STUDY PROTOCOL

Evaluation of breath odour associated with use of conventional Cigarettes vs e-cigarettes

- Pilot Study -

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Abbreviations

AE	Adverse Event
AR	Adverse Reaction
CRF	Case Report Form
DMP	Data Management Plan
DMR	Data Management Report
DVP	Data Validation Plan
eCRF	Electronic CRF
IRB	Independent Institutional Review Board
GCP	Good Clinical Practice
ICD	International Classification of Diseases and Related Health Problems
ICH	International Conference on Harmonization
MedDRA	Medical Dictionary for Regulatory Activities
pCRF	Paper CRF
PP	Per Protocol
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SD	standard deviation
SP	Safety Population

1 Study Design

1.1 Objective

The purpose of this pilot study is to assess if there is a difference in oral breath odour following use of cigarettes or use e-cigarettes in healthy subjects that regularly smoke cigarettes or use e-cigarettes. Breath odour will be assessed by trained odour judges before and after a single use of the respective product. Assessments will be also performed on a non-smoking control group.

The study will be reviewed by an IRB for ethical approval.

1.2 Efficacy Assessment

The following efficacy assessment(s) will be performed:

- Sensory evaluation of oral odour - Intensity scoring
- Sensory evaluation of oral odour - Hedonic scale

1.3 Type of Product(s)

Commercially available cigarettes and e-cigarettes, see table 1.

1.4 Study Outline

- Exploratory
- Open-label
- Inter- and intra-individual comparison.

1.5 Type of Statistics

- Comparison between all treatments for sensory evaluations of odour

1.6 Assessment Times

t0: Before product use

t1: 5 minutes ± 2 minutes after product use

2 Test Materials

Table 1: Table of Treatments

Code/proDERM	Product/Code/Sponsor/Concentration
A	e-Cigarette – Vype™ ePen III, single variant
B	Cigarette – N491 (a commercial product that has been produced without branding to enable blind testing)
C	Non-smokers

The test material(s) will be commercially available products, as supplied by the Sponsor. Test and control materials, if applicable, will be identified by a proDERM code (e.g. "A", "B" etc.) and/or by a Sponsor identification code in a separate delivery form. Test materials will be used undiluted, as specified in the delivery form. The Sponsor will identify potential hazard of the test materials supplied by the sponsor or his designee(s) associated with this study. The test materials will be stored at room temperature in the containers in which they are received unless otherwise specified in the delivery form. Test material remaining at the conclusion of the study will be destroyed at least 6 weeks or returned to the Sponsor after issuance of the final report unless requested otherwise. Devices (e-Cigarettes) are to be returned to the Sponsor at the end of the study unless advised to destroy.

2.1 Climatic Conditions

The investigation will take place at room temperature and relative humidity.

2.2 Test Area

Breath (Oral cavity)

2.3 Application Volume, Mode and Frequency

Subjects will be instructed to smoke one cigarette / or use an e-cigarette for 8 puffs in their normally used routine.

- Users of e-cigarettes will be asked to use test product A.
- Cigarette smokers will be asked to use the supplied cigarettes (B).

2.4 Accountability and Destruction

The responsibility for the test product(s) accountability at the study site rests with proDERM. Records of the test product's receipt and disposition of unused product(s) or alternative return to the Sponsor will be maintained. proDERM will ensure that the test product(s) will be used as directed by this protocol and product information sheets supplied by the Sponsor.

2.5 Duration of Treatment

1 day per subject

3 Study Population

3.1 Subject Numbers

A minimum of 55 subjects will be screened for this test from the general population of Schenefeld/Hamburg and the neighboring communities so that about 33 subjects are expected to be randomized and 30 subjects are expected to finish in the study. All subjects will have a complete understanding of the test procedure.

3.2 Selection of Subjects

All below mentioned inclusion, exclusion criteria and instructions for the subjects will be checked by a questionnaire before the start of the study and during the study. Conditions developing during the course of the study listed in the exclusion criteria and instructions as well as protocol deviations do not necessarily lead to the subject's exclusion. The investigator decides whether the subject is still eligible.

