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Protocol

Exploring the cessation efficacy and harm reduction potential of heated tobacco and nicotine pouch products in smokers and smokeless tobacco users: study protocol of a 6-month randomized controlled switching trial

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ABSTRACT

Background: Despite decades of research on pharmacological and behavioural smoking cessation treatments, current quit aids are of limited success. The introduction of new, combustion-free nicotine and tobacco products extended the tool kit for people who smoke to switch away from their risky habit. We performed a systematic review including 120 studies resulting in several recommendations for a robust study design to determine the cessation efficacy of a new nicotine or tobacco product. Consequently, we prepared this study protocol to assess the cessation efficacy of heated tobacco products (HTPs) and nicotine pouches (NPs).
Methods: 250 subjects (125 exclusive smokers and 125 exclusive smokeless tobacco (SLT) users) will be recruited and offered a choice of HTPs in case of smokers and a choice of NPs in case of SLT users in order to switch. Subjects will undergo four visits (baseline, 1, 3, and 6 months) to collect biospecimens and for physical examinations. Use behaviour and questionnaires will be monitored on a regular basis by means of a smartphone-app. We describe a sensitive and specific compliance monitoring using suitable biomarkers of exposure. The sample size of 250 subjects and duration of 6 months will allow the quit rates to be assessed with sufficient statistical power. Finally, the choice between different products shall reflect the individuals' preferences.
Conclusions: This protocol can be applied generically, providing a robust determination of a products' cessation efficacy.
Trial Registration: The trial will be registered in the International Clinical Trials Registry Platform.

Keywords: Smoking cessation, Cessation efficacy, Compliance, Harm reduction, Heated tobacco product, Nicotine pouch

INTRODUCTION

Smoking combustible cigarettes (CCs) remains a leading cause of numerous non-communicable diseases, including cancer and cardiovascular diseases, contributing to several million preventable deaths worldwide each year.[1,2] With the introduction of new nicotine and tobacco products, referred to as combustion-free nicotine/tobacco products (CF-N/T-P), like electronic cigarettes (ECs), heated tobacco products (HTPs), snus and tobacco-free nicotine pouches (NPs), a variety of alternatives to CCs and toxic forms of smokeless tobacco (SLT) like moist snuff are nowadays available. These products show reduced exposure to harmful constituents as present in tobacco smoke and are therefore debated as potentially reduced risk products.[3-6] There are two aspects which need to be

fulfilled in order to satisfy the propagated role as reduced risk product in terms of tobacco harm reduction. Firstly, the products must substantially reduce the relative exposure as compared to CCs, but also in their absolute exposure in order to determine their overall risk. Secondly, these products must be a substantial aid for smokers and users of toxic forms of SLT to transition away from their destructive habit and switch completely. Although a recent Cochrane review concluded with strong evidence that ECs are more efficient than the commonly marketed and prescribed nicotine replacement therapies (NRTs), data from randomized controlled trials (RCTs) on the cessation efficacy of HTPs and NPs remain scarce. In Japan, the introduction of HTPs has recently been associated with the reduction in smoking rates.[7,8] One RCT showed switching rates for HTPs comparable to those of ECs.[9] In Sweden, snus use is very popular. Simultaneously, smoking prevalence dropped drastically over the past decades.[10] While these observations may be a first hint towards the effectiveness of HTPs and NPs in terms of quitting, well-designed RCTs are needed to provide evidence on this topic.

We recently completed a systematic review to summarize the common characteristics of RCTs designed to evaluate the cessation efficacy of ECs and other CF-N/T-P. This study protocol describes our approach, focusing on HTPs and NPs, to assess their potential impact on public health by examining their effectiveness in smoking and/or smokeless tobacco use cessation in comparison to NRT. We developed the protocol based on insights gained from our systematic review, identifying common limitations and proposing best practices for future clinical trials.

METHODS

Trial design

This protocol describes a multi-site randomized controlled trial of 250 experienced daily smokers of CC switching to either an HTP or NRT product and 250 experienced daily users of SLT switching to either an NP or NRT product, respectively. The study is planned to be conducted within 18 months, from September 2024 to February 2026. The trial design is depicted in Figure 1.

