Titolo del Protocollo: A 12-weeks open label, non-inferiority trial comparing HnB products vs ECs in terms of efficacy and adoption rates, acceptability, tolerability, and tobacco harm reduction in healthy smokers, not motivated to quit.	**Versione**: 1.0 26 Settembre 2017
Prodotto: Sigaretta elettronica/HnB (Heat-not-Burn)	**Sponsor**: AOU Policlinico Vittorio Emanuele - University of Catania Centro per la cura e la prevenzione del tabagismo
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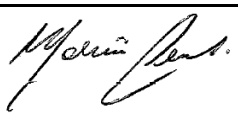
Maurizio Ceracchi	Statistician	08/07/2020	
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VERSION HISTORY

Version	Date	Description of the Change(s)
Final 1.0	03 January 2020	First Final version of the document
Final 1.1	04 June 2020	Section 4: PP population definition added. Section 5.2: description of derived datasets added. Sections 6.8 and 7.5: VO2MAX analysis for the Step Test added. Section 7: specification of the analysis populations added Section 7.1: definition of "Continuous Quitter" added Section 7.2.1: Russell Standard analysis included Section 7.2.2: section modified Section 8: specification of the analysis populations added Appendix 1: Index of the TFLs fixed All the mock tables fixed.
Final 2.0	08 July 2020	Section 4: PP V7 population definition added. Section 9.7: new section included. Appendix 5: DRM Minute included.

INDEX

1 INTRODUCTION

This Statistical Analysis Plan (SAP) is based on the study Protocol Final Version (dated September 26, 2017). The main objective of this document is to provide guidance for the production of the analyses of all the variables included in the Database of the study which will be frozen when the last data is validated in accordance with the Fullcro's SOPs.

This document will also provide guidance for the production of the Statistical Report (SR), the in-text tables, the in-text listings and the Tables/Figures/Listings (TFLs) which will be part of the SR as Appendices (they will regard the data of all patients and all variables included in the Database).

The Statistical analysis will begin once the data validation is complete and will proceed according to this plan. In case of deviations from this SAP, explanations in the Statistical Report (SR) will be provided.

This document refers to the analysis of all the variables included in the Clinical Data Base.

All details on the decisions made during the Data Review Meeting (DRM) will be described in an *ad hoc* section in Version 2.0 of the present document that will be produced before the Database freezing.

1.1 References

- ✓ ICH E6_R1_Guideline GCP
- ✓ SOP_DM 04_Convalida dei sistemi
- ✓ SOP_DM_03 Data Management
- ✓ SOP_IT_01 Gestione dell'infrastruttura IT

1.2 List of abbreviations and acronyms

AE Adverse Event

BoBE Biomarkers of Biological Effects

BP Blood Pressure

DRM Data Review Meeting

EC Electronic Cigarette

eCO Exhaled breath Carbon monoxide

GCP Good Clinical Practice

HnB Heat-not-Burn

HR Heart Rate

ITUQ Intent to use questionnaire

LOCF Last Observation Carried Forward

mCEQ Modified Cigarette Evaluation Questionnaire

PT Preferred Term

SR Statistic Report

SAE Serious Adverse Event

SOC System Organ Class

2 STUDY DESCRIPTION

2.1 Introduction

This is a 12-weeks, open label, non-inferiority trial comparing HnB products vs. ECs in terms of efficacy, adoption rate and acceptability, tolerability, and tobacco harm reduction in healthy smokers, not motivated to quit, randomized (1:1) to switch to one of these products. Evaluation of efficacy, adoption rates, acceptability and tolerability will be also recorded at 24 weeks (follow-up).

2.2 Study Objectives

The primary objective of this study is to compare the efficacy of HnB and EC, in terms of quit rates at week 12, by self-reporting abstinence from classic cigarette [validated by an Exhaled breath Carbon monoxide (eCO) measurement ≤10ppm)].

The secondary objectives are:

1) to compare the smoking reduction derived from the use of HnB and EC, intended as a 50% reduction in the number of conventional cigarette/day at week 12, defined through self-reporting;
2) to compare the adoption rate, and adherence to product use [by collecting (empty) refill bottles and used heathsticks on a daily basis, verified by a study diary filled daily by the subject];
3) to compare the acceptability of HnB and of EC, through the assessment of product satisfaction, risk perception, effects on craving and nicotine withdrawal, product preferences, subjective and sensorial effects by:
   a) Modified Cigarette Evaluation Questionnaire (mCEQ) adapted for EC and HnB users;
   b) three of 8 items of "Smoking Cue Appeal" adapted for EC and HnBusers;
   c) "Intent to use questionnaire" (ITUQ) – items 4-6;
   d) PRI-P CC Perceived Health Risk scale (for classic cigarette)
   e) PRI-P RRP Perceived Health Risk scale (for reduced risk products)
   f) percentage of choice of a particular subtype of heatstick (HnB) or e-liquid.
4) to compare the tolerability of HnB and EC, in terms of: self-reported adverse and serious adverse events by study participants, vital signs (BP, HR and body weight) measurements.
5) to compare the tobacco harm reduction between HnB and EC, in terms of:
   a) changes in Biomarkers of Biological Effects (BoBE) such as: eCO in the exhaled breath (i.e. eCO), step test values;

b) measurement of 14 selected Biomarkers of Exposure (BoE) in spot urine samples of study participants:

1 tobacco-specific nitrosamine, total NNAL (NNK); 8 volatile organic toxicants (derivates of mercapturic acid, MA): 2-hydroxyethylmercapturic acid (HEMA) also known as ethylene oxide, 2-hydroxy-3-butenyl- mercapturic acid and isomers (MHBMA) also known as 1,3-butadiene, 3-hydroxy-1-methyl propyl- mercapturic acid (HMPMA) also known as crotonaldehyde, 3-hydroxypropylmercapturic acid (3-HPMA) also known as acrolein, S-phenylmercapturic acid (S-PMA) also known as benzene, 2-carbamoylethylmer- capturic acid (acrylamide mercapturic acid (AAMA) also known as acrylamide (AAMA and GAMA), 2- cyanoethylmercapturic acid (CEMA) also known as acrylonitrile, 2-hydroxypropylmercapturic acid (2-HPMA) also known as propylene oxide; 4 polycyclic aromatic hydrocarbons: naphthalene, fluorine, phenanthrene, pyrene (1-OHP); cotinine; creatinine.

c) self-perception of "Tobacco Harm Reduction process" through changes in quality of life scores (EQ-5Dquestionnaire);

6) to compare the reliability of HnB and EC, in terms of incidence and kind of malfunctioning events, through self-reporting.

2.3 Study Design

This is a 12-weeks, open label, non-inferiority trial.

2.4 Product Administered

Participants randomized in study group with HnB (group A) will receive one iQOS kit and a 12 weeks supply of heatsticks; those in study with EC (group B) will receive one JustFog Starter Kit and a 12 weeks supply of e-liquids.

2.5 Study Plan

This study has been structured considering a Screening visit (V0), a Baseline visit (V1), a week 1 visit, a week 2 visit, a week 4 visit, a week 8 visit, a week 12 visit. A prospective evaluation of efficacy, adoption rates, acceptability and tolerability will be also recorded at 24-weeks, through a follow-up visit (V7).

3 SAMPLE SIZE

Sample size determination (better detailed in the study protocol) for no-inferiority testing is based on the assumptions that:

1) expected quit rates based on most recent EC literature is about 20-25% and

2) that differences in quit rates between products under investigation should not exceed 10-15% (as per non- inferiority definition).

For sample size definition, Farrington-Manning Score Test for Proportion Difference was used, assuming:

- asymptotic normal distribution, upper one-tailed
- alpha 0.05
- nominal power 0.80

Thus:

- Null Proportion Diff. -0.15
- Ref Proportion 0.25
- N per group: 104

According to these hypotheses the required number of participants per study arm was 104. Hence 220 participants, 110 per group, had to be included.

4 ANALYSIS POPULATIONS

In the study protocol the analysis populations were not defined.

As for the safety analyses

the **Safety population**, defined as all the subject who assumed at least one dose of the product, will be considered for the safety analyses.

As for the efficacy analyses

The **Intention-To-treat** population, defined as all the subjects who assumed at least one dose of the study product and had at least one observation after the baseline, will be considered for all the other analyses.

The **Per-Protocol** population, defined as all the subjects that completed all the visits.

The **Per-Protocol V7** population (see DRM Minute in Appendix 5), defined as all the subjects that completed all the visits, included the Follow-up visit (Visit 7).

5 GENERAL INFORMATION FOR THE ANALYSES

According to the study protocol the statistical analysis will be descriptive in nature.

All the data will be described using standard descriptive statistics, i.e. n, missing, mean, standard deviation, (25th, 50th, 75th) percentiles for numerical variables. As for the categorical variables, frequency tables with count and percentage will be used. In the core of the Statistical Report, the continuous variables will be presented as mean values ± standard deviation (SD) or median value and interquartile range [IQR], and categorical variables as numbers and percentages. The descriptive analyses will be presented by group. As indicated in the study protocol, for the primary endpoint, the quit rate at 3 months in the experimental study group will be calculated with a non-inferiority threshold of 15%. The quit rates will be evaluated on an intention-to-treat basis: subjects known to have failed will be considered as treatment failures in the primary analysis along with subjects lost to follow-up.

All the analyses will be performed using SAS® Vers. 9.4.

5.1 Premature discontinuation and missing data managing

Patients with missing values will not be excluded from the analysis, their data will not be replaced; frequency of missing data will be given for all analyzed variables. For possible inferential analyses, the LOCF (Last Observation Carried Forward) will be adopted.

5.2 Derived datasets

At the moment of the preparation of the present SAP, three derived dataset is forecasted to be created, i.e. the one containing the MedDRA codes for the Adverse Events, the one containing the information about the adherence to the device and the one containing the analysis populations, that will be prepared after the database freezing. In case additional derived dataset will be needed during the analysis phase, details will be provided in the Statistical Report.

6 PATIENTS CHARACTERISTICS AT BASELINE

6.1 Patients' Disposition

The patients' enrolment will be summarized (Appendix 2: Table D.1) and listed (Appendix 3: Listing D.1). Enrolled, completed and not completed patients, including the reasons, will be summarized with frequency and percentages.

6.2 Inclusion and Exclusion criteria

The data of the Inclusion and exclusion criteria for all the screened patients will be listed (Appendix 3: Listings D.2 and D.3).

6.3 Demographics and smoking habits

The following demographic and baseline variables will be analyzed: age, gender at birth and education (Appendix 2: Table D.2a). As for the smoking habits, a dedicated table, in which details are presented as summary and frequency tables, will be prepared. Number of cigarettes per day will be summarized (Appendix 2: Table D.2b).
These data will also be listed (Appendix 3: Listing D.4, Listing D.5).

6.4 Medical History

The medical conditions will be coded with the MedDRA dictionary (last available version) and be analyzed as previous and present Medical History using the variable "Ongoing" for creating the two sets of data. The past and present incidence of the different conditions by system organ class and preferred term will be described with frequencies and percentages (Appendix 2: Tables D.3 and D.4a). Present Medical History is defined "In treatment" if the disease is still being treated at the time of the signing of the informed consent and "Not in treatment" otherwise. Present Medical History In treatment and Not in treatment will be summarized through further tables. (Appendix 2: Tables D.4b and D.4c)
These data will also be listed (Appendix 3: Listings D.6, D.7, D.8, D.9).