The subjects will be instructed to inform the study site in case of medical problems or changes in therapies.

Inclusion Criteria

- Written Informed Consent to participate in the study
- Willingness to actively participate in the study and to come to the scheduled visits
- Subjects must demonstrate the ability to comprehend the Informed Consent Form (ICF), be able to communicate well with the Investigator or their appropriately qualified designee, understand and comply with the requirements of the study, and be judged suitable for the study in the opinion of the Investigator or their appropriately qualified designee
- Female or male
- 21 to 60 years of age
- Average oral hygiene (tooth brushing at least twice a day)
- Good general health as judged by the Investigator or their appropriately qualified designee based on their medical history
- 1/3 of the panel: regular cigarette smoker (manufactured filter cigarettes, excluding menthol cigarettes; have smoked for at least 3 consecutive years prior to screening; typically smoke at least 10 cigarettes per day) with CO-level >7 ppm at Screening
- 1/3 of the panel: regular e-cigarette consumer r, willing to use a test e-cigarette (uses a minimum of 160 puffs per day for more than 6 months prior to screening, uses only e-cigarettes) with CO-level ≤6 ppm at Screening
- 1/3 non-smokers (have never smoked (<100 cigarettes in their life and none within 1 year prior to screening) and willing to continue not to smoke or use any form of tobacco for the duration of the study (exhaled CO level ≤ 6ppm).

Exclusion Criteria

- Female subjects: Pregnancy or lactation
- Drug addicts, alcoholics
- AIDS, HIV-positive or infectious hepatitis if known to the subjects
- Conditions which exclude a participation or might influence the test reaction/evaluation
- Participation or being in the waiting period after participation in similar cosmetic and/or pharmaceutical studies
- Any pathological change of the oral mucosa or gingival (e.g. allergic reactions, ulceration candidiasis)
- Active caries
- Current periodontitis or non-physiological tooth mobility (mild gingival inflammation is accepted)
- Usage of medication, food supplementation, homeopathic therapy which could cause malador on the judgement of the dentist (like homeopathic therapy, antibiotics)
- Xerostomia caused by medication like (anorectica, anticholinergica, antidepressiva, antipsychotica) on the judgement of the dentist
- Ongoing dental treatment or any other medical treatment of the oral cavity (e.g.oral appliances)
- Oral prophylaxis treatment within the last week and during the study
- Current chronic heartburn or other chronic stomach problems

- Current intake of any antibiotics within 14 days prior to screening
- 3 days before and during the study no pain medication at all
- Usage of "roll your own" tobacco cigarettes, chewing tobacco or snuff/snus, dual-users of a cigarette and e-cigarette, or dual-users of a cigarette and tobacco heating product
- Employees and immediate relatives of the tobacco industry and the clinical site.
- History of or acute tuberculosis

Instructions for Subjects

Instructions prior to the Start of the Study:

The subjects will be instructed **not** to…

- drink alcohol 2 day before the scheduled visit.

The subjects will be instructed to…

- Cigarette smokers and e-cigarette users only:

  Smoke/vape according their normal routine during the day prior to their scheduled visit

  Smoke at least one cigarette or inhale 8 puffs of their e-cigarette within 2 hour prior to their scheduled visit on Day 1

Instructions throughout the Course of the Study:

The subjects will be instructed **not** to…

- drink alcohol 2 days prior to the scheduled visit on Day 1.
- drink coffee, eat spicy food, garlic, onion, alcohol within the last 2 day prior to the scheduled visit on Day 1.
- use lozenges, mouthwashes, chewing gums, etc. 12 hours prior to the scheduled visit on Day 1.
- use any products that might affect the olfactory sense (e.g. body lotions, shampoos, hair spray, perfume and/or lipstick) in the morning prior to the assessment on Day 1.