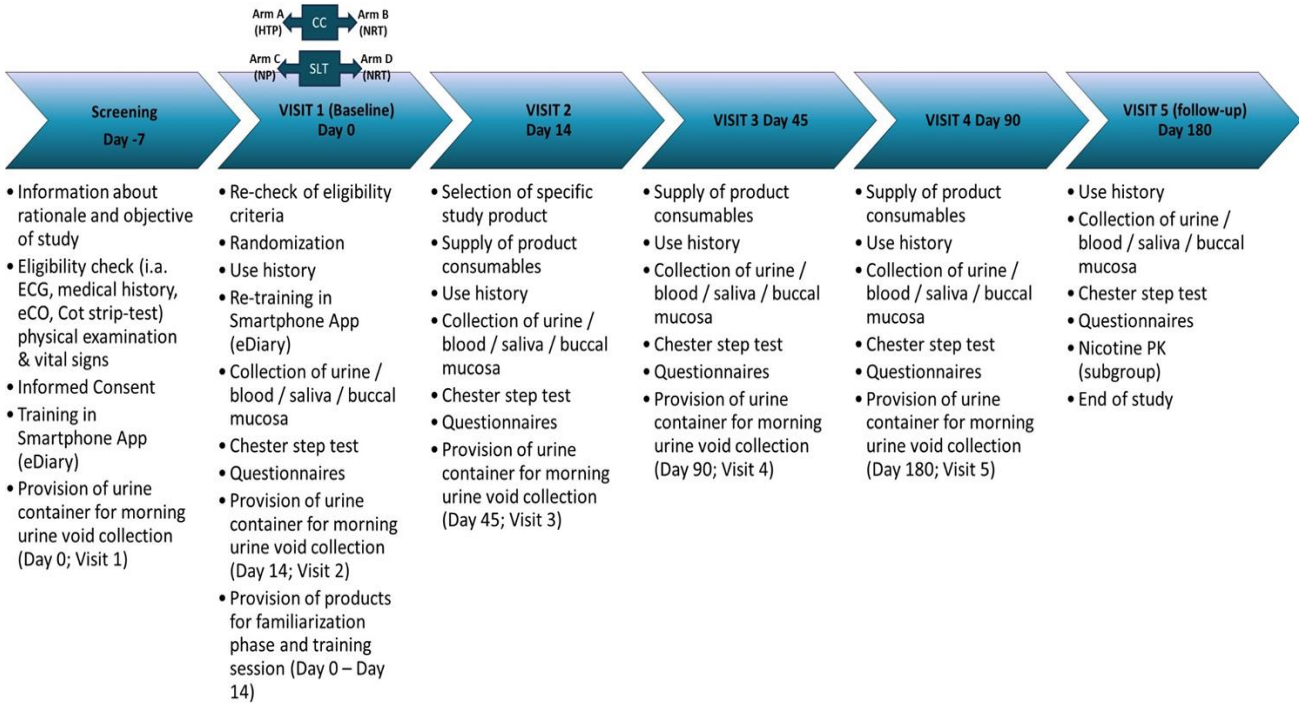

Figure 1: Study flowchart.

For this purpose, two separate study populations of subjects will be recruited: solus, experienced smokers of CCs (n=250), who will be randomized 1:1 to switch to HTP (arm A) or NRT (arm B); and solus, experienced SLT users (n=250) who will be randomized 1:1 to switch to NP (arm C) or NRT (arm D). Subjects will be 19 years of age or older, judged as suited to be included into the study based on screening and inclusion/exclusion criteria assessments. An attempt will be made to include at least 40% females in each arm, and similar (non-significant) age and BMI distributions between arms.

Recruited subjects will attend the clinic for screening up to 7 days before study start (day-7). Each subject will undergo the consenting procedure in which they will receive verbal and written information about the study. If they are then willing to participate in the study, they will sign the informed consent form (ICF) prior to any screening procedures taking place. Subjects will be selected for enrolment into the study itself based on medical history, tobacco use status and history, physical examination, vital signs and alcohol consumption screening. Pregnancy testing will be performed on female

subjects. Subjects' eligibility for inclusion will be determined based on the results of the screening procedures and will determine whether subjects are invited back for inclusion in the study.