6.5 Patients' Characteristics and Vital Signs at Baseline

The values of each vital sign variable, i.e. Height, Weight, BMI, FatM, FatP, Total Body Water, Fat Free Mass, Body Muscle Mass, Body Bone Mass, Metabolica Age, Visceral Fat, PAS, PAD and HR will be summarized at baseline in each group through n, missing, mean, standard deviation, (25th, 50th, 75th) percentiles (Appendix 2: Table D.5). These data will also be listed (Appendix 3: Listing S.2).

6.6 Urine collection and storage

Urine collection and storage will be summarized in each group with frequency table regarding to the device given to the subject and with descriptive statistics for the containers delivered (Appendix 2: Table D.6). These data will also be listed (Appendix 3: Listing D.10).

6.7 Fagestorm test for nicotine dependence

The results of the Fagestorm test for nicotine dependence (FTCD) will be presented as frequencies and percentages for the single questions and total scores derived from the questionnaire through n, missing, mean, standard deviation and 25th, 50th, 75th percentiles (Appendix 2: Table D.7). These data will also be listed (Appendix 3: Listing D.11).

6.8 Step test

The values of Step Test, i.e Baseline, Step 1 to 5 and will be summarized by HR and SpO2 in each group through n, missing, mean, standard deviation and 25th, 50th, 75th percentiles (Appendix 2: Table D.8a). The other items at baseline, i.e. Baseline condition recovery time, Stop time and V02MAX (see Section 7.5 for the definition) will be summarized similarly (Appendix 2: Table D.8b). These data will also be listed (Appendix 3: Listing D.12)

6.9 Device delivery

The data of the device delivery regarding the preferred flavor of chopstick chosen, the device's functioning and the patient training for the device will be summarized in each group through frequency tables for all screened subjects (Appendix 2: Table D.9) and will be listed (Appendix 3: Listings D.13).

7 STATISTICAL ANALYSES OF THE EFFICACY ENDPOINTS

The analyses od the primary and secondary endpoints will be carried out of both the ITT and PP populations. Moreover, as for the Step Test and the Quality of Life (i.e. EQ-5D), a further analysis in the subpopulation od the "Continuous Quitter" will be presented.

7.1 Analysis of primary endpoint

The primary endpoint aims to compare the efficacy of HnB and EC in terms of quit rates at week 12 by means a non-inferiority threshold of 15%.

A "Continuous Quitter" is defined as a subject who has a number of conventional cigarette/day equal to zero from Visit 4 to Visit 6. The Farrington-Manning Score Test for Proportion Difference will be used for comparing the quit rates of the two groups. The SAS® PROC FREQ with the METHOD=FM option will be used. The quit rates of the two groups, along with the relevant 95% Confidence Intervals, will be summarized in Table E.1 (Appendix 2).

7.2 Analysis of secondary endpoints

The secondary endpoints refer to the smoking reduction, the compliance to the study product and the acceptability of HnB or EC. The analyses to be performed on the smoking reduction and the adoption rate will be presented in sections 7.2.1 and 7.2.2 respectively. As for the latter, the endpoint will be analyzed through the product satisfaction, the risk perception, the effects on craving and nicotine withdrawal, the product preferences, the subjective and sensorial effects and presented in the sections from 7.2.3 to 7.2.8. In sections 7.3 and 7.4 the results of the analyses on the EQ-5D and the step test by visit will be presented.

7.2.1 Smoking reduction derived from the use of HnB and EC

The smoking reduction derived from the use of HnB and EC, will be computed at each visit. The analysis will be presented considering both the definition of "Reducer" included in the study protocol and the so called "Russell Standard" (clinical) for outcome assessment in clinical trials of smoking cessation treatments.

As for the protocol definition, a subject will be classified as "Reducer" if at least a 50% reduction in the number of conventional cigarette/day at each visit will be observed. The results will be summarized as frequency table. The comparison between the two groups will be performed at each visit with the chi-square test. The results will be included in Table E.2a (Appendix 2).

As for the Russell Standard analysis, due to the fact that the study endpoint was a 12 weeks, a small deviation was adopted. In fact, the timepoint considered in the Russell Standard is 52 week. In our case, the 12 week and the 24 week (i.e. the Follow-up observation) will be considered for the analysis. The results will be included in Table E.2b (Appendix 2).

7.2.2 Adoption rate and adherence to product use

The adoption rate and adherence to the product use will be analyzed on the basis of the subject's diary. The Sponsor will collect information relevant to the number of days of observation (i.e. last visie day – Informed Consent day) and the total of days of the device use. Those information will be collected in a derived dataset. The adherence to the producet will be computed in term of rate according to the following formula:

$$Rate = \frac{Total\ days\ of\ device\ use}{Total\ days\ of\ study\ observation}$$

A subject is defined as "compliant" if the rate is at least a 90%. The comparison between the two groups will be performed with the chi-square test. The results will be included in Table E.3 (Appendix 2).

7.2.3 Modified Cigarette Evaluation Questionnaire

The modified Cigarette Evaluation Questionnaire (mCEQ) will be presented as descriptive summary table by visit. Acceptability of HnB and of EC will be analized through the assessment of several questionnaires. The analyses will be presented in three multi-item domains (i.e. Smoking Satisfaction, Psychological Reward and Avversion) and two single-item domains (i.e. Cravin Reduction and Enjoiment of Respiratory Tract Sensation). Changes from the Baseline Visit to all the subsequent study visits will be also generated. The results will be included in Table E.4a1 (Appendix 2).

The t-test will be carried out on the differences at final visit to baseline. In case the normality assumption is not verified, the corresponding non parametric test will be adopted. The results will be included in Table E.4a2 (Appendix 2). These data will also be listed (Appendix 3: Listing E.2).

7.2.4 Smoking Cue Appeal Questionnaire

The Smoking Cue Appeal Questionnaire will be presented as frequency table of the scores for each question included in the questionnaire. Each table will compare, for each visit in which the questionnaire was administered, the Hnb group and the EC group frequency of answers (Table E.4b1).

The t-test will be carried out on the differences at final visit to baseline. In case the normality assumption is not verified, the corresponding non parametric test will be adopted (Table E.4b2). These data will also be listed (Appendix 3: Listing E.3).

7.2.5 Intention To Use Questionnaire (ITUQ)

Intention To Use Questionnaire (ITUQ) will be presented as frequency table of the scores for each question included in the questionnaire. Each table will compare, for each visit in which the questionnaire was administered, the Hnb group and the EC group frequency of answers (Table E.4c1).

The t-test will be carried out on the differences at final visit to baseline. In case the normality assumption is not verified, the corresponding non parametric test will be adopted (Table E.4c2). These data will also be listed (Appendix 3: Listing E.4).

7.2.6 Risk Perception (PRI-P CC)

Risk Perception (PRI-P CC) Questionnaire will be presented as frequency table of the scores for each question included in the questionnaire. Each table will compare, for each visit in which the questionnaire was administered, the Hnb group and the EC group frequency of answers (Table E.4d1).

The t-test will be carried out on the differences at final visit to baseline. In case the normality assumption is not verified, the corresponding non parametric test will be adopted (Table E.4d2). These data will also be listed (Appendix 3: Listing E.5).

7.2.7 Risk Perception (PRI-P RRP)

Risk Perception (PRI-P RRP) Questionnaire will be presented as frequency table of the scores for each question included in the questionnaire. Each table will compare, for each visit in which the questionnaire was administered, the Hnb group and the EC group frequency of answers (Table E.4e1)

The t-test will be carried out on the differences at final visit to baseline. In case the normality assumption is not verified, the corresponding non parametric test will be adopted Table E.4e2). These data will also be listed (Appendix 3: Listing E.6).

7.2.8 Device Delivery

Device delivery will be summarized with frequency table for each group. The results will be included in Table E.4f. These data will also be listed (Appendix 3: Listing D.9).

7.3 Biomarker of Biological Exposure

Exhaled breath Carbon monoxide (eCO) will be summarized by timepoint using descriptive summaries as described in Section 5. The parameter will be measured across all the study visits.

Changes from the Baseline Visit to all the subsequent study visits will be also generated. Table E.5 will include the summaries of the data by group. The t-test will be carried out on the changes from baseline to last visit. In case the normality assumption is not verified, the corresponding non parametric test will be adopted.

7.4 EQ-5D

The Euro Quality of Life Questionnaire (EQ-5D) will be presented as descriptive summary table by visit. Acceptability of HnB and of EC will be analized through the assessment of several questionnaires. The analyses will be presented throught the five dimensions (i.e. Mobility, Self-Care, Usual Activities, Pain/Discomfort, Anxiety/Depression) and a Visual Analogue Scale (EQ VAS). Changes from the Baseline Visit to all the subsequent study visits will be also generated. The results will be included in Table E.6 (Appendix 2).

The t-test will be carried out on the differences at final visit to baseline. In case the normality assumption is not verified, the corresponding non parametric test will be adopted. The results will be

included in Table E.4a2 (Appendix 2). These data will also be listed (Appendix 3: Listing E.1). The analysis will be presented by all subjects and "Continuous Quitters".

7.5 Step test by visit

The Step test data will be presented as descriptive summary table by visit. The seven items regarding Heart Rate and Oxygen Saturation (i.e. Baseline, Step 1 to 5 and Baseline condition recovery time) will be analysed by HR and SpO2. The two items,(i.e. Stop time and V02MAX, will by analysed using the same methods (Table E.7a). In details, the latter, is the result of the so called "Chester Step Test" who was computed for each subject at site and reported in the eCRF.

An inferential analysis will be carried out on the changes from baseline by item. The results will be presented in Table E.7b. The data will also be listed (Appendix 3: Listing D.8). The analysis will be presented by all subjects and "Continuous Quitters".

8 STATISTICAL ANALYSES OF SAFETY ENDPOINTS

The Safety will be evaluated on all the subjects in the study through the analysis of the Adverse Events (AEs), i.e. those events, occurred during the study, which could be related or not related with the devices, and the Vital Signs.

No methods for replacing missing values will be applied. The Safety population will be considered for this analysis, therefore all the listings will be built with reference to the full set of enrolled patients.

As for the Vital Signs, a further analysis in the subpopulation od the "Continuous Quitter" will be presented.

8.1 Extent of Exposure and study duration

The study duration (from Baseline to last Visit) will be summarized in Table S.1 and listed in term of baseline date, final visit date and time interval in days in Listing S.1.

8.2 Adverse Events

Adverse Events will be coded using the MedDRA dictionary (last version available). All the events (i.e., all the conditions which started or deteriorated after the Informed Consent signing) observed during the study will be listed (Listing S.2).

The following summary tables (N, %), replied by Group, will be presented:

- ✓ Overview of AEs: number of subjects with any AEs, study product related AEs, serious AEs, study product related serious AEs, AEs leading to withdrawal, AEs leading to death (Table S.2a).

- ✓ Incidence of AEs by SOC and PT (Table S.2b).
- ✓ Incidence of serious AEs by SOC and PT (Table S.2c)
- ✓ Incidence of study treatment related AEs (defined as suspected with respect to product relationship in the opinion of the Investigator) by SOC and PT (Table S.2d).
- ✓ Incidence of AEs leading to study withdrawal by SOC and PT (Tables S.2e).
- ✓ Incidence of AEs by severity and by SOC and PT (Table S.2f).

8.3 Vital signs

Each Vital Sign, i.e. Weight, Height (at baseline only), BMI, Body Fat (FatM and FatP) Total Body Water, Fat Free Mass, Bone Body Mass, Matabolic Age, Visceral Fat, PAS, PAD and HR will be summarized by timepoint using descriptive summaries as described in Section 5.
All the variables will be measured across all the study visits. Changes from the Baseline Visit to all the subsequent study visits will be also generated.
Table S.3 will include the summaries of the Vital Signs by group. A listing will be also produced (Listing S.2).

