heart rate, respiratory rate, ECG and skin temperature. The sensor-vest is a lightweight Lycra vest, used during the time you use study products and will be applied about an hour before you start to use the study product. The sensor measurements will last for about 4 hours after the start of each study product use. Data recorded via the sensor-vest will be transferred to an external computer at the study clinic. No data will be entered into the study database.

During visit 2, Day 1 to Day 5, a total of 13 blood samples per day will be taken from a vein in your arm to measure how nicotine is absorbed in your body and the time the nicotine is left in the blood. To avoid more than one stick, a type of cannula that remains in the vein throughout the test period will be used. The samples will be analyzed to measure nicotine level in your blood at different times. Further, your heart rate will be regularly measured during all days This is done by putting a measurement device (pulse oximeter) on your finger.

You will repeatedly respond to five questionnaires about your experience using the different study products.
Each question is ranked using a graded scale. You will also be asked to estimate on a 10 cm horizontal scale how likely it is that you will use the product again.

The study staff will provide you with a study product each day during the stay at the clinic. You are not allowed to eat, drink, chew gum or brush your teeth from 30 minutes before using the study product, while the product is being used and 30 minutes after the use. After use, all study products will be collected by the study staff and frozen until time for analyses.

You will be served breakfast, lunch, and dinner while you stay at the clinic.

Telephone call (approx. 30 minutes)
The last visit is a telephone follow-up approximately a week after end of use of the study products. The study nurse or study doctor will call you to ask if you have experienced any health problems and if you have taken any medicines since the last visit.

Restrictions you need to consider during the study period

For your safety and for the study results to be as reliable as possible, it is important that you follow certain restrictions during the study, regarding for example, food and medication. The restrictions that apply for this study are listed in Restriction, appendix 1.

Possible consequences and risks of participating in the study

There are no direct benefits for you to participate in this study other than the thorough health control that is performed. Neither there are no direct risks with the examinations that are done to consider if you are suitable to participate in the study.

It can hurt when the ECG electrodes are pulled off and you can get a slight redness on the chest skin.

Blood sampling may be uncomfortable and cause bruising. In rare cases it can cause fainting and infection of the skin at the injection site.

The total blood volume that will be taken from you during the study will be approximately 309 ml. This can be compared with 450 ml taken during a blood donation at the blood center.

Use of the sensor-vest can cause skin irritation or rash. If this should happen, the use will be immediately discontinued.

Traditional snus and cigarettes contain tobacco and nicotine. Tobacco products are harmful and addictive. The best ways to avoid risks with tobacco is to completely refrain to use it.

Oral tobacco-free products can be harmful to health and contain nicotine which is an addictive substance. The best ways to avoid risks with tobacco is to completely refrain to use it.

Use of the study products is not expected to lead to greater exposure to nicotine than your usual daily use of nicotine products. For safety reasons, pregnant women are not allowed to

participate in the study. Participating women of childbearing potential must use contraception or be sexually abstinent (only if this is in accordance with the woman's normal lifestyle).

There are always risks with using nicotine products and unexpected side effects that are not known today can arise. All possible actions will be taken to reduce the risks. All side effects occurred during the study will be carefully documented and reported. If you feel unwell or feel that your health is affected in some way, it is important that you immediately inform the study staff, even if you do not think the health problem is related to the oral tobacco-free study product. If the study staff deems it necessary, you can be recommended to do further examinations and samplings to ensure your medical safety.

Possible benefits of participating in the study

Participation in this study is for research purposes and there are no benefits to participate in the study except that you are carefully examined.

What happens to my personal data (EU Data Protection Regulation, GDPR)?

Medical records will be kept at the clinic throughout the study, in accordance with the Patient Data Act. The medical record contains your name, birth date and personal security number, so-called personal data.

During the study, we will collect and register information about you (this information is collectively referred to as "study data"). Study data includes e.g. gender, age, ethnicity, health data (such as previous illnesses) as well as results of examinations in the study. The examination results and answers that we collect from you will be kept confidential, meaning no unauthorized persons can have access to it.

Your consent to the processing of collected study data applies and is valid for all time to come unless you withdraw your consent. If you withdraw your consent, the responsible doctor will not continue to collect or process any new study data. However, the study data collected before you withdrew your consent will be used and processed by Sponsor.

All study data processed by the Sponsor will be coded, i.e. your name and personal security number have been replaced with a code. Only the responsible doctor and his staff have access to the code key with which it is possible to link the personal data to you.
The collected study data is processed, (i.e. stored, processed and compiled) both manually and with computer technology.