Compliance with the preset criteria in terms of smoking (arm A and B), and SLT use (arm C and D), respectively, will be assessed by urinary cotinine strip test (cotinine cut off: ≥200 ng/ml for nicotine use; <200 ng/mL no nicotine use) and exhaled carbon monoxide (eCO) (eCO cut off: ≥7 ppm: smoking; <7 ppm: no smoking). Moreover, the history of tobacco and nicotine use will be documented by questionnaire as well as further screening assessments.

During the baseline visit on day 0 (visit 1), subjects will be randomized into one of the four arms. While smokers will be randomized into either arm A (HTP) or arm B (NRT), SLT users will be randomized into either arm C (NP) or arm D (NRT). Based on the randomization, the subjects will be provided with a set of corresponding products for the 14-day familiarization period. Subjects will be re-trained in the collection and storage of the first morning urine void for the subsequent visits. They will be provided with the sample container for urine collection, a cooling bag with cool packs, a ziplock bag, and written instructions on collection and storage of the urine, which they will have to collect on the morning of their next visit (visit 2; day 14). In addition, subjects will be instructed to record their product use once daily to document use of the study product and CC/SLT (depending on the arm) over the last 24 hours.

On visit 2 (day 14), subjects will select a specific product from the selection of products used during the 14-day familiarization period. Proper use of the product will be re-checked in the clinic by trained staff. Subjects in arm A are restricted to one HTP device but they are free in the choice of different flavors (sticks). Subjects in arm C can use different flavors, preferably from one brand. Change of the brand/flavor throughout the study is allowed, especially if a subject fail to quit completely or reduce CC or SLT use by at least 50%. Subjects in arm B/D can use different product types of the offered NRTs. Subjects will be provided with sufficient supplies until the next visit (visit 3) based on the use history evaluated from the data filed in the app.

Procedures from visit 2 will be repeated at visit 3 (day 45), visit 4 (day 90), and visit 5 (day 180).

Sample size

There are only few reports (if any) on the cessation efficacy of HTP and NP products, as discussed in the Introduction section. Due to the lack of data and the exploratory nature of the study, the sample size calculation is estimated based on the assumption that these products have a similar switching rate as ECs as previously indicated for HTPs by Caponnetto et al. There, an abstinence rate of 39% was observed when switching from smoking to HTPs after 3 months.[9] Assuming a relapse rate of 40% between month 3 and 6, a quit rate of 25% would be achieved. With these assumptions, a sample size of 104 subjects per intervention was calculated for a statistical significance level of 5% (non-parametric; alpha: 0.05) and 80% power (beta: 0.20). Our study includes 125 subjects per intervention which should easily meet this criterion taking into account the rigorous compliance monitoring to detect smoking abstinence by means of the long-term biomarker of acrylonitrile exposure cyanoethylvalin (CeVal).[11,12]

Screening

Subjects must participate in a preliminary examination in order to determine their eligibility for the study and to ensure that none of the exclusion criteria and all of the inclusion criteria are fulfilled. All subjects will be examined by a physician after they have received verbal and written information about the study and have given their written consent to participate in the study. The information collected during the initial screening process at the time of screening are: (i) informed consent, (ii) inclusion and exclusion criteria, (iii) medical history and demographics, (iv) physical examination (including body weight and height; BMI), (v) history of nicotine use and product use status questionnaire, (vi) laboratory tests, vital signs, electrocardiography (ECG), (vii) alcohol breath test, (viii) urine drug screen, (ix) urine pregnancy test for women in child-bearing age, (x) urine cotinine test (dipstick), (xi) exhaled carbon monoxide (eCO), (xii) questioning for drug abuse, (xiii) lung function assessment/ spirometry.