8.4 End study information

Table S.4 (Appendix 2) will include all the information recorded in the End Study Form of the eCRF, i.e. completeness of the study and frequency table of the reasons for the study interruption. As for the study duration (variable "End Study Date") the analysis will be presented in Table S.1 (see Section 9.1). The data will also be listed in Listing S.3 (Appendix 3).

9 DESCRIPTION OF THE STATISTICAL REPORT AND GENERAL FORMAT OF TFLS

9.1 Presentation of the Data

Tables and listings will be produced in accordance with the principles outlined by the ICH E3 guideline "Note for Guidance on Structure and Content of Clinical Study Report" (CPMP/ICH/137/95).
Quantitative variables will be summarized using the SAS UNIVARIATE or SUMMARY procedures.
Categorical variables will be summarized using the SAS FREQ procedure.

Tables and listings will be produced in accordance with the principles outlined by the ICH E3 guideline and numbered as follows (where n is a sequential number):

- ✓ Table D.n/Listing Dn for the Baseline characteristics and data collected during the visits other than the Safety ones;
- ✓ Table E.n for the Efficacy data (the Efficacy data will be listed in one of the other three set of listings);
- ✓ Table S.n/Listing S.n for the Safety data.

9.2 Tables, Graphs and Listings Layout

The statistical analyses will be performed by the Biostatistician in charge in Fullcro S.r.l.. All tables, figures and listings of the Statistical Report will be generated using the software package SAS® Ver. 9.4.

As for the format of the SAS® outputs (tables and listings), all the pages will contain the following information:

- ✓ Protocol identification.
- ✓ Name of the Sponsor.
- ✓ Specification of document version.
- ✓ Date when the output was generated.

In addition, the following recommendations shall be fulfilled:

- ✓ titles should be fully explicative for the content of the tables/listings;
- ✓ all abbreviations used in any part of the output must be defined in footnotes.

As for character and spacing of the SAS® outputs, the following recommendations shall be fulfilled:

- ✓ SAS Monospace, Size: 8 or 7 (7 or 6 for listings);
- ✓ Margins (for both vertical and horizontal outputs):
  - Upper 2.5 cm;
  - Lower 1.0 cm;
  - Left 2.5 cm;
  - Right 1.0 cm.

Post-text tables and post-text listings will be included as appendices in the SR.
The post-text tables will be numbered according to presented in the list included in Appendix 1.
The rule for numbering the post-text listings will be as for post-text tables, but a prefix PL will be added.

9.3 General Description of the Statistical Report (SR)

The Statistical Report (SR) of this study will follow the recommendations given in the guideline ICH topic E3.

American English will be used for writing the SR.

The core of the SR will be written with Microsoft Word®; all data summaries (tables) and listings will be prepared by using SAS® Version 9.4. In-text tables will be generated with Word. A complete list of the in-text tables is not provided in this document. However, the standard format of these tables must be compliant with the sample illustrated below.

Panel 1: Sample of in-text tables

Table # Sample of in-text tables

Variable	Group HnC	Group EC
Continuous variable (unit):		
N	xx	xx
Missing	xx	xx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)
Median	xx.x	xx.x
Q1 – Q3	xx.x – xx.x	xx.x – xx.x
Categorical variable – n (%):		
Class 1	xx (xx.x)	xx (xx.x)
Class 2	xx (xx.x)	xx (xx.x)
…		
Class k	xx (xx.x)	xx (xx.x)

Source: Post-text table # and/or listing #

It is mandatory that every in-text table be cross-referenced with the corresponding post-text tables and listings. In addition, the titles must be auto-explicative and all acronyms must be described in footnotes. When relevant, the time of assessment must be specified.

9.4 Responsibilities

The SR of the present study will be written by the Biostatistician in charge in Fullcro S.r.l. and approved by the Sponsor's representative.

9.5 Structure of the Statistical Report

The SR will be divided in sections, titled and numbered.

9.6 Format of the Statistical Report

All the pages of the SR core (text) should contain the following information:

- ✓ Protocol identification;
- ✓ Page number;
- ✓ Name of the Sponsor;
- ✓ Specification of document version and date;
- ✓ Information on the level of restriction.

As for character and spacing of the SR core (text), the following recommendations shall be fulfilled:

- ✓ Century Gotic (type size 10);
- ✓ Line spacing 1.5;
- ✓ Justified;
- ✓ Margins as for vertical format:
    - Upper 4.0 cm;
    - Lower 4.2 cm;
    - Left 2.5 cm;
    - Right 2.0 cm.
- ✓ Margins as for horizontal format:
- ✓ Upper 3.5 cm;
- ✓ Lower 2.0 cm;
- ✓ Left 4.2 cm;
- ✓ Right 4.0 cm.
- ✓ Header 2.0 cm (from upper edge of page);
- ✓ Footer 2.5 cm (from lower edge of page).

9.7 Decision taken during the DRM

As described in the Minute included in Appendix 5, on the 10th June 2020 the Data Review Meeting of the study was held in call conference manner. All the decision taken were reported in the Minute. The main decision regarded the analysis population definition. All the protocol violations were evaluated, therefore the following populations were approved by the team:

Population **Safety**: 220

Population **Intention-To-Treat**: 217

Population **Per-Protocol**: 193

Population **Per-Protocol V7**: 177

10 APPENDIX

Appendix 1 List of TLFs

Appendix 2 Mock Tables: Tables

Appendix 3 Mock Table: Listings

Appendix 4 Study Flow Chart

Appendix 5 DRM Minute

APPENDIX 1
List of Tables/Listings to be generated for the Statistical Report

Table number	Baseline Characteristics - Table title
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Table D.2a	Summary of Demographic and Screening/Baseline Characteristics by group
Table D.2b	Summary of Smoking Information at Screening/Baseline by group
Table D.3	Summary of Past Medical History by group
Table D.4a	Summary of Present Medical History by group
Table D.4b	Summary of Present Medical History Not in Treatment by group
Table D.4c	Summary of Present Medical History in Treatment by group
Table D.5	Summary of Patients' Characteristics/Vital Signs at Screening/Baseline by group
Table D.6	Summary of Urine Collection And Storage at Screening/Baseline by group
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Table number	Efficacy Analyses - Table title
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Table E.1b	Summary of the Primary End-point: Quit Rate at final visit comparison
Table E.2	Summary of the Secondary End-point. Smoking reduction derived from the use of HnB and EC at week 12
Table E.3	Summary of the Secondary End-point. Adoption rate and adherence to product use at week 12
Table E.4a1	Summary of the Secondary End-point. mCEQ Questionnaire (scores) by visit
Table E.4a2	Summary of the Secondary End-point. mCEQ Questionnaire. Inferential analysis on the mean changes at final visit from baseline
Table E.4b1	Summary of the Secondary End-point. Smoking Cue Appeal Questionnaire (questions) by visit
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Table E.4c2	Summary of the Secondary End-point. ITUQ Questionnaire. Inferential analysis on the mean changes at final visit from baseline
Table E.4d1	Summary of the Secondary End-point. Risk Perception (PRI-P CC) Questionnaire (scores) by visit
Table E.4d2	Summary of the Secondary End-point. Risk Perception (PRI-P CC). Inferential analysis on the mean changes at final visit from baseline
Table E.4e1	Summary of the Secondary End-point. Risk Perception (PRI-P RRP) Questionnaire (scores) by visit

Table E.4e2	Summary of the Secondary End-point. Risk Perception (PRI-P RRP) Questionnaire. Inferential analysis on the mean changes at final visit from baseline
Table E.4f	Summary of the Secondary End-point. Device delivery by group
Table E.5	Summary of the Secondary Endpoint. Biomarkers of Biological Exposure (BoBE) - eCO (ppm)
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Table number	Safety Analyses - Table title
Table S.1	Summary of Exent of Exposure and Compliance by group
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Table S.3	Summary of Vital Signs by Visit
Table S.4	Summary of End Study Information

Listing number	Listing title
Listing D.1	Patients' Disposition
Listing D.2	Eligibility: Inclusion Criteria
Listing D.3	Eligibility: Exclusion Criteria
Listing D.4a	Demographic Data
Listing D.4b	Smoking Information
Listing D.5	Past and Present Medical History
Listing D.6	Urine collection and Storage
Listing D.7	Fagerstrom test for nicotine dependence
Listing D.8	Step Test

Listing D.9	Device Consignment
Listing D.10	Product use recording
Listing E.1	EQ-5D
Listing E.2	mCE Questionnaire
Listing E.3	Smoking Cue Appeal Questionnaire
Listing E.4	ITUQ Questionnaire
Listing E.5	Risk Perception (PRI-P CC) Questionnaire
Listing E.6	Risk Perception (PRI-P RRP) Questionnaire
Listing S.1	Extent of Exposure and Study Duration
Listing S.2	Adverse Events
Listing S.3	Vital Signs

APPENDIX 2
Mock tables: Tables

BASELINE CHARACTERISTICS

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Table D.1 Patients Accountability by group
Population: All enrolled subjects

	Group HnB	Group EC
Enrolled	XXXX (XX.X%)	XXXX (XX.X%)
Screening failures	XXXX (XX.X%)	XXXX (XX.X%)
Safety	XXXX (XX.X%)	XXXX (XX.X%)
Intention-To-Treat	XXXX (XX.X%)	XXXX (XX.X%)
Reason for withdrawal:		
Reason 1	XX (XX.X%)	XX (XX.X%)
Reason 2	XX (XX.X%)	XX (XX.X%)
Reason 3	XX (XX.X%)	XX (XX.X%)

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For further information see Listing X.X

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Table D.2a Summary of Demographic and Screening/Baseline Characteristics by group
Population: Safety

		Group HnB N=XXXX	Group EC N=XXXX
Age at the time of IC Signature Date	N	XX	XX
	N missing	XX	XX
	Mean	XX.X	XX.X
	Std. deviation	XX.X	XX.X
	Median	XX.X	XX.X
	Q1-Q3	X.X - XX.X	X.X - XX.X
Gender at birth	Male	XX (XX.X%)	XX (XX.X%)
	Female	XX (XX.X%)	XX (XX.X%)
Education	Primary School	XX (XX.X%)	XX (XX.X%)
	Secondary School	XX (XX.X%)	XX (XX.X%)
	High School	XX (XX.X%)	XX (XX.X%)
	University	XX (XX.X%)	XX (XX.X%)

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For further information see Listing D.4

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Table D.2b Summary of Smoking Information at Screening/Baseline by group (1 of 2)
Population: Safety

		Group HnB	Group EC
		N=XXXX	N=XXXX
N. cigarettes/die Screening	N	XX	XX
	N missing	XX	XX
	Mean	XX.X	XX.X
	Std. deviation	XX.X	XX.X
	Median	XX.X	XX.X
	Q1-Q3	X.X - XX.X	X.X - XX.X
How long has the subject smoked at least 10 cigarettes/die? (years)	N	XX	XX
	N missing	XX	XX
	Mean	XX.X	XX.X
	Std. deviation	XX.X	XX.X
	Median	XX.X	XX.X
	Q1-Q3	X.X - XX.X	X.X - XX.X
Years of Smoking (years)	N	XX	XX
	N missing	XX	XX
	Mean	XX.X	XX.X
	Std. deviation	XX.X	XX.X
	Median	XX.X	XX.X
	Q1-Q3	X.X - XX.X	X.X - XX.X
N. of quit attempts	N	XX	XX
	N missing	XX	XX
	Mean	XX.X	XX.X
	Std. deviation	XX.X	XX.X
	Median	XX.X	XX.X
	Q1-Q3	X.X - XX.X	X.X - XX.X
Exhaled breath Carbon monoxide (eCO) Screening (ppm)	N	XX	XX
	N missing	XX	XX
	Mean	XX.X	XX.X
	Std. deviation	XX.X	XX.X
	Median	XX.X	XX.X
	Q1-Q3	X.X - XX.X	X.X - XX.X