The responsible study doctor uses study data to conduct the study. The Sponsor will use coded study data to compile and evaluate the study results. The study results may be used by the Sponsor for research and development purposes of products, and/or making claims about the products, and/or submitted to regulatory agencies to seek marketing approval or to support

the continued marketing of these products. The Sponsor may also publish the results of this study in a peer-reviewed scientific publication.

The handling of your personal data is regulated by the European Union (EU) Data Protection Regulation. Collected data will be stored for at least 10 years after the end of the study.

Collected study data will be transferred to the Sponsor (British American Tobacco (Investments) Limited), and to companies working on behalf of the Sponsor. Your study data may be transferred to recipients in countries outside Sweden and the EU. These countries may have laws that do not have the same level of protection regarding the processing of personal data provided for in the EU Data Protection Regulation, however, the sponsor will ensure through contractual arrangement that the recipient handles the data in accordance with the regulation.

Persons appointed by the Sponsor will compare collected study data with relevant information in your medical record. The persons must be approved by the doctor in charge of the medical record and must also sign a confidentiality agreement before they can have access to your medical record. Competent authority representatives have the right to read your medical record to review if the study has been correctly conducted.

Responsible for your personal data in medical record is the research principal CTC Clinical Trial Consultants AB, Dag Hammarskjölds väg 10B, 752 37 Uppsala. Responsible for your research data is British American Tobacco (BAT). According to the EU Data Protection Regulation, you have the right to free of charge access the information about you that is handled in the study, and if necessary, get any data errors corrected. You can also request that information about you should be deleted and that the processing of your personal data should be restricted.

If you want to take part of your collected study data, you must contact the responsible doctor in writing, see contact information under the section Responsible for the study. Your application must be signed and contain the name of the study. Data protection officer for CTC Clinical Trial Consultants AB contact is contacted via email: dpo@ctc-ab.se. If you want to know more about how the Sponsor stores and handles your data, you can contact the following British American Tobacco email address: Data_Privacy@bat.com

If you are dissatisfied with the handling of your personal data, you have the right to submit complaints to the Privacy Protection Authority (IMY), which is the supervisory authority. You will find an e-service for this procedure on their website (www.IMY.se).

What happens to my samples?

Routine blood samples are analyzed at Clinical Chemistry and Pharmacology, Uppsala University Hospital Uppsala.

For security reasons blood samples for HIV and hepatitis B and C are taken. The samples are analyzed at Clinical Microbiology, Uppsala University Hospital Uppsala. If any of these tests indicate that you are infected, it will be reported in accordance the Swedish Communicable Diseases Act and you will be referred for further treatment.

All blood samples are marked with a social security number and sent for analysis with a referral to laboratory. The samples are destroyed shortly after analysis.

Routine analyzes of urine samples, urine drug tests and any pregnancy tests in urine will be performed at the clinic where the study is performed. The samples are destroyed shortly after analysis.

Plasma samples for nicotine analyses are marked with a social security number and sent for analysis with a referral to Anapharm Europe S.L.U. Encuny 22, 2nd floor, 08038 Barcelona, Spain. The samples are destroyed shortly after the study is finalized and reported.

All samples stored for longer than 6 months as described above will be handled in accordance with the Biobanks in Health Care Act (2002: 297). Plasma samples are stored coded in the principal biobank at CTC Clinical Trial Consultants AB, Uppsala (biobank number IVO 893). The fact that the samples are coded means that they cannot be linked directly to you as a person without a code key. The code key is safely stored by the responsible doctor.

The samples may only be used in the manner for which you have given your consent. If unplanned research is to be added, the Ethics Review Authority will decide whether you should be consulted for consent again.

You have the right to later withdraw (cancel) the consent to the samples being saved in the manner described in this clinical research information. In that case, your samples will be discarded or deidentified. If you want to withdraw the consent you should contact the responsible study doctor Johan Nilsson, MD, PhD, CTC Clinical Trial Consultants AB, Dag Hammarskjölds väg 10B, 752 37 Uppsala, Sweden tel: 018-30 33 00,
email: johan.nilsson@ctc-ab.se
However, the results already obtained from the samples cannot be recalled.

How do I get information about the results of the study?

During the study, all study data is collected in a database. When the database is closed after the end of the study, study data will be analyzed. After the study is completed and the clinical study report is available, you can contact the responsible doctor to get information about which treatment you have received in the study.
Data from the study, 2022-000403-13 may be published in e.g. medical journal or presented at scientific meetings. In these cases, it will not be possible to identify patients that have participated in the study.