Inclusion criteria

The subjects cannot be enrolled before all inclusion criteria are confirmed. Subjects meeting all of the criteria listed below will be included in the clinical trial such as ≥19 years of age, males and females, physically and mentally healthy, without a legal guardian, as judged by the PI or other appropriately qualified staff at site, based on: (i) medical history, (ii) physical examination, (iii) Vital signs (blood pressure, pulse rate), (iv) ECG, (v) clinical laboratory evaluations, (vi) lung function assessment/ spirometry, given written informed consent to participate in the study, motivated to quit smoking (arm A/B) and SLT (arm C/D), respectively, and to switch to HTP (arm A/B), NP (arm C/D) or NRT (all arms) and at least one serious quit attempt, defined as complete abstinence for at least 24 hours.

Additional inclusion criteria for arm A/B (CC smokers) are solus smokers of commercially manufactured combustible cigarettes with a nicotine content ≥5 mg per cigarette for at least 12 consecutive months prior to screening, daily consumption of at least 10 cigarettes per day since at least 12 months prior to screening, verify nicotine use by urinary cotinine test strip (cut-off: ≥200 ng/ml) and verify smoking status by exhaled CO ≥7 ppm at screening and willingness to quit or at least reduce CC consumption by switching to an HTP or NRT product.

Additional inclusion criteria for arm C/D (SLT users) are solus use of smokeless tobacco product with a nicotine content ≥5 mg/g of SLT for at least 12 consecutive months prior to screening, daily consumption of SLT since at least 12 months prior to screening, verify nicotine use by urinary cotinine test strip (cut-off: ≥200 ng/ml), verify smoking abstinence by exhaled CO below 7 ppm at screening and willingness to quit or at least reduce SLT consumption by switching to an NP or NRT product.

Exclusion criteria

Subjects will be excluded from the study if any of the following criteria are met at screening or at Visit 1 are pregnant and/or lactating women or women who intend to get pregnant during the course of the study, current or history of alcohol abuse and/or use of anabolic steroids or drugs of abuse, as judged by the PI, subjects who have a positive urine drugs of abuse or breath alcohol test during screening, subjects with a history or presence of diagnosed hypertension, cardiovascular disease, a chronic respiratory disease like asthma, COPD, chronic bronchitis (either self-reported or diagnosed by the investigator), mental illnesses including major depression, panic disorder, psychosis, or bipolar disorder as diagnosed and treated by psychiatrists or clinical psychologists, regular use of any medication, especially those which may interfere with the cyclooxygenase pathway (eg, anti-inflammatory drugs including aspirin and ibuprofen) or drugs known to be strong inducers/inhibitors of CYP450 enzymes within 14 days prior to screening or during the study; use of hormonal contraceptives (females) and non-prescription pain medication (paracetamol) are permitted, subjects who are positive for hepatitis B, hepatitis C, HIV, subjects with any clinically relevant, abnormal finding during the physical examination, medical history, ECG, lung function and clinical laboratory tests during screening as observed by the PI or appropriately qualified designee, subjects who have been diagnosed or are being diagnosed during the study with any form of malignancy or carcinoma, use of any tobacco/nicotine delivery device (except for own brands of cigarettes (arm A/B) or SLT (arm C/D)) within the last 3 months and use of nicotine replacement therapy or other (smoking) cessation therapies within the last 3 months.

Use and questionnaire recording via mobile app

An app for use recording in the field of tobacco product use and smoking cessation was recently developed by researchers from the University of Catania for the DIASMOKE study (NCT04231838). This app will be used after slight modifications to include questionnaires.

Clinical assessments

Continuous abstinence rate (CAR) will be assessed based on the use recordings from visit 3 to visit 4 (CAR from 1.5 to 3 months) and visit 4 to visit 5 (CAR from 3 to 6 months).

Urine, blood, buccal mucosa, and saliva will be collected at each visit (visit 1 to visit 5). Subjects will collect the first morning urine void at home in the provided urine collection container. Blood samples will be taken at each visit (visit 1 to visit 5) and further processed to receive plasma from vacutainer 1 and washed red blood cells from vacutainer 2. Buccal mucosa cells will be collected on a sterile cytobrush by twirling it on the complete inner cheek for 15 seconds.[13] Saliva will be collected by spitting into 50 ml Falcon tubes.