The subjects will be instructed to…

- brush their teeth as usual in the morning of assessment Day1.
- Cigarette smokers and e-cigarette users only: Smoke at least one cigarette or inhale 8 puffs of their e-cigarette within 2 hour prior to their scheduled visit on Day 1
- eat and drink as usual but until at least 2 hours prior to the assessments on Day 1 and then refrain from eating or drinking (except of sipping water is accepted) during the study
- On assessment day 1 subjects will be supplied a toothbrush and toothpaste and be asked to brush their teeth for 2 minutes 2 hours before baseline assessment
- All subjects will take their normal brand of cigarettes or e-cigarette plus e-liquid with them so that this information can be recorded in the CRF and images taken

3.3 Prior and Concomitant Diagnosis and Therapy

Any treatment that is not listed in the exclusion criteria is allowed at the discretion of the Investigator. As a rule, the use of hormonal contraceptives (if taken for at least three months prior to the first application and continuously during the study), and medications for regulation of thyroid function or blood pressure are allowed.

Prior and concomitant therapy and changes thereof will be documented in the CRF (trade name or generic name, reason, start and end of intake, dosage and route).

All diseases which occur during the study period are to be treated according to standard medicinal practice. The disease and the treatment will be documented in the CRF. If the treatment is not allowed during the study, the subject will be excluded from further participation.

3.4 Selection of Odour judges

6 trained odour judges will be selected. All below mentioned inclusion, exclusion criteria and instructions for the odour judges will be checked by a questionnaire before the start of the study and during the study. Conditions developing during the course of the study listed in the exclusion criteria and instructions as well as protocol deviations do not necessarily lead to the subject's exclusion. The investigator decides whether the subject is still eligible.

Inclusion Criteria

- Male and female
- Non-smokers (have never smoked (<100 cigarettes/oral tobacco products in their life and none within 1 year prior to screening) and willing to continue not to smoke or use any form of tobacco for the duration of the study (exhaled CO level ≤ 6ppm).
- From 18 to 60 years of age
- Written Informed Consent Form to participate in the study
- Willingness to actively participate in the study and to come to the scheduled visits
- Willingness not to drink alcohol within the last 2 days prior to the scheduled visits
- Willingness not to use products that might affect the senses (e.g. body lotions, shampoos, perfume and lipstick) 12 hours prior to the malodour assessments
- Willingness to abstain from consuming tea, coffee, juices, chewing gum/menthol confectionary 2 hours prior to the study etc. and only to drink water during the assessments

Exclusion Criteria

- Pregnancy or lactation
- Drug addicts, alcoholics
- AIDS or infectious hepatitis if known to the subjects
- Conditions which exclude a participation or might influence the test reaction/evaluation for example upper respiratory tract infection
- Consuming spicy food, garlic, onion or alcohol within the last 2 days prior to malodour assessments

4 Informed Consent

For studies with subjects the following procedure will be effective: Each subject must provide the Investigator/Investigator's designee with written informed consent prior to enrollment in the study. They will receive a copy of the informed consent statement.

The original signed copy for each subject participating in the study will be retained in the Investigator's study records. The consent statement shall meet the requirements of any applicable regulation. The Investigator or the Investigator's designee will inform each subject as to the purpose and nature of the study in compliance with applicable regulations.

The subjects are informed that they can withdraw their consent at any time and that they can stop their participation in this study at any time without disadvantages. They are also informed that proDERM can also prematurely terminate his participation in the study, for example for administrative reasons.

5 Test Procedure

5.1 Description of Test Procedure

Screening:

The subjects will come to the Study Site. They will be informed about the study by a dentist and give their written consent. Medical history and concomitant therapies will be documented. A dentist will perform an oral and dental examination. The eligibility of each subject will be evaluated according to the inclusion/exclusion criteria by a dentist. Exhaled CO-levels will be measured. Subjects fulfilling the inclusion/exclusion criteria will be enrolled into the study. Images of the normally used brand of cigarettes or e-cigarettes/e-liquid will be taken for documentation purposes and the brand will be documented.