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For further information see Listing D.5

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Table D.2b Summary of Smoking Information at Screening/Baseline by group (2 of 2)
Population: Safety

		Group HnB	Group EC
		N=XXXX	N=XXXX
Brand of used cigarettes	Brand#1	XX (XX.X%)	XX (XX.X%)
	Brand#2	XX (XX.X%)	XX (XX.X%)
	. . . . .		
	Brand#n	XX (XX.X%)	XX (XX.X%)

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For further information see Listing D.5

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Treatment: HnB vs EC

Table D.3 Summary of Past Medical History by group
Population: Safety

System Organ Class	Preferred Term	Group HnB N=XXXX	Group EC N=XXXX
SOC #1	TOTAL	XX (XX.X%)	XX (XX.X%)
	PREFERRED TERM #1	XX (XX.X%)	XX (XX.X%)
	PREFERRED TERM #2	XX (XX.X%)	XX (XX.X%)
	. . . . .		
	PREFERRED TERM #n	XX (XX.X%)	XX (XX.X%)
SOC #2	TOTAL	XX (XX.X%)	XX (XX.X%)
	PREFERRED TERM #1	XX (XX.X%)	XX (XX.X%)
	PREFERRED TERM #2	XX (XX.X%)	XX (XX.X%)
	. . . . .		
	PREFERRED TERM #n	XX (XX.X%)	XX (XX.X%)
. . . . .	TOTAL	XX (XX.X%)	XX (XX.X%)
	PREFERRED TERM #1	XX (XX.X%)	XX (XX.X%)
	PREFERRED TERM #2	XX (XX.X%)	XX (XX.X%)
	. . . . .		
	PREFERRED TERM #n	XX (XX.X%)	XX (XX.X%)
SOC #n	TOTAL	XX (XX.X%)	XX (XX.X%)
	PREFERRED TERM #1	XX (XX.X%)	XX (XX.X%)
	PREFERRED TERM #2	XX (XX.X%)	XX (XX.X%)
	. . . . .		
	PREFERRED TERM #n	XX (XX.X%)	XX (XX.X%)

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The percentages are computed considering the total of the past medical history abnormalities by group
Coded using MedDRA dictionary (<last available version>)
For further information see Listing X.X

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Table D.4a Summary of Present Medical History by group
Population: Safety

System Organ Class	Preferred Term	Group HnB N=XXXX	Group EC N=XXXX
SOC #1	TOTAL	XX (XX.X%)	XX (XX.X%)
	PREFERRED TERM #1	XX (XX.X%)	XX (XX.X%)
	PREFERRED TERM #2	XX (XX.X%)	XX (XX.X%)
	. . . . .		
	PREFERRED TERM #n	XX (XX.X%)	XX (XX.X%)
SOC #2	TOTAL	XX (XX.X%)	XX (XX.X%)
	PREFERRED TERM #1	XX (XX.X%)	XX (XX.X%)
	PREFERRED TERM #2	XX (XX.X%)	XX (XX.X%)
	. . . . .		
	PREFERRED TERM #n	XX (XX.X%)	XX (XX.X%)
. . . . .	TOTAL	XX (XX.X%)	XX (XX.X%)
	PREFERRED TERM #1	XX (XX.X%)	XX (XX.X%)
	PREFERRED TERM #2	XX (XX.X%)	XX (XX.X%)
	. . . . .		
	PREFERRED TERM #n	XX (XX.X%)	XX (XX.X%)
SOC #n	TOTAL	XX (XX.X%)	XX (XX.X%)
	PREFERRED TERM #1	XX (XX.X%)	XX (XX.X%)
	PREFERRED TERM #2	XX (XX.X%)	XX (XX.X%)
	. . . . .		
	PREFERRED TERM #n	XX (XX.X%)	XX (XX.X%)

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The percentages are computed considering the total of the current medical history abnormalities by group
Coded using MedDRA dictionary (<last available version>)
For further information see Listing X.X

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Table D.4b Summary of Present Medical History not in Treatment by group
Population: Safety

System Organ Class	Preferred Term	Group HnB N=XXXX	Group EC N=XXXX
SOC #1	TOTAL	XX (XX.X%)	XX (XX.X%)
	PREFERRED TERM #1	XX (XX.X%)	XX (XX.X%)
	PREFERRED TERM #2	XX (XX.X%)	XX (XX.X%)
	. . . . .		
	PREFERRED TERM #n	XX (XX.X%)	XX (XX.X%)
SOC #2	TOTAL	XX (XX.X%)	XX (XX.X%)
	PREFERRED TERM #1	XX (XX.X%)	XX (XX.X%)
	PREFERRED TERM #2	XX (XX.X%)	XX (XX.X%)
	. . . . .		
	PREFERRED TERM #n	XX (XX.X%)	XX (XX.X%)
. . . . .	TOTAL	XX (XX.X%)	XX (XX.X%)
	PREFERRED TERM #1	XX (XX.X%)	XX (XX.X%)
	PREFERRED TERM #2	XX (XX.X%)	XX (XX.X%)
	. . . . .		
	PREFERRED TERM #n	XX (XX.X%)	XX (XX.X%)
SOC #n	TOTAL	XX (XX.X%)	XX (XX.X%)
	PREFERRED TERM #1	XX (XX.X%)	XX (XX.X%)
	PREFERRED TERM #2	XX (XX.X%)	XX (XX.X%)
	. . . . .		
	PREFERRED TERM #n	XX (XX.X%)	XX (XX.X%)

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The percentages are computed considering the total of the current medical history abnormalities by group
Coded using MedDRA dictionary (<last available version>)
For further information see Listing X.X

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Table D.4c Summary of Present Medical History in Treatment by group

Population: Safety		Group HnB	Group EC
System Organ Class	Preferred Term	N=XXXX	N=XXXX
SOC #1	TOTAL	XX (XX.X%)	XX (XX.X%)
	PREFERRED TERM #1	XX (XX.X%)	XX (XX.X%)
	PREFERRED TERM #2	XX (XX.X%)	XX (XX.X%)
	. . . . .		
	PREFERRED TERM #n	XX (XX.X%)	XX (XX.X%)
SOC #2	TOTAL	XX (XX.X%)	XX (XX.X%)
	PREFERRED TERM #1	XX (XX.X%)	XX (XX.X%)
	PREFERRED TERM #2	XX (XX.X%)	XX (XX.X%)
	. . . . .		
	PREFERRED TERM #n	XX (XX.X%)	XX (XX.X%)
. . . . .	TOTAL	XX (XX.X%)	XX (XX.X%)
	PREFERRED TERM #1	XX (XX.X%)	XX (XX.X%)
	PREFERRED TERM #2	XX (XX.X%)	XX (XX.X%)
	. . . . .		
	PREFERRED TERM #n	XX (XX.X%)	XX (XX.X%)
SOC #n	TOTAL	XX (XX.X%)	XX (XX.X%)
	PREFERRED TERM #1	XX (XX.X%)	XX (XX.X%)
	PREFERRED TERM #2	XX (XX.X%)	XX (XX.X%)
	. . . . .		
	PREFERRED TERM #n	XX (XX.X%)	XX (XX.X%)

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The percentages are computed considering the total of the current medical history abnormalities by group
Coded using MedDRA dictionary (<last available version>)
For further information see Listing X.X

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Table D.5 Summary of Patients' Characteristics/Vital Signs at Baseline by group. (1 of n)
Population: <Safety/Continuous Quitter>

Parameter	Statistic	Group HnB	Group EC
		N=XXXX	N=XXXX
Parameter #1	N	XX	XX
<um>	N missing	XX	XX
	Mean	XXX.X	XXX.X
	Std. deviation	XX.X	XX.X
	Median	XXX.X	XXX.X
	Q1-Q3	XX.X - XXX.X	XX.X - XXX.X
Parameter #2	N	XX	XX
<um>	N missing	XX	XX
	Mean	XXX.X	XXX.X
	Std. deviation	XX.X	XX.X
	Median	XXX.X	XXX.X
	Q1-Q3	XX.X - XXX.X	XX.X - XXX.X
. . . . .	N	XX	XX
<um>	N missing	XX	XX
	Mean	XXX.X	XXX.X
	Std. deviation	XX.X	XX.X
	Median	XXX.X	XXX.X
	Q1-Q3	XX.X - XXX.X	XX.X - XXX.X
Parameter #n	N	XX	XX
<um>	N missing	XX	XX
	Mean	XXX.X	XXX.X
	Std. deviation	XX.X	XX.X
	Median	XXX.X	XXX.X
	Q1-Q3	XX.X - XXX.X	XX.X - XXX.X

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For further information see Listing X.X

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Table D.6 Summary of Urine Collection And Storage at Screening/Baseline by group
Population: Safety

		Group HnB	Group EC
		N=XXXX	N=XXXX
Instruction for urine collection and storage given to the subject	Yes	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)
N. of unire containers Delivered	N	XX	XX
	N missing	XX	XX
	Mean	XX.X	XX.X
	Std. deviation	XX.X	XX.X
	Median	XX.X	XX.X
	Q1-Q3	XX.X - XXX.X	XX.X - XXX.X
Has the subject returned the urine to the center? (Baseline)	Yes	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)

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For further information see Listing X.X

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Table D.7 Summary of Fagerstrom test for nicotine dependence by group
Population: Safety

		Group HnB	Group EC
		N=XXXX	N=XXXX
Quanto tempo dopo il risveglio fuma la prima sigaretta?	Entro 5 min	XX (XX.X%)	XX (XX.X%)
	Dopo 6-30	XX (XX.X%)	XX (XX.X%)
	Dopo 31-60 min	XX (XX.X%)	XX (XX.X%)
	Dopo 60 min	XX (XX.X%)	XX (XX.X%)
Trova difficile non fumare nei luoghi dove è vietato?	Si	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)
A quale sigaretta farebbe più fatica a rinunciare?	Alla 1^ del mattino	XX (XX.X%)	XX (XX.X%)
	A qualsiasi altra	XX (XX.X%)	XX (XX.X%)
Quante sigarette fuma al giorno?	Più di 30	XX (XX.X%)	XX (XX.X%)
	21-30	XX (XX.X%)	XX (XX.X%)
	11-20	XX (XX.X%)	XX (XX.X%)
	10 o meno	XX (XX.X%)	XX (XX.X%)
Tende a fumare più spesso nelle prime ore dopo il risveglio che durante il resto del giorno?	Si	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)
Fuma anche se è malato e deve rimanere a letto la maggior parte del giorno?	Si	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)

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For further information see Listing X.X

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Table D.8a Summary of Step Test, Step1 to Step 5, at Baseline by group
Population: Safety

		Group HnB		Group EC	
		Heart Rate	SpO2	Heart Rate	SpO2
Step 1	N	XX	XX	XX	XX
	N missing	XX	XX	XX	XX
	Mean	XX.X	XX.X	XX.X	XX.X
	Std. deviation	XX.X	XX.X	XX.X	XX.X
	Median	XX.X	XX.X	XX.X	XX.X
	Q1-Q3	X.X - XX.X	X.X - XX.X	X.X - XX.X	X.X - XX.X
. . . . .	N	XX	XX	XX	XX
	N missing	XX	XX	XX	XX
	Mean	XX.X	XX.X	XX.X	XX.X
	Std. deviation	XX.X	XX.X	XX.X	XX.X
	Median	XX.X	XX.X	XX.X	XX.X
	Q1-Q3	X.X - XX.X	X.X - XX.X	X.X - XX.X	X.X - XX.X
Step 5	N	XX	XX	XX	XX
	N missing	XX	XX	XX	XX
	Mean	XX.X	XX.X	XX.X	XX.X
	Std. deviation	XX.X	XX.X	XX.X	XX.X
	Median	XX.X	XX.X	XX.X	XX.X
	Q1-Q3	X.X - XX.X	X.X - XX.X	X.X - XX.X	X.X - XX.X