The chester step test will be conducted at each visit as described in Sykes et al.[14]

Abuse liability of the products will be determined in accordance with the recommendations given by Vansickel et al.[15] For this purpose, appropriate questionnaires will be applied during a pharmacokinetic assessment of nicotine (Nicotine PK) in a subset of 50 subjects from arm A and 50 subjects from arm C. 25 subjects from each arm who completely switched at day 180 (visit 5) of the study to HTP (arm A; n=25) and to NP (arm C; n=25), as well as 25 subjects from each Arm, who reported reduced use of CC (arm A; n=25) and SLT (arm C; n=25) but did not completely switch at day 180 (visit 5) will be selected for nicotine PK assessment at visit 5. Subjects will attend an ad libitum use session of their study product (HTP or NP) following blood draws for PK analysis.

Subjects from arm A will consume one heat stick of their preferred device and stick flavor during the study (based on use recorded in the eDiary) ad libitum for 5 minutes. Number of puffs will be recorded by the clinical staff. The blood samples for nicotine analysis will be collected within 5 minutes prior to initiation of the ad libitum session (i.e., -5 minutes, baseline sample), and approximately 1.5, 3, 4, 5, 6, 7, 10, 15, 45, 90, and 180 minutes after initiation of the ad libitum session. In parallel, subjects will complete four questionnaires to assess product liking and cravings. A 7-point evaluation scale (PES) with 21 questions will be administered at -5, 15 and 180 minutes. The urge to use questionnaire will be completed up to 30 seconds before the next blood draw. Product liking (VAS) and intent to use again (VAS) questionnaires will be completed within approximately 2 minutes after the scheduled blood draw.

Subjects from arm C will consume one NP of their preferred brand and flavor during the study (based on use recorded in the eDiary) for 30 minutes by placing it between the upper lip and gum. The blood samples for nicotine analysis will be collected within 5 minutes prior to initiation of the ad libitum session (i.e., -5 minutes, the baseline sample), and approximately 5, 10, 15, 20, 25, 30, 35, 45, 60, 120, and 180 minutes after initiation of the ad libitum session. Subjects will complete the same questionnaires as those subjects from arm A but at different time points for the PES questionnaire, namely at -5, 45 and 180 minutes.

The schedule of events is summarized in Table 1.

Table 1: Schedule of events.

Assessment	Screening visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
	Day 7	Day 0	Day 14	Day 45	Day 90	Day 180
Informed consent	X					
Inclusion/exclusion criteria	X					
Demographics[1]	X					
Weight, height, and BMI	X					
Medical/surgical history	X					
History of nicotine use	X	X				
Physical examination	X					
Laboratory tests, ECG, blood pressure, and pulse rate	X					
Alcohol test	X					
Urine drug screen	X					
Pregnancy test[2]	X					
Training in eDiary (App)	X	X				
Exhaled carbon monoxide	X					
Urine cotinine screen (dipstick)	X					
Lung function / spirometry	X					
eDiary evaluation		X	X	X	X	X
Provision of urine collection kit	X	X	X	X	X	
Provision of investigational products		X[3]	X[4]	X[4]	X[4]	
Collection of biospecimens (urine, blood, saliva, buccal mucosa)		X	X	X	X	X
Questionnaire evaluation		X	X	X	X	X
Nicotine PK assessment[5]						X
Adverse events		X	X	X	X	X

[1]Demographics include sex, age, ethnicity, and race. [2]Women of childbearing potential only. [3]Choice of products will be offered in the familiarization period. [4]Selected product will be supplied. Changing product brand/flavor type/nicotine strength within the study is allowed. [5]Assessment in subset of arm A and arm C.

Study objectives

The primary objective of this study is to explore the cessation efficacy of HTPs and NPs to quit smoking of CCs and use of SLT, respectively, in comparison to common NRT treatments. Cessation will be determined by abstinence from CC/SLT at 3 months and 6 months (follow-up). Quitting of CC/SLT and exclusive use of HTP/NP will be verified by measuring the appropriate biomarkers of exposure (BoEs) CeVal to detect smoking and distinguish from HTP use, propylene glycol (PG) to detect EC use, anatabine/anabasine (AT/AB) to detect SLT use.