Day 1:

The subjects will return to the study site.

Exhaled CO-levels will be measured; subjects who do not match the criteria will be excluded. Subject will brush their teeth for 2 minutes using the supplied toothpaste and toothbrush.

First baseline (t0) organoleptic scores will be assessed 2 hours +/- 15 minutes after brushing by 6 experienced and trained odour judges. Then, the smoking subjects will use the test product at the study site (outside of the test institute building) according to Sponsor's product instructions and under supervision of a technician. Non-smokers will have a waiting period. Smoking and e-cigarette subjects will return to the study room and 5 minutes ± 2 min after use of product, the organoleptic assessments will be started for all subjects.

5.2 Test Schedule

A scheme of the test procedure is given as Appendix 1 to Protocol.

5.3 Investigational Method(s)

The following investigational method(s) will be performed:

ORAL ODOUR SCORING BY ODOUR JUDGES

The assessments will be performed by 6 experienced, trained odour judges.

Before each odour assessment subjects keep their mouth closed for 30 sec and then expire slowly through a hole. On the opposite side of a non-transparent separation wall the trained odour judge smells and assigns a score in a blind and unbiased way independent from each other odour judge. The order of odour judges should always remain the same.

INTENSITY SCORING FOR SENSORY EVALUATION OF ORAL ODOUR

The odour judges will perform the assessment of oral odour of smoke of the participating subjects, using the following score:

0	=	Smoke odour cannot be detected
1	=	Questionable smoke odour, barely detectable
2	=	Slight smoke odour, exceeds the threshold of smoke odour recognition
3	=	Smoke odour is definitely detected
4	=	Strong smoke odour
5	=	Very strong smoke odour

HEDONIC SCALE FOR SENSORY EVALUATION OF ORAL ODOUR

The odour judges will perform the assessment of oral odour of the participating subjects, using the following 9-point hedonic scale with respect to perceivable odour:

-4 - extremely unpleasant
-3 - very much unpleasant
-2 - moderately unpleasant
-1 - slightly unpleasant
0 - neither pleasant nor unpleasant
1 - slightly pleasant
2 - moderately pleasant
3 - very much pleasant
4 - extremely pleasant

MEASUREMENT OF EXHALED CARBON-MONOXIDE LEVELS

The exhaled CO-level will be measured using a calibrated device provided purchased from Bedfont piCOTM Smokerlyzer®.

- 1 measurement per assessment time

IMAGES

To document the normally used brand of cigarettes or e-cigarettes, images with a Canon G9X camera will be taken. The images will not be edited nor embedded into the eCRF.

- 1 image per enrolled subject

6 Adverse Events

6.1 Definitions

Adverse Reaction

According to ICH GCP adverse reactions (**ARs**) are defined as "all noxious and unintended responses to a medicinal product related to any dose". For clinical studies with consumer products the following interpretation is adopted: The phrase "responses to a medicinal product" means that a causal relationship between the test material and an adverse event (**AE**) is at least a reasonable possibility, i.e. the relationship cannot be ruled out. Therefore, an AE which the **physician** classifies as having a causal relationship to the test material of at least 'possible' (i.e. possible, probable) is defined as an AR.

Adverse Event

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

For clinical studies with consumers the following interpretation is adopted: An Adverse event (AE) is any adverse, noxious or pathological change in a patient or clinical investigation subject compared to pre-existing conditions, that occurs during any phase of a clinical trial including pre-treatment, run-in, wash-out, or follow-up periods. An AE is defined as being independent of assumption of any causality (e.g. to trial or concomitant therapy or primary or concomitant disease or trial design).

Serious Adverse Event

The term "serious" is based on event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. According to ICH GCP a serious adverse event (SAE) is any untoward medical occurrence that at any dose:

results in death,

is life-threatening,

requires inpatient hospitalization or prolongation of existing hospitalization,

results in persistent or significant disability/incapacity,

is a congenital anomaly/birth defect.