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For further information see Listing X

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Table D.8b Summary of Step Test, other informations, at Baseline by group
Population: Safety

		Group HnB		Group EC	
		Heart Rate	SpO2	Heart Rate	SpO2
Basal Condition Recovery Time (seconds)	N	XX	XX	XX	XX
	N missing	XX	XX	XX	XX
	Mean	XX.X	XX.X	XX.X	XX.X
	Std. deviation	XX.X	XX.X	XX.X	XX.X
	Median	XX.X	XX.X	XX.X	XX.X
	Q1-Q3	X.X - XX.X	X.X - XX.X	X.X - XX.X	X.X - XX.X
Stop Time	N	XX		XX	
	N missing	XX		XX	
	Mean	XX.X		XX.X	
	Std. deviation	XX.X		XX.X	
	Median	XX.X		XX.X	
	Q1-Q3	X.X - XX.X		X.X - XX.X	
VO2MAX	N	XX		XX	
	N missing	XX		XX	
	Mean	XX.X		XX.X	
	Std. deviation	XX.X		XX.X	
	Median	XX.X		XX.X	
	Q1-Q3	X.X - XX.X		X.X - XX.X	

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For further information see Listing X

EFFICACY ENDPOINTS

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Table E.1a Summary of the Primary End-point. Quit Rate at all visits
Population: <Per-Protocol/Intention-To-Treat>

			Group HnB	Group EC
			N=XXXX	N=XXXX
Quit rate	Visit 1	N(%)	XXX(XX.X%)	XXX(XX.X%)
	Visit 2	N(%)	XXX(XX.X%)	XXX(XX.X%)
	…	N(%)	XXX(XX.X%)	XXX(XX.X%)
	Visit n	N(%)	XXX(XX.X%)	XXX(XX.X%)

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As for the PP population, a "Continuous Quitter" is defined as the subject who did not smoke conventional sigarettes from visit 4 to visit 6
The p-value was derived from the XXXX test
For further information see Listing X.X

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Table E.1b Summary of the Primary End-point. Quit Rate at final visit comparison
Population: <Per-Protocol/Intention-To-Treat>

		Group HnB	Group EC
		N=XXXX	N=XXXX
Quit Rate	Rate	XX.X%	XX.X%
	95%CIs	[XX.XX,XXX.X]	[XX.XX,XXX.X]

H0: P1-P2 ≤ -Margin
H1: P1-P2 > -Margin

Margin=X.XXX

Score (Farrington-Manning)

Proportion Difference	ASE (F-M)	Z	Pr>Z
X.XXXX	X.XXXX	X.XXXX	X.XXXX

Noninferiority Limit	95% Confedent Limits	
X.XXXX	X.XXXX	X.XXXX

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As for the PP population, a “Continuous Quitter” is defined as the subject who did not smoke conventional sigarettes from visit 4 to visit 6
For further information see Listing X.X

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Table E.2a Summary of Smoking Reduction derived from the use of HnB and EC at week 12
Population: <Per-Protocol/Intention-To-Treat>

		Group HnB	Group EC	p-value
		N=XXXX	N=XXXX	
Smoking Reduction	Rate	XX.X%	XX.X%	X.XXXX
	95%CIs	[XX.XX,XXX.X]	[XX.XX,XXX.X]	

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<Source: [..]\\Work_In_Progress\[..]\Gestione Dati\Dati SAS\xxxxx.sas7bdat> Generated on XXXXXXXXX XX:XX
Smoking reduction is intended as a least a 50% reduction in the number of conventional cigarette/day at week 12.
The p-value was derived from the XXXX test
For further information see Listing X.X

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Table E.2b Summary of Smoking Reduction derived from the use of HnB and EC according to the Russell Standard
Population: <Per-Protocol/Intention-To-Treat>

		Group HnB	Group EC	
Quit timepoint		N=XXX	N=XXX	p-value
Self-reported 4 week	Rate 95%CIs	XX.X% [XX.XX,XXX.X]	XX.X% [XX.XX,XXX.X]	X.XXXX
eCO checked* 4 weeks	Rate 95%CIs	XX.X% [XX.XX,XXX.X]	XX.X% [XX.XX,XXX.X]	X.XXXX
eCO checked* 12 weeks	Rate 95%CIs	XX.X% [XX.XX,XXX.X]	XX.X% [XX.XX,XXX.X]	X.XXXX
eCO checked* 24 weeks	Rate 95%CIs	XX.X% [XX.XX,XXX.X]	XX.X% [XX.XX,XXX.X]	X.XXXX
Lost to FU 24 weeks	Rate 95%CIs	XX.X% [XX.XX,XXX.X]	XX.X% [XX.XX,XXX.X]	X.XXXX

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<Source: [..]\\Work_In_Progress\[..]\Gestione Dati\Dati SAS\xxxxx.sas7bdat> Generated on XXXXXXXXX XX:XX

* expired-air 'CO-verified (eCO) 4-week quitter' is the subject that was found to be less than 10ppm in the past 2 weeks
The p-value was derived from the XXXX test
For further information see Listing X.X

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Table E.3 Summary of Adoption Rate and Adherence to product use at week 12
Population: <Per-Protocol/Intention-To-Treat>

		Group HnB	Group EC	p-value
		N=XXXX	N=XXXX	
Adoption Rate	Rate	XX.X%	XX.X%	X.XXXX
	95%CIs	[XX.XX,XXX.X]	[XX.XX,XXX.X]	

<File: [..]\\Work_In_Progress\[..]\Statistica\Programmi\xxxxx.sas>
<Source: [..]\\Work_In_Progress\[..]\Gestione Dati\Dati SAS\xxxxx.sas7bdat> Generated on XXXXXXXXX XX:XX
A subject is defined as "Compliant" if he/she used at least a 90% of the product
The p-value was derived from the XXXX test
For further information see Listing X.X

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Table E.4a1 Summary of the mCE Questionnaire (scores) by visit < Group HnB / Group EC >
Population: <Per-Protocol/Intention-To-Treat>

		Observed Values at Visit							Changes From Visit 1 to Visits n						
Parameter	Visit	N	N miss	Mean	STD	CI 95%	Median	Range (Q1-Q3)	N	N miss	Mean	STD	CI 95%	Median	Range (Q1-Q3)
Satisfaction	Visit 4	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	XX.XX - XXX.X							
	Visit 5	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	XX.XX - XXX.X							
	Visit 6	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	XX.XX - XXX.X							
	Visit 7	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	XX.XX - XXX.X	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	XX.XX - XXX.X
Psychological Reward	Visit 4	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	XX.XX - XXX.X							
	Visit 5	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	XX.XX - XXX.X							
	Visit 6	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	XX.XX - XXX.X							
	Visit 7	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	XX.XX - XXX.X	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	XX.XX - XXX.X
Aversion	Visit 4	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	XX.XX - XXX.X							
	Visit 5	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	XX.XX - XXX.X							
	Visit 6	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	XX.XX - XXX.X							
	Visit 7	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	XX.XX - XXX.X	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	XX.XX - XXX.X
Enjoyment of Sensation	Visit 4	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	XX.XX - XXX.X							
	Visit 5	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	XX.XX - XXX.X							
	Visit 6	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	XX.XX - XXX.X							
	Visit 7	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	XX.XX - XXX.X	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	XX.XX - XXX.X
Craving Reduction	Visit 4	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	XX.XX - XXX.X							
	Visit 5	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	XX.XX - XXX.X							
	Visit 6	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	XX.XX - XXX.X							
	Visit 7	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	XX.XX - XXX.X	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	XX.XX - XXX.X
TOTAL	Visit 4	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	XX.XX - XXX.X							
	Visit 5	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	XX.XX - XXX.X							
	Visit 6	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	XX.XX - XXX.X							
	Visit 7	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	XX.XX - XXX.X	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	XX.XX - XXX.X

<File: [..]\\Work_In_Progress\[..]\Statistica\Programmi\xxxxx.sas>
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For further information see Listing X.X

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Table E.4a2 mCE Questionnaire (scores). Inferential analysis on the mean changes at final visit from baseline
Population: <Per-Protocol/Intention-To-Treat>

		Group HnB N=XXXX	Group EC N=XXXX	p-value
Satisfaction	Mean	XX.X	XX.X	X.XXXX
Psychological Reward	Mean	XX.X	XX.X	X.XXXX
Aversion	Mean	XX.X	XX.X	X.XXXX
Enjoyment of Sensation	Mean	XX.X	XX.X	X.XXXX
Craving Reduction	Mean	XX.X	XX.X	X.XXXX
TOTAL	Mean	XX.X	XX.X	X.XXXX

<File: [..]\\Work_In_Progress\[..]\Statistica\Programmi\xxxxx.sas>
<Source: [..]\\Work_In_Progress\[..]\Gestione Dati\Dati SAS\xxxxx.sas7bdat> Generated on XXXXXXXXX XX:XX
The p-value was derived from the XXXX test
For further information see Listing X.X

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Table E.4b1 Summary of Smoking Cue Appeal Questionnaire by visit. <Question 1 of 8>
Population: <Per-Protocol/Intention-To-Treat>

<Question>

Visit	Score	Group HnB	Group EC
Visit 4	1	XX (XX.X%)	XX (XX.X)
	2	XX (XX.X%)	XX (XX.X)
	3	XX (XX.X%)	XX (XX.X)
	4	XX (XX.X%)	XX (XX.X)
	5	XX (XX.X%)	XX (XX.X)
	6	XX (XX.X%)	XX (XX.X)
	7	XX (XX.X%)	XX (XX.X)
Visit 5	1	XX (XX.X%)	XX (XX.X)
	2	XX (XX.X%)	XX (XX.X)
	3	XX (XX.X%)	XX (XX.X)
	4	XX (XX.X%)	XX (XX.X)
	5	XX (XX.X%)	XX (XX.X)
	6	XX (XX.X%)	XX (XX.X)
	7	XX (XX.X%)	XX (XX.X)
Visit 6	1	XX (XX.X%)	XX (XX.X)
	2	XX (XX.X%)	XX (XX.X)
	3	XX (XX.X%)	XX (XX.X)
	4	XX (XX.X%)	XX (XX.X)
	5	XX (XX.X%)	XX (XX.X)
	6	XX (XX.X%)	XX (XX.X)
	7	XX (XX.X%)	XX (XX.X)
Visit 7	1	XX (XX.X%)	XX (XX.X)
	2	XX (XX.X%)	XX (XX.X)
	3	XX (XX.X%)	XX (XX.X)
	4	XX (XX.X%)	XX (XX.X)
	5	XX (XX.X%)	XX (XX.X)
	6	XX (XX.X%)	XX (XX.X)
	7	XX (XX.X%)	XX (XX.X)

<File: [..]\\Work_In_Progress\[..]\Statistica\Programmi\xxxxx.sas>
<Source: [..]\\Work_In_Progress\[..]\Gestione Dati\Dati SAS\xxxxx.satd7sas> Generated on XXXXXXXXX XX:XX
Legend: 1. Estremamente sgradevole ; 2. Molto sgradevole ; 3. Sgradevole ; 4. Né piacevole, né sgradevole ; 5. Piacevole
6. Molto piacevole ; 7. Estremamente piacevole