Use behavior, reflected by use per day (e.g. sticks per day, pouches per day or cigarettes per day), will be correlated with BoE representative of different harmful and potentially harmful constituents present in CC and SLT at different time points up to 6 months.

Finally, the abuse liability will be measured by nicotine PK at the end of the study in pre-selected subjects from Arms A and C who completely switched to HTP or NP and subjects who still smoke or use SLT to evaluate possible differences in their Nic PK profiles after ad lib use of NP/HTP. PK will be combined with questionnaires for craving/withdrawal symptoms and product liking. Altogether, these endpoints shall allow a global evaluation of the products potential to reduce CC/SLT use and CC/SLT use-induced harm.

Long-term abstinence at 3 months from CC/SLT by CAR from month 1 to 3 and changes in the following BoE levels will be assessed as primary endpoints: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and N-nitrosonornicotine (NNN) in plasma and urine as well as mercapturic acids (MAs) derived from acrylamide, acrolein, 1,3-butadiene, acrylonitrile, propylene oxide, crotonaldehyde, benzene, styrene, glycidol, and isoprene in urine of users who switch to HTP; NNAL and NNN in saliva of users who switch to NP.

Long-term abstinence at 6 months from CC/SLT by CAR from month 3 to 6 and 7-day point prevalence of abstinence at 3 and 6 months (eDiary) will be assessed as secondary endpoints together with the questionnaires for product liking (Modified Cigarette Evaluation Questionnaire (mCEQ); Modified Smoking Cue Appeal Survey (mSCAS); Product Evaluation Scale (PES); Visual Analogue Scale (VAS)) and withdrawal symptoms (Fagerstrom Test for Nicotine Dependence (FTND); Minnesota Nicotine Withdrawal Scale (MNWS)) (eDiary).

Exploratory endpoints encompass the use per day, nicotine PK, and a larger set of BoEs and biomarkers of potential harm (BoPH) to further exploit the potential reduction in exposure and harm after switching to HTPs and NPs. These include total nicotine equivalents in urine, metabolites of polyaromatic hydrocarbons (PAHs) of benzo[a]pyrene (BaP), pyrene, phenanthrene, and naphthalene in urine, DNA adducts of buccal mucosa in users who switch to NP, MAs of the VOCs of acrylamide, acrolein, 1,3-butadiene, acrylonitrile, propylene oxide, crotonaldehyde, benzene, styrene, glycidol, and isoprene in urine of users who switch to NP, growth differentiation factor 15 (GDF-15) in plasma, 8-iso prostaglandin F2α (8-iso PGF2α), 11-dehydrothromboxane B2 (11-dh-TXB2), 2,3-dinor-thromboxane B2 (2,3-d-TXB2), leukotriene E4 (LTE4) in urine, soluble intercellular adhesion molecule 1 (sICAM-1) in plasma, 8-hydroxydeoxyguanosine (8-OH-dG) in urine, cough (eDiary), chester step test (VO_2max).

Study products

Subjects in arm A can choose between two brands of HTP and a variety of the corresponding HTP sticks from Philip Morris International and British American Tobacco.

Subjects in arm C can choose between different NPs from Altria Client Services, Swedish Match, and British American Tobacco.

Subjects in arm B and arm D can choose between different NRTs from Johnson&Johnson.

Subjects will familiarize with the products and asked to choose their favorite product after 14 days of familiarization at visit 2. They will use their chosen product throughout the study.

Statistical analysis

Descriptive statistics will be provided overall for the parameters collected during the study based on the analysis population.

Analyses regarding group differences will be performed using a significance level of 5% ($p<0.05$). Due to the exploratory nature of the study, no multiplicity corrections will be performed. Analyses may be adjusted for covariates, eg, age and sex.