6.2 Recording and Reporting

All adverse events (excluding those parameters being scored as part of the protocol) will be documented in the study records.

Subjects will be questioned for AEs on each follow-up visit using non leading questions. The obligation to document AEs starts with enrolment of the subject in a study until 5 days following last administration of test product (if reported by the subjects).

Details recorded will include the nature of the adverse event, onset date/time, duration, severity, outcome and relationship to test product. Any adverse event requiring medical attention will be referred to the appropriate proDERM medical personnel.

In case of ARs it is the responsibility of the Investigator to inform the Sponsor within 3 working days at the latest. ARs will also be reported in the final report.

All SAE will be reported during the course of the study. After awareness of the SAE, the Investigator will report within 24 hours or on the following working day the SAE to the Sponsor. Additionally, the SAE will be reported in the final report.

7 Safety Criteria

All safety criteria adverse events and changes in concomitant therapy will be recorded and reported in the final report.

8 Ethics Committee and Regulatory Approvals

Consumer products have to be safe for testing in human subjects. European legislation has therefore produced general requirements on the minimum quality of such consumer products. Commercially available consumer products can be considered per se as safe for human testing as the products have been commercially launched and are in use by the general population. We consider this valid for this specific study, because the cigarette brand and e-cigarette/e-liquid to be assessed are commercially available in the European Union and a number of other countries. The principle requirements of the Declaration of Helsinki will be taken into account to protect the rights, safety and well-being of subjects participating in the study.

Before initiating the trial, the Investigator will have written and dated full approval from an independent institutional review board (IRB) for the protocol, protocol amendment(s), if applicable, and the subject informed consent form.

As this is a clinical study with consumer products regulatory approval is not required.

Nevertheless the study will be reviewed by an independent institutional review board (IRB) for ethical approval on Sponsor's request.

9 Insurance

The Sponsor has taken out an insurance policy with an established insurance company in accordance with current regulatory requirements to cover their liability in the event of damage or injury resulting from the research project.

An insurance is filed for the subjects (name and address of the insurance company and insurance number will be shown in the Informed Consent Form) to guarantee indemnity for the unlikely case of damage occurring as a result of participation in the study.

10 Subject Privacy

The Sponsor and the Investigator affirm and uphold the principles of respecting subjects' privacy. Throughout this trial, all data forwarded to the Sponsor will only be identified by an identification number.

The Investigator and the subjects agree that representatives of the Sponsor or representatives of authorities who are bound to secrecy will be allowed to review individual-related data to verify the correct conduct of the study.

11 Data Quality and Quality Control

11.1 Source Data

No subject files will be used in this study. Source data will be documented in pCRFs (e.g. in- and exclusion criteria, subject diaries), eCRFs (e.g. medical history, termination form) and/or other source documents (e.g. recordings from automated instruments, laboratory notes).

11.2 In Process Quality Control

In process control for consistency and plausibility of data to be analyzed (e.g. instrumental measurements, visual scores) and not to be analyzed data (e.g. investigational product, inclusion-, exclusion criteria, demographic data, screening enrolment-log, written informed consent, dates of subject's visits to the center, subject's diary) will be performed by the Investigator or his/her designee.

11.3 External Monitoring

The Sponsor or a designated person (Monitor) may, upon appointment, perform monitoring visits at any time during and after the study. The Investigator and his/her staff will co-operate with the sponsor and be available during monitoring visits to answer questions and to provide any missing information for a reasonable period of time. Monitoring personnel is granted access to all source data relevant to the study and the subjects that take part at the study. Since there will be no subject's file used in this study the CRF will be the source data, because of direct data entry. Monitoring visits will be documented with a monitoring report and forwarded to the Investigator.

12 Sponsor Inspections/Audits

The Sponsor may, upon appointment, visit the Study Center at any time during and after the study.