For further information see Listing X.X

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Table E.4b2 Smoking Cue Appeal Questionnaire. Inferential analysis on the mean changes at final visit from baseline
Population: <Per-Protocol/Intention-To-Treat>

		Group HnB N=XXXX	Group EC N=XXXX	p-value
Question 1	Mean	XX.X	XX.X	X.XXXX
Question 2	Mean	XX.X	XX.X	X.XXXX
…	Mean	XX.X	XX.X	X.XXXX
Question 8	Mean	XX.X	XX.X	X.XXXX
TOTAL	Mean	XX.X	XX.X	X.XXXX

<File: [..]\\Work_In_Progress\[..]\Statistica\Programmi\xxxxx.sas>
<Source: [..]\\Work_In_Progress\[..]\Gestione Dati\Dati SAS\xxxxx.sas7bdat> Generated on XXXXXXXXX XX:XX
For the inferential analysis, the scores were considered as numbers.
The p-value was derived from the XXXX test
For further information see Listing X.X

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Table E.4c1 Summary of the ITU Questionnaire by visit. <Question 4 (of questions 4-5-6)>
Population: <Per-Protocol/Intention-To-Treat>

<Question>

Visit	Score	Group HnB	Group EC
Visit 4	1	XX (XX.X%)	XX (XX.X)
	2	XX (XX.X%)	XX (XX.X)
	3	XX (XX.X%)	XX (XX.X)
	4	XX (XX.X%)	XX (XX.X)
	5	XX (XX.X%)	XX (XX.X)
	6	XX (XX.X%)	XX (XX.X)
	7	XX (XX.X%)	XX (XX.X)
Visit 5	1	XX (XX.X%)	XX (XX.X)
	2	XX (XX.X%)	XX (XX.X)
	3	XX (XX.X%)	XX (XX.X)
	4	XX (XX.X%)	XX (XX.X)
	5	XX (XX.X%)	XX (XX.X)
	6	XX (XX.X%)	XX (XX.X)
	7	XX (XX.X%)	XX (XX.X)
Visit 6	1	XX (XX.X%)	XX (XX.X)
	2	XX (XX.X%)	XX (XX.X)
	3	XX (XX.X%)	XX (XX.X)
	4	XX (XX.X%)	XX (XX.X)
	5	XX (XX.X%)	XX (XX.X)
	6	XX (XX.X%)	XX (XX.X)
	7	XX (XX.X%)	XX (XX.X)
Visit 7	1	XX (XX.X%)	XX (XX.X)
	2	XX (XX.X%)	XX (XX.X)
	3	XX (XX.X%)	XX (XX.X)
	4	XX (XX.X%)	XX (XX.X)
	5	XX (XX.X%)	XX (XX.X)
	6	XX (XX.X%)	XX (XX.X)
	7	XX (XX.X%)	XX (XX.X)

<File: [..]\\Work_In_Progress\[..]\Statistica\Programmi\xxxxx.sas>
<Source: [..]\\Work_In_Progress\[..]\Gestione Dati\Dati SAS\xxxxx.satd7sas> Generated on XXXXXXXXX XX:XX
Legend: 1. Assolutamente falso ; 2. Falso ; 3. Piuttosto falso ; 4. Piuttosto vero ; 5. Vero ; 6. Molto vero ; 7. Verissimo

For further information see Listing X.X

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Table E.4c2 ITU Questionnaire. Inferential analysis on the mean changes at final visit from baseline
Population: <Per-Protocol/Intention-To-Treat>

		Group HnB N=XXXX	Group EC N=XXXX	p-value
Question 4	Mean	XX.X	XX.X	X.XXXX
Question 5	Mean	XX.X	XX.X	X.XXXX
Question 6	Mean	XX.X	XX.X	X.XXXX
TOTAL	Mean	XX.X	XX.X	X.XXXX

<File: [..]\\Work_In_Progress\[..]\Statistica\Programmi\xxxxx.sas>
<Source: [..]\\Work_In_Progress\[..]\Gestione Dati\Dati SAS\xxxxx.sas7bdat> Generated on XXXXXXXXX XX:XX
For the inferential analysis, the scores were considered as numbers.
The p-value was derived from the XXXX test
For further information see Listing X.X

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Table E.4d1 Summary of the Risk Perception (PRI-P CC) Questionnaire by visit. <Question 1 of 18>
Population: <Per-Protocol/Intention-To-Treat>

<Question>

Visit	Score	Group HnB	Group EC
Visit 4	1	XX (XX.X%)	XX (XX.X)
	2	XX (XX.X%)	XX (XX.X)
	3	XX (XX.X%)	XX (XX.X)
	4	XX (XX.X%)	XX (XX.X)
	5	XX (XX.X%)	XX (XX.X)
	6	XX (XX.X%)	XX (XX.X)
Visit 5	1	XX (XX.X%)	XX (XX.X)
	2	XX (XX.X%)	XX (XX.X)
	3	XX (XX.X%)	XX (XX.X)
	4	XX (XX.X%)	XX (XX.X)
	5	XX (XX.X%)	XX (XX.X)
	6	XX (XX.X%)	XX (XX.X)
Visit 6	1	XX (XX.X%)	XX (XX.X)
	2	XX (XX.X%)	XX (XX.X)
	3	XX (XX.X%)	XX (XX.X)
	4	XX (XX.X%)	XX (XX.X)
	5	XX (XX.X%)	XX (XX.X)
	6	XX (XX.X%)	XX (XX.X)
Visit 7	1	XX (XX.X%)	XX (XX.X)
	2	XX (XX.X%)	XX (XX.X)
	3	XX (XX.X%)	XX (XX.X)
	4	XX (XX.X%)	XX (XX.X)
	5	XX (XX.X%)	XX (XX.X)
	6	XX (XX.X%)	XX (XX.X)

<File: [..]\\Work_In_Progress\[..]\Statistica\Programmi\xxxxx.sas>
<Source: [..]\\Work_In_Progress\[..]\Gestione Dati\Dati SAS\xxxxx.satd7sas> Generated on XXXXXXXXX XX:XX
Legend: 1. Nessun rischio ; 2. Rischio basso ; 3. Rischio moderato ; 4. Rischio alto ; 5. Rischio molto alto ; 6. Non so

For further information see Listing X.X

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Table E.4d2 Risk Perception (PRI-P CC) Questionnaire. Inferential analysis on the mean changes at final visit from baseline

		Group HnB N=XXXX	Group EC N=XXXX	p-value
Question 1	Mean	XX.X	XX.X	X.XXXX
Question 2	Mean	XX.X	XX.X	X.XXXX
…	Mean	XX.X	XX.X	X.XXXX
Question 18	Mean	XX.X	XX.X	X.XXXX
TOTAL	Mean	XX.X	XX.X	X.XXXX

<File: [..]\\Work_In_Progress\[..]\Statistica\Programmi\xxxxx.sas>
<Source: [..]\\Work_In_Progress\[..]\Gestione Dati\Dati SAS\xxxxx.sas7bdat> Generated on XXXXXXXXX XX:XX
For the inferential analysis, the scores were considered as numbers. Score 6 was not included.
The p-value was derived from the XXXX test
For further information see Listing X.X

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Table E.4e1 Summary of the Risk Perception (PRI-P RRP) Questionnaire by visit. <Question 1 of 18>
Population: <Per-Protocol/Intention-To-Treat>

<Question>

Visit	Score	Group HnB	Group EC
Visit 4	1	XX (XX.X%)	XX (XX.X)
	2	XX (XX.X%)	XX (XX.X)
	3	XX (XX.X%)	XX (XX.X)
	4	XX (XX.X%)	XX (XX.X)
	5	XX (XX.X%)	XX (XX.X)
	6	XX (XX.X%)	XX (XX.X)
Visit 5	1	XX (XX.X%)	XX (XX.X)
	2	XX (XX.X%)	XX (XX.X)
	3	XX (XX.X%)	XX (XX.X)
	4	XX (XX.X%)	XX (XX.X)
	5	XX (XX.X%)	XX (XX.X)
	6	XX (XX.X%)	XX (XX.X)
Visit 6	1	XX (XX.X%)	XX (XX.X)
	2	XX (XX.X%)	XX (XX.X)
	3	XX (XX.X%)	XX (XX.X)
	4	XX (XX.X%)	XX (XX.X)
	5	XX (XX.X%)	XX (XX.X)
	6	XX (XX.X%)	XX (XX.X)
Visit 7	1	XX (XX.X%)	XX (XX.X)
	2	XX (XX.X%)	XX (XX.X)
	3	XX (XX.X%)	XX (XX.X)
	4	XX (XX.X%)	XX (XX.X)
	5	XX (XX.X%)	XX (XX.X)
	6	XX (XX.X%)	XX (XX.X)

<File: [..]\\Work_In_Progress\[..]\Statistica\Programmi\xxxxx.sas>
<Source: [..]\\Work_In_Progress\[..]\Gestione Dati\Dati SAS\xxxxx.satd7sas> Generated on XXXXXXXXX XX:XX
Legend: 1. Nessun rischio ; 2. Rischio basso ; 3. Rischio moderato ; 4. Rischio alto ; 5. Rischio molto alto ; 6. Non so

For further information see Listing X.X

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Table E.4e2 Risk Perception (PRI-P RRP) Questionnaire. Inferential analysis on the mean changes at final visit from baseline
Population: <Per-Protocol/Intention-To-Treat>

		Group HnB N=XXXX	Group EC N=XXXX	p-value
Question 1	Mean	XX.X	XX.X	X.XXXX
Question 2	Mean	XX.X	XX.X	X.XXXX
…	Mean	XX.X	XX.X	X.XXXX
Question 18	Mean	XX.X	XX.X	X.XXXX
TOTAL	Mean	XX.X	XX.X	X.XXXX

<File: [..]\\Work_In_Progress\[..]\Statistica\Programmi\xxxxx.sas>
<Source: [..]\\Work_In_Progress\[..]\Gestione Dati\Dati SAS\xxxxx.sas7bdat> Generated on XXXXXXXXX XX:XX
For the inferential analysis, the scores were considered as numbers. Score 6 was not included.
The p-value was derived from the XXXX test
For further information see Listing X.X

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Table E.4f Summary of Device Delivery by group
Population: <Per-Protocol/Intention-To-Treat>

		Group HnB N=XXXX	Group EC N=XXXX
Preferred flavor of chopstick chosen	Heets Amber	XX (XX.X%)	XX (XX.X%)
	Heets Yellow	XX (XX.X%)	XX (XX.X%)
	Heets Turquoise	XX (XX.X%)	XX (XX.X%)
Has the devices been tested and does it works?	Yes	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)
Has the subject been trained for the allocated device?	Yes	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)

<File: [..]\\Work_In_Progress\[..]\Statistica\Programmi\xxxxx.sas>
<Source: [..]\\Work_In_Progress\[..]\Gestione Dati\Dati SAS\xxxxx.sas7bdat> Generated on XXXXXXXXX XX:XX
For further information see Listing X.X

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Table E.5 Summary of the Biomarkers of Biological Exposure (BoBE) – eCO (ppm)
Population: <Per-Protocol/Intention-To-Treat>

		Observed Values at Visit							Changes From Visit 1 to Visits n						
	Visit	N	N miss	Mean	STD	CI 95%	Median	Range (Q1-Q3)	N	N miss	Mean	STD	CI 95%	Median	Range (Q1-Q3)
Group HnB	Screening	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)							
	Visit 1	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)							
	Visit 2	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)							
	Visit 3	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)							
	Visit 4	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)							
	Visit 5	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)							
	Visit 6	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)							
	Follow-up	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)
Group EC	Screening	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)							
	Visit 1	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)							
	Visit 2	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)							
	Visit 3	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)							
	Visit 4	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)							
	Visit 5	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)							
	Visit 6	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)							
	Follow-up	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)

p-value=X.XXXX

<File: [..]\\Work_In_Progress\[..]\Statistica\Programmi\xxxxx.sas>
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The p-value was derived from the XXXX test on the comparison of the mean differences (Visit 6-Screening)
For further information see Listing X.X