Compliance with product use will be biochemically verified by analysis of CeVal in washed erythrocytes to detect smoking, urinary PG to assess e-cigarette vaping abstinence and urinary AB/AT to verify compliance with NP use.

DISCUSSION

The efficacy of ECs in promoting smoking cessation has been the subject of numerous studies, yielding conflicting outcomes.[7,16-18] Our recent review detected common flaws in switching and cessation trials which may result in imprecise conclusions, including poor compliance, inadequate product familiarization and limited consideration of product variations to accommodate changing user preferences during longitudinal studies (manuscript under review). This study protocol was meticulously designed to address these limitations and incorporate best practices. The Cochrane review concluded that ECs can help people to quit smoking with high certainty evidence.[7] In contrast, alternative products such as HTPs and NPs have been less studied. Our protocol aims to fill this gap by investigating HTPs and NPs as promising additions to ECs in reducing CC use. HTPs proved their potential in Japan where they were introduced as early as 2014, and their use prevalence raised up to 12% in 2022.[19,20] HTPs show strongly reduced emissions of harmful constituents in the aerosol compared to CC smoke.[21,22] Consequently, they can be categorized as a lower risk product in the risk-continuum of tobacco and nicotine products and thus represent another option, alongside ECs, in the context of inhalable product alternatives for harm reduction.[23,24] Tobacco-free nicotine pouches share almost none of the harmful constituents as present in tobacco smoke as they only consist of nicotine and few other ingredients like maltitol, cellulose as fillers, sodium carbonate as pH adjusters, flavorings, and the sweetener acesulfame.[25] As such, they have a high potential for harm reduction especially for users of toxic SLT.

Many longitudinal studies in the field suffer from poor compliance, emphasizing the need for strict biochemical verification using specific biomarkers tailored to distinguish between different product types. Most studies to date use exhaled eCO to verify smoking.[26,27] With a half-life of 2-3 hours, eCO can only detect short-term CC use with no verification of the subjects' use behavior during the course of a longitudinal study.[28] The implementation of hemoglobin adducts like CeVal is well suited for the detection of CC and HTP use over several months due to the long half-life of Hb adducts in blood (manuscript under revision). This allows us to monitor their use with high sensitivity, even if subjects visit the clinic at time intervals of one to three months.

Another strength of our design is the bioanalysis of a large panel of BoE to characterize the exposure to harmful constituents after switching to HTP/NP relative to CC/SLT. The non-targeted analysis of DNA adducts in

buccal mucosa of switchers to NPs, the BoPH and the clinical measures of respiratory and cardiovascular function will add important information regarding the absolute exposure and the overall harm to consumers of these products.

Additionally, we consider the influence of the attractiveness of the product by allowing subjects to choose from popular brands, flavors, and nicotine strengths during a 14-day familiarization period. An innovative aspect of our approach lays in the additional nicotine PK assessed at the last visit in subjects who quit smoking and SLT use completely as well as those who only reduced CC and SLT use. The PK data will be correlated with the questionnaire results and compared between the groups to observe potential differences in the PK profiles based on consumer preferences and the extent to which they have reduced their CC/SLT consumption.

CONCLUSION

Considering the rigorous study compliance ensured during the trial, we expect statistically significant outcomes that will provide a precise assessment of the efficacy of HTP and NP in promoting smoking and SLT cessation. The PK analysis conducted at the last study visit shall yield a robust understanding of the causality between individual nicotine delivery and product liking influencing quit success rates. Biomarker and clinical analysis will complement the data providing a comprehensive evaluation of harm reduction associated with these products.

This adaptable study protocol, incorporating essential elements for a comprehensive risk assessment of CF-N/T-P, can be applied to various product categories with minor adjustments, such as modifying the panel of biomarkers and tailoring of questionnaires. Recognizing that technical or budgetary constraints may limit the use of the full set of endpoints in any study, the protocol serves as a guiding framework for researchers. It aims to facilitate the generation of high certainty evidence to address this critical research question, ensuring the robustness and relevance of future investigations in this field.

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Conflict of interest: None declared
Ethical approval: The study will be approved by the Institutional Ethics Committee

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