INFORMATION TO CLINICAL RESEARCH PATIENTS

Study: 407-129_2021_BAT_AL

Insurance and compensation

The Sponsor has an insurance that covers cost for injuries related to the use of the study product. CTC Clinical Trial Consultants AB has a Liability Insurance that covers for injuries that would occur during your stay at the clinic. If you think that you have an injury because of your participation in the study, you should contact the responsible study doctor.

The compensation for a fully completed study is 19700 SEK. If it becomes relevant with extra visits and / or extra sampling, corresponding compensation is paid for the time required. The compensation is taxable. Deductions will be made for meals served at the clinic in accordance with the Swedish Tax Agency regulations.

You will get compensation for visit travels to and from the clinic upon presentation of a receipt.

If you are a reserve in the study, you will receive a taxable compensation of SEK 2 400SEK.

If you have only been to the first study visit, the health examination, no compensation will be paid.

If you end your participation prematurely (on your own initiative or by decision of the responsible doctor or Sponsor), you may be reimbursed in relation to your actual participation or you will receive full compensation. The compensation is paid provided you have complied with the restrictions and recommendations for your safety.

For safety reasons and to get as reliable study results as possible, drug tests are taken during the study. A positive drug test may lead to that you cannot continue participation in the study and may lose the financial compensation.

INFORMATION TO CLINICAL RESEARCH PATIENTS

Study: 407-129_2021_BAT_AL

Responsible for the study

If there is anything further you are wondering about or need to get in touch with us, you are welcome to call:

	Name	Phone number
Responsible doctor:	_____	_____
Responsible nurse:	_____	_____

INFORMATION TO CLINICAL RESEARCH PATIENTS

Study: 407-129_2021_BAT_AL

Screeningnummer: _____

Study title

A single dose, randomised, crossover study to assess the nicotine pharmacokinetics of oral nicotine products in healthy adult users of smokeless pouch products.

Subjects' consent, Study BAT51121037

- I have received both oral and written information about the above clinical research study
- I have been informed about the purpose, conduct and my rights and responsibilities when I participate in the clinical research study
- I have had opportunity to discuss the study and my questions have been answered
- I am aware that I will receive a copy of this information
- I know that my participation in the study is entirely voluntary
- I know that I can withdraw my consent to participate in the study at any time, without having to justify my decision

By signing this informed consent, I agree to/that:

- participate in this clinical research study
- information about me is processed in the manner described in the information to clinical research patients
- my samples are stored in the hospital's biobank as described in the information to clinical research patients
- a person appointed by the Sponsor, or a person from the competent authority may compare the collected study data with relevant information in my medical record, in a manner so no unauthorized person may take part of the study data

Signature of clinical research subject

……. …….

Signature *Date (subjects signature date)*

…….

Name in block letters

Signature of the doctor who has informed and received the signed informed consent:

……. …….

Signature *Date*

…….

Name in block letters

A copy of the information to clinical research patients and the signed consent should be handed over to the subject and the original of the signed consent should be kept at the study clinic

Appendix 1
Restrictions

- If you experience any cold or flu symptoms, you must not come to the clinic. Please, contact the study staff to rebook the visit
- Women of childbearing potential must use contraceptives at least 28 days prior to study start and 30 days after the last nicotine dose. If you would become pregnant, you immediately need to inform the study staff.
- During all days at the clinic stay, you will only be allowed to use your own nicotine products four hours after the end of the blood samples are taken and until 20:00 in the evening.
- You must not change the brand of your usual snus/nicotine product during the study.
- You are not allowed to eat, drink, chew gum or brush your teeth from 30 minutes before the time you place the study product under your upper lip until 30 minutes after you have taken it out.
- You must not drink alcohol from 48 hours before and during the stay at the study clinic.
- You should not eat poppy seeds 3 days before you come to the clinic to start the study, visit 2 Day -1.
- You must not eat, or drink caffeinate beverages or food (eg coffee, tea) while using the study products and blood sampling is in progress. Consumption is permitted during the period between last blood samples taken (4 hours after using the study product) and up to 12 hours before start of next use of study product. During the permitted time, you can drink a maximum of five cups of coffee.
- During visit 2 (Day -1 to ay 7) you are not allowed to use any nicotine products other than the study products 12 hours before to 4 hours after application of the study product.
- You must not drink energy drinks that contain xanthine or taurine (i.e. Red bull) during visit 2 (Day -1 to Day 7).
- Do not use body lotion, oils, perfumes, deodorant, or powder in the body area where the sensor vest (Equivital LifeMonitor) is located until after the last use on Day 7.
- You should not donate blood or plasma during the study period and for three months after Day 7 on study visit 2.

- You must not participate in any other clinical study during the study period, i.e. from the first to the last visit (follow-up).