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Table E.6 Summary of EQ-5D Questionnaire (scores). < Group HnB / Group EC >
Population: <Per-Protocol/Intention-To-Treat/Continuous Quitters>

		Observed Values at Visit							Changes From Visit 1 to Visits n						
Parameter	Visit	N	N miss	Mean	STD	CI 95%	Median	min-max	N	N miss	Mean	STD	CI 95%	Median	min-max
Mobility (1-5)	Visit 1	XX	XX	XX.X	XX.X	[X.X , X.X]	XX.X	(X - X)							
	Visit 4	XX	XX	XX.X	XX.X	[X.X , X.X]	XX.X	(X - X)							
	Visit 5	XX	XX	XX.X	XX.X	[X.X , X.X]	XX.X	(X - X)							
	Visit 6	XX	XX	XX.X	XX.X	[X.X , X.X]	XX.X	(X - X)							
	Visit 7	XX	XX	XX.X	XX.X	[X.X , X.X]	XX.X	(X - X)	XX	XX	XX.X	XX.X	[X.X , X.X]	XX.X	(X - X)
Self-care (1-5)	Visit 1	XX	XX	XX.X	XX.X	[X.X , X.X]	XX.X	(X - X)							
	Visit 4	XX	XX	XX.X	XX.X	[X.X , X.X]	XX.X	(X - X)							
	Visit 5	XX	XX	XX.X	XX.X	[X.X , X.X]	XX.X	(X - X)							
	Visit 6	XX	XX	XX.X	XX.X	[X.X , X.X]	XX.X	(X - X)							
	Visit 7	XX	XX	XX.X	XX.X	[X.X , X.X]	XX.X	(X - X)	XX	XX	XX.X	XX.X	[X.X , X.X]	XX.X	(X - X)
.....															
Health-today (0-100)	Visit 1	XX	XX	XX.X	XX.X	[X.X , X.X]	XX.X	(X - X)							
	Visit 4	XX	XX	XX.X	XX.X	[X.X , X.X]	XX.X	(X - X)							
	Visit 5	XX	XX	XX.X	XX.X	[X.X , X.X]	XX.X	(X - X)							
	Visit 6	XX	XX	XX.X	XX.X	[X.X , X.X]	XX.X	(X - X)							
	Visit 7	XX	XX	XX.X	XX.X	[X.X , X.X]	XX.X	(X - X)	XX	XX	XX.X	XX.X	[X.X , X.X]	XX.X	(X - X)

<File: [..]\\Work_In_Progress\[..]\Statistica\Programmi\xxxxx.sas>
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For further information see Listing X.X

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Table E.7a Summary of Step Test by group < Group HnB / Group EC >
Population: <Per-Protocol/Intention-To-Treat>

		Observed Values at Visit							Changes From Visit 1 to Visit 7						
Parameter	Visit	N	N miss	Mean	STD	CI 95%	Median	Range (Q1-Q3)	N	N miss	Mean	STD	CI 95%	Median	Range (Q1-Q3)
Baseline	Visit 1	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)							
HR	Visit 4	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)							
	Visit 6	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)							
	Visit 7	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)
SpO2	Visit 1	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)							
	Visit 4	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)							
	Visit 6	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)							
	Visit 7	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)
Step 1	Visit 1	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)							
HR	Visit 4	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)							
	Visit 6	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)							
	Visit 7	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)
SpO2	Visit 1	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)							
	Visit 4	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)							
	Visit 6	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)							
	Visit 7	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)
…..															
Recovery	Visit 1	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)							
HR	Visit 4	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)							
	Visit 6	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)							
	Visit 7	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)
SpO2	Visit 1	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)							
	Visit 4	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)							
	Visit 6	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)							
	Visit 7	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)

<File: [..]\\Work_In_Progress\[..]\Statistica\Programmi\xxxxx.sas>
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The percentages are calculated on the total of the enrolled patients by group
For further information see Listing X.X

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Table E.7b Summary of Step Test – inferential analysis of VO2MAX
Population: <Per-Protocol/Intention-To-Treat>

		Group HnB	Group EC
VO2MAX	N	XX	XX
	N missing	XX	XX
	Mean	XX.X	XX.X
	Std. deviation	XX.X	XX.X
	Median	XX.X	XX.X
	Q1-Q3	X.X - XX.X	X.X - XX.X

p-value=X.XXXX

<File: [..]\\Work_In_Progress\[..]\Statistica\Programmi\xxxxx.sas>
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The p-values was derived from the t-test
For further information see Listing X

SAFETY ENDPOINTS

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Table S.1 Summary of Extent of Exposure by group
Population: Safety

		Group HnB	Group EC
		N=XXX	N=XXX
Extent of Exposure	N	XX	XX
	N missing	XX	XX
	Mean	XX.X	XX.X
	Std. deviation	XX.X	XX.X
	Median	XX.X	XX.X
	Q1-Q3	XX.X - XX.X	XX.X - XX.X

<File: [..]\\Work_In_Progress\[..]\Statistica\Programmi\xxxxx.sas>
<Source: [..]\\Work_In_Progress\[..]\Gestione Dati\Dati SAS\xxxxx.sas7bdat> Generated on XXXXXXXXX XX:XX
The Extent of exposure is computed as (Visit 6 date – Baseline date)
For further information see Listing X.X

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Table S.2 Summary of Adverse Drug Reactions by group
Population: Safety

	Group HnB	Group EC
	N=XXX	N=XXX
ADRs	XX (XX.X%)	XX (XX.X%)
SADRs	XX (XX.X%)	XX (XX.X%)
Related ADRs	XX (XX.X%)	XX (XX.X%)

<File: [..]\\Work_In_Progress\[..]\Statistica\Programmi\xxxxx.sas>
<Source: [..]\\Work_In_Progress\[..]\Gestione Dati\Dati SAS\xxxxx.sas7bdat> Generated on XXXXXXXXX XX:XX

The percentages are calculated on the total of the enrolled patients by group
ADRS classified as Possible/Probably/Definite are considered as Related ADRS
For further information see Listing X.X

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Table S.3 Summary of Vital Signs by group < Group HnB / Group EC >
Population: <Safety/Continuous Quitters>

		Observed Values at Visit							Changes From Visit 1 to Visits 6 and 7						
Parameter <Unit>	Visit	N	N miss	Mean	STD	CI 95%	Median	Range(Q1-Q3)	N	N miss	Mean	STD	CI 95%	Median	Range (Q1-Q3)
parameter #1 <um>	Baseline	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)							
	Visit 2	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)							
	. . . . .	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)
	Follow-up	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)
parameter #2 <um>	Baseline	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)							
	Visit 2	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)							
	. . . . .	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)
	Follow-up	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)
. . . . .															
parameter #n <um>	Baseline	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)							
	Visit 2	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)							
	. . . . .	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)
	Follow-up	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)	XX	XX	XX.XX	XX.XX	[XX.XX,XXX.X]	XX.XX	(XX.XX - XXX.X)

<File: [..]\\Work_In_Progress\[..]\Statistica\Programmi\xxxxx.sas>
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For further information see Listing X.X

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Table S.4 Summary of End of Study Information by group
Population: Safety

		Group HnB N=XXXX	Group EC N=XXXX
Was the study completed According to the Protocol?	Yes	XX (XX.X%)	XX (XX.X%)
	No	XX (XX.X%)	XX (XX.X%)
Study duration (days)	N	XX	XX
	N missing	XX	XX
	Mean	XX.X	XX.X
	Std. deviation	XX.X	XX.X
	Median	XX.X	XX.X
	Q25-Q75	X.X - XX.X	X.X - XX.X
If no, specify (Reason)	Reason#1	XX (XX.X%)	XX (XX.X%)
	Reason#2	XX (XX.X%)	XX (XX.X%)
	. . . . .	. . . . .	. . . . .
	Reason#n	XX (XX.X%)	XX (XX.X%)

<File: [..]\\Work_In_Progress\[..]\Statistica\Programmi\xxxxx.sas>
<Source: [..]\\Work_In_Progress\[..]\Gestione Dati\Dati SAS\xxxxx.sas7bdat> Generated on XXXXXXXXX XX:XX
For further information see Listing X.X

APPENDIX 3
Mock tables: Listings

BASELINE CHARACTERISTICS

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Listing D.1 Patients' Disposition

Screening Number	Random. Number	Age/Gender	Enroled (Y/N)	Completed (Y/N)
XXXXX	XXXXX	XX/XXXX	X	X
XXXXX	XXXXX	XX/XXXX	X	X
XXXXX	XXXXX	XX/XXXX	X	X
XXXXX	XXXXX	XX/XXXX	X	X
XXXXX	XXXXX	XX/XXXX	X	X
XXXXX	XXXXX	XX/XXXX	X	X
XXXXX	XXXXX	XX/XXXX	X	X
XXXXX	XXXXX	XX/XXXX	X	X
XXXXX	XXXXX	XX/XXXX	X	X
XXXXX	XXXXX	XX/XXXX	X	X

<File: [..]\\Work_In_Progress\[..]\Statistica\Programmi\xxxxx.sas>
<Source: [..]\\Work_In_Progress\[..]\Gestione Dati\Dati SAS\xxxxx.sas7bdat> Generated on XXXXXXXXX XX:XX

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Listing D.2 Eligibility: Inclusion Criteria < Group HnB / Group EC >

Screening Number	Random. Number	Age/Gender	Inclusion Crit. #1	Inclusion Crit. #2	Inclusion Crit. #3	Inclusion Crit. #4	Inclusion Crit. #5	Inclusion Crit. #6
XXXXXX	XXXXXX	XX/XXXX	X	X	X	X	X	X
XXXXXX	XXXXXX	XX/XXXX	X	X	X	X	X	X
XXXXXX	XXXXXX	XX/XXXX	X	X	X	X	X	X
XXXXXX	XXXXXX	XX/XXXX	X	X	X	X	X	X
XXXXXX	XXXXXX	XX/XXXX	X	X	X	X	X	X
XXXXXX	XXXXXX	XX/XXXX	X	X	X	X	X	X
XXXXXX	XXXXXX	XX/XXXX	X	X	X	X	X	X

<File: [..]\\Work_In_Progress\[..]\Statistica\Programmi\xxxxx.sas>
<Source: [..]\\Work_In_Progress\[..]\Gestione Dati\Dati SAS\xxxxx.sas7bdat> Generated on XXXXXXXXX XX:XX

Incl.Crit.#1: Able to comply with study procedures.
Incl.Crit.#2: Male or female healthy smokers aged ≥19.
Incl.Crit.#3: Smoking at least 10 cigarettes a day.
Incl.Crit.#4: Smoking for at least one year.
Incl.Crit.#5: Not currently attempting to quit smoking or wishing to do so in the next 30 days (this will be verified at screening by the answer ''NO'' to both questions ''Do you intend to quit in the next 30 days?'' and ''Are you interested in taking part in one of our smoking cessation programs?'').
Incl.Crit.#6: Female smokers not planning to become pregnant are using an acceptable form of contraception.