13 Data Management

13.1 Data Management

A CRF will be specifically designed for the recording of the data which are to be collected according to this protocol. In this study, an electronic and/or paper CRF will be used for the majority of the data recordings. Data from instrumental measurement may be recorded separately.

For this study, a Data Management Plan (DMP), a Data Validation Plan (DVP) and a Data Management Report (DMR) will be generated. International classifications like ICD-10 or MedDRA will not be used.

13.2 Recording of Data

All data for each subject to be generated according to the protocol must be recorded completely. All data to be listed that were not captured electronically will be entered manually or by scanning into the data base or imported from other electronic sources. The completeness and consistency of the data entries will be checked by data management as part of the data management process.

Self-evident corrections will be performed by the data management. Otherwise implausible or missing data must be explained and/or corrected by the Investigator.

The database will be locked after completion of all checks and possible corrections.

14 Statistical Considerations / Evaluation

14.1 Randomization

Randomization Type

Not applicable.

Unblinding and Derandomization

Not applicable.

14.2 Sample Size Determination

As this is an exploratory study, no sample size calculation was performed. The sample size was chosen based on the experience of proDERM with this type of study.

14.3 Analysis Population

For this study the following analysis populations will be defined:

Screening Population: Includes all subjects who provided at least written informed consent and reason for termination are documented.

Safety Population (SP): Includes all subjects who were enrolled into the study. Safety will be done on all available data for safety population.

Per Protocol (PP) population: Includes all subjects randomized in the study in accordance with both the in- and exclusion criteria who finished the study according to protocol without major protocol violations and who will not have withdrawn their consent.

Major violations may be for example:

- inclusion / non-inclusion criteria not respected,
- interfering therapy,
- poor compliance to study treatment administration or protocol requirements,
- unblinding.

All protocol violations are judged by the Investigator whether deviations are regarded as minor or major and thereby whether a subject has to be excluded from PP population.

14.4 Analysis of Data

The statistical analysis is specified in detail in the statistical analysis plan (SAP). If the content of the SAP deviates from the proceeding as described in the protocol, this is documented in the SAP, together with reasons and consequences. For this study the following analysis will be defined:

Missing Data

No replacement of missing data will be performed and the affected assessments will be regarded as lost for analysis.

Demographic Data

Demographic variables (age, gender, smoker or non-smoker, type of normally consumed tobacco or, e-cigarette) will be given for each defined analysis population. Data will be summarized using frequency distributions (number and percentage) for categorical/ordinal variables and mean, standard deviation and range for continuous variables.

Data Listing

Medical history (concomitant diagnoses and therapies) and reasons for termination will be listed for all subjects in the screening population.

Safety and tolerability data (AEs, concomitant medication) will be listed for the Safety Population.

The assessment time at t0 (before product use) will be defined as Baseline.

Sensory evaluation of oral odour (intensity scoring and hedonic scale):

- Raw Data will be listed by treatment, assessment time and odour judge for all subjects in PP population.
- Mean scores over all graders will be given per subject, treatment and assessment time.
- Differences to Baseline will be calculated per subject, treatment and assessment time on mean scores.

Measurement of exhaled carbon-monoxide levels will not be listed but reordered in an excel document.

Descriptive Data Analysis

Sensory evaluation of oral odour (intensity scoring and hedonic scale):

- N, mean, standard deviation, median, minimum, maximum and 95% confidence limits will be given for calculated values by treatment and assessment time for each parameter.
- The mean values of calculated values (e.g. mean values and differences to baseline) over subjects will be presented in bar charts by treatment and assessment time with 95% confidence intervals for each parameter.

Statistical Data Analysis

The statistical analysis for the sensory evaluations is based on the PP Population only.

Due to the explorative character of the study, no adjustment for multiplicity will be done.

Primary Hypotheses

Comparison of treatment A and B will be performed on differences to Baseline values for each parameter separately by a one-sided t-Test for independent samples with a significance level of 0.025 (alpha).