<Ordered by: Screening Number>
<Stratified by: Group>

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Listing D.3 Eligibility: Exclusion Criteria <Group HnB / Group EC >

Screening Number	Random. Number	Age/Gender	Exclusion Crit. #1	Exclusion Crit. #2	Exclusion Crit. #3	Exclusion Crit. #4
XXXXXX	XXXXXX	XX/XXXX	X	X	X	X
XXXXXX	XXXXXX	XX/XXXX	X	X	X	X
XXXXXX	XXXXXX	XX/XXXX	X	X	X	X
XXXXXX	XXXXXX	XX/XXXX	X	X	X	X
XXXXXX	XXXXXX	XX/XXXX	X	X	X	X
XXXXXX	XXXXXX	XX/XXXX	X	X	X	X
XXXXXX	XXXXXX	XX/XXXX	X	X	X	X

<File: [..]\\Work_In_Progress\[..]\Statistica\Programmi\xxxxx.sas>
<Source: [..]\\Work_In_Progress\[..]\Gestione Dati\Dati SAS\xxxxx.sas7bdat> Generated on XXXXXXXXX XX:XX

Excl.Crit.#1: Use of smokeless tobacco, or any other tobacco products (including e-cigarettes, cigars, chewing tobacco, snus, etc.) within the last 3 months, at baseline and during the whole study;
Excl.Crit.#2: Use of nicotine replacement therapy or other smoking cessation therapies within the last 3 months and at baseline;
Excl.Crit.#3: Self-reported pregnancy, planned pregnancy or breastfeeding;
Excl.Crit.#4: Tobacco industry employees and 1st degree relatives will be excluded in order to safeguard independence of the study.

<Ordered by: Screening Number>
<Stratified by: Group>

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Listing D.4a Demographic Data < Group HnB / Group EC >

Screening Number	Random. Number	Inf. Cons. Date	Age/Gender	Education
XXXXXX	XXXXXX	XX/XX/XXXX	XX/XXXX	XXXXXXXXXX
XXXXXX	XXXXXX	XX/XX/XXXX	XX/XXXX	XXXXXXXXXX
XXXXXX	XXXXXX	XX/XX/XXXX	XX/XXXX	XXXXXXXXXX
XXXXXX	XXXXXX	XX/XX/XXXX	XX/XXXX	XXXXXXXXXX
XXXXXX	XXXXXX	XX/XX/XXXX	XX/XXXX	XXXXXXXXXX
XXXXXX	XXXXXX	XX/XX/XXXX	XX/XXXX	XXXXXXXXXX
XXXXXX	XXXXXX	XX/XX/XXXX	XX/XXXX	XXXXXXXXXX
XXXXXX	XXXXXX	XX/XX/XXXX	XX/XXXX	XXXXXXXXXX
XXXXXX	XXXXXX	XX/XX/XXXX	XX/XXXX	XXXXXXXXXX
XXXXXX	XXXXXX	XX/XX/XXXX	XX/XXXX	XXXXXXXXXX
XXXXXX	XXXXXX	XX/XX/XXXX	XX/XXXX	XXXXXXXXXX
XXXXXX	XXXXXX	XX/XX/XXXX	XX/XXXX	XXXXXXXXXX
XXXXXX	XXXXXX	XX/XX/XXXX	XX/XXXX	XXXXXXXXXX
XXXXXX	XXXXXX	XX/XX/XXXX	XX/XXXX	XXXXXXXXXX
XXXXXX	XXXXXX	XX/XX/XXXX	XX/XXXX	XXXXXXXXXX
XXXXXX	XXXXXX	XX/XX/XXXX	XX/XXXX	XXXXXXXXXX
XXXXXX	XXXXXX	XX/XX/XXXX	XX/XXXX	XXXXXXXXXX
XXXXXX	XXXXXX	XX/XX/XXXX	XX/XXXX	XXXXXXXXXX
XXXXXX	XXXXXX	XX/XX/XXXX	XX/XXXX	XXXXXXXXXX

<File: [..]\\Work_In_Progress\[..]\Statistica\Programmi\xxxxx.sas>
<Source: [..]\\Work_In_Progress\[..]\Gestione Dati\Dati SAS\xxxxx.sas7bdat>   Generated on XXXXXXXXX XX:XX

<Ordered by: Screening Number>
<Stratified by: Group>

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Listing D.4b Smoking information < Group HnB / Group EC >

Screening Number	Random. Number	Age/Gender	How long smoked at least 10 cigarettes/die (years)	Brand of used cigarettes	Years of smoking	Number of quit attempts	Visit	Number of cigarette/die	Exhaled breath Carbon monoxide
XXXXXX	XXXXXX	XX/XXXX	XX	XXXXXXXXXX	XX	XX	XXXXXX	XX	XXX
							XXXXXX	XX	XXX
							XXXXXX	XX	XXX
							XXXXXX	XX	XXX
							XXXXXX	XX	XXX
							XXXXXX	XX	XXX
							XXXXXX	XX	XXX
							XXXXXX	XX	XXX
XXXXXX	XXXXXX	XX/XXXX	XX	XXXXXXXXXX	XX	XX	XXXXXX	XX	XXX
							XXXXXX	XX	XXX
							XXXXXX	XX	XXX
							XXXXXX	XX	XXX
							XXXXXX	XX	XXX
							XXXXXX	XX	XXX
							XXXXXX	XX	XXX
							XXXXXX	XX	XXX
XXXXXX	XXXXXX	XX/XXXX	XX	XXXXXXXXXX	XX	XX	XXXXXX	XX	XXX
							XXXXXX	XX	XXX
							XXXXXX	XX	XXX
							XXXXXX	XX	XXX
							XXXXXX	XX	XXX
							XXXXXX	XX	XXX
							XXXXXX	XX	XXX
							XXXXXX	XX	XXX

<File: [..]\\Work_In_Progress\[..]\Statistica\Programmi\xxxxx.sas>
<Source: [..]\\Work_In_Progress\[..]\Gestione Dati\Dati SAS\xxxxx.sas7bdat> Generated on XXXXXXXXX XX:XX

<Ordered by: Screening Number>
<Stratified by: Group>

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Listing D.5 Past and Present Medical History < Group HnB / Group EC >

Screening Number	Random. Number	Age/Gender	Date of Visit	Description	Date of Onset	Date Resolved	Ongoing (Y/N)	Comment
XXXXXX	XXXXXX	XX/XXXX	XX/XX/XXXX	XXXXXXXXXX	XX/XX/XXXX	XX/XX/XXXX	X	XXXXXXXXXX
XXXXXX	XXXXXX	XX/XXXX	XX/XX/XXXX	XXXXXXXXXX	XX/XX/XXXX	XX/XX/XXXX	X	XXXXXXXXXX
XXXXXX	XXXXXX	XX/XXXX	XX/XX/XXXX	XXXXXXXXXX	XX/XX/XXXX	XX/XX/XXXX	X	XXXXXXXXXX
XXXXXX	XXXXXX	XX/XXXX	XX/XX/XXXX	XXXXXXXXXX	XX/XX/XXXX	XX/XX/XXXX	X	XXXXXXXXXX
XXXXXX	XXXXXX	XX/XXXX	XX/XX/XXXX	XXXXXXXXXX	XX/XX/XXXX	XX/XX/XXXX	X	XXXXXXXXXX
XXXXXX	XXXXXX	XX/XXXX	XX/XX/XXXX	XXXXXXXXXX	XX/XX/XXXX	XX/XX/XXXX	X	XXXXXXXXXX
XXXXXX	XXXXXX	XX/XXXX	XX/XX/XXXX	XXXXXXXXXX	XX/XX/XXXX	XX/XX/XXXX	X	XXXXXXXXXX
XXXXXX	XXXXXX	XX/XXXX	XX/XX/XXXX	XXXXXXXXXX	XX/XX/XXXX	XX/XX/XXXX	X	XXXXXXXXXX
XXXXXX	XXXXXX	XX/XXXX	XX/XX/XXXX	XXXXXXXXXX	XX/XX/XXXX	XX/XX/XXXX	X	XXXXXXXXXX
XXXXXX	XXXXXX	XX/XXXX	XX/XX/XXXX	XXXXXXXXXX	XX/XX/XXXX	XX/XX/XXXX	X	XXXXXXXXXX

<File: [..]\\Work_In_Progress\[..]\Statistica\Programmi\xxxxx.sas>
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Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Listing D.6 Urine Collection and Storage < Group HnB / Group EC >

Screening Number	Random. Number	Age/Sex	Instruction given to the subject?	No. of urine Containers delivered	Visit	Has the subject returned the urine to the center?
XXXXXX	XXXXXX	XX.X/XXXX	XXX	XXX	XXXXXXX	
					XXXXXXX	XXX
				XXX	XXXXXXX	
					XXXXXXX	XXX
XXXXXX	XXXXXX	XX.X/XXXX	XXX	XXX	XXXXXXX	
					XXXXXXX	XXX
				XXX	XXXXXXX	
					XXXXXXX	XXX
XXXXXX	XXXXXX	XX.X/XXXX	XXX	XXX	XXXXXXX	
					XXXXXXX	XXX
				XXX	XXXXXXX	
					XXXXXXX	XXX
XXXXXX	XXXXXX	XX.X/XXXX	XXX	XXX	XXXXXXX	
					XXXXXXX	XXX
				XXX	XXXXXXX	
					XXXXXXX	XXX
XXXXXX	XXXXXX	XX.X/XXXX	XXX	XXX	XXXXXXX	
					XXXXXXX	XXX
				XXX	XXXXXXX	
					XXXXXXX	XXX

<File: [..]\\Work_In_Progress\[..]\Statistica\Programmi\xxxxx.sas>
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<Ordered by: Screening Number>
<Stratified by: Group>

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Listing D.7 Fagerstrom test for nicotine dependance < Group HnB / Group EC >

Screening Number	Random. Number	Visit	Age/Gender	Q1	Q2	Q3	Q4	Q5	Q6
XXXXXX	XXXXXX	XXXXXX	XX/XXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX
XXXXXX	XXXXXX	XXXXXX	XX/XXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX
XXXXXX	XXXXXX	XXXXXX	XX/XXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX
XXXXXX	XXXXXX	XXXXXX	XX/XXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX
XXXXXX	XXXXXX	XXXXXX	XX/XXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX
XXXXXX	XXXXXX	XXXXXX	XX/XXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX
XXXXXX	XXXXXX	XXXXXX	XX/XXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX

<File: [..]\\Work_In_Progress\[..]\Statistica\Programmi\xxxxx.sas>
<Source: [..]\\Work_In_Progress\[..]\Gestione Dati\Dati SAS\xxxxx.sas7bdat>   Generated on XXXXXXXXX XX:XX

Q1: Quanto tempo dopo il risveglio fuma la prima sigaretta?
Q2: Trova difficile non fumare nei luoghi dove è vietato?
Q3: A quale sigaretta farebbe più fatica a rinunciare?
Q4: Quante sigarette fuma al giorno?
Q5: Tende a fumare più spesso nelle prime ore dopo il risveglio che durante il resto del giorno?
Q6: Fuma anche se è malato e deve rimanere a letto la maggior parte del giorno?

<Ordered by: Screening Number>
<Stratified by: Group>

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Listing D.8 Step Test < Group HnB / Group EC >

Screening Number	Ranom. Number	Age/Gender	Visit	Basale HR	Basale SpO2	Step 1 HR	Step 1 SpO2	Step 2 HR	Step 2 SpO2	Step 3 HR	Step 3 SpO2	Step 4 HR	Step 4 SpO2	Step 5 HR	Step 5 SpO2	Recovery HR	Recovery SpO2	Stop Time	V02MAX
XXXXXX	XXXXXX	XX.X/XXXX	XXXXXXX	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XXXX	XX.XX
			XXXXXXX	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XXXX	XX.XX
			XXXXXXX	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XXXX	XX.XX
			XXXXXXX	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XXXX	XX.XX
XXXXXX	XXXXXX