The following hypothesis will be tested for the intensity scoring:

$H_0: \mu_A \geq \mu_B$

$H_1: \mu_A < \mu_B$

The following hypothesis will be tested for the hedonic scale:

$H_0: \mu_A \leq \mu_B$

$H_1: \mu_A > \mu_B$

Where μA denotes the mean difference to Baseline for treatment A and μB denotes the mean difference to Baseline for treatment B.

Secondary Hypotheses

A significance level of 0.05 (alpha) is chosen for the secondary analysis.

- Comparisons of treatments (A vs. C, B vs. C) will be performed on differences to Baseline values for each parameter separately by a t-Test for independent samples.
- Comparisons of assessment times will be performed on mean scores for each treatment and parameter separately by a paired t-Test.

The computation of the statistical data will be carried out with a commercially available statistics program (SAS for Windows).

15 Deviations / Protocol Modifications

Any deviation from this Protocol will be discussed with the Sponsor and appropriately documented. The Investigator is responsible for any deviation from the protocol and documentation of this deviation in the study records and the final report.

If it becomes necessary to make a change to the approved Protocol (i.e. signed), the Investigator and the Sponsor will agree to the change before it is implemented. The change and the reason for it will be documented in an amendment. If a change is necessary on an emergency basis, the Sponsor will be notified as soon as possible after the action has been taken.

16 Final Report

16.1 Contents

The report will include the following:

- Adverse events (if any)
- Serious adverse events (if any)
- Identification of study personnel
- Any protocol deviations and/or additional remarks
- Adverse reactions (if any) that cannot be described by employed scoring scales
- Interpretation of data
- Figures illustrating the main results
- Tables with main results
- List of Subjects enrolled and completing the study, and subjects not analyzed, if any, with reasons. Subject numbers only will be detailed.
- Complete listing of raw data for all valid subjects
- Listing of calculated values
- Statistical analysis
- QA statement
- Images of cigarettes- /e-cigarettes-brand will be provided on USB stick and will not be included in the final report

16.2 Corrections or Additions to the Final Report

Corrections or additions to the approved (i.e. signed) version of the final report will be in the form of a discernible second version of the final report or by an amendment. This amendment will clearly identify the part of the final report that is being added to or corrected and will be signed and dated by the person responsible.

17 Quality Assurance

The study will be conducted, the analysis performed and the report prepared approximating the main principles of Good Clinical Practice (GCP), and in accordance with relevant national regulations, and approved protocol(s). The principle requirements of the Declaration of Helsinki will be taken into account to protect the rights, safety and well-being of subjects participating in the study.

If, after a study is underway, it becomes necessary to make changes to the approved protocol(s), the revisions and reasons for changes will be documented. Appropriate corrections, additions, or deletions that are made to the study documentation will be dated, explained (if necessary), and initialed by responsible personnel. Processing of clinical research data and data analysis will involve verification of data integrity and statistical procedures. The final analysis will be done on the basis of the complete data of valid cases, reasons for data exclusion will be given. The final analysis will serve as a basis for the study report.

An independent quality assurance unit will be engaged to audit clinical research studies to identify, evaluate and communicate the state of compliance with applicable protocol(s), and the quality system of proDERM. The audit program approved by management will ensure that audits will be performed at regular intervals. Objective evidence pertaining to the correct conduct of studies, the performance of quality control measures for completeness and accuracy of research data, data

analysis, and reporting of results will be given and reported to management and to the Investigator, as appropriate.

18 Archiving

All raw data pertaining to the study will be available for inspection by the Sponsor for compliance monitoring. In addition, specified scientists designated by the Sponsor may, upon appointment, examine any set of data. The study report, and informed consents of the subjects related to the study will be stored for at least 10 years. All other study related data will be stored for at least 3 years.

Administrative Structure

Sponsor: R&D, British American Tobacco, Centre Regents Park Road, Southampton, U.K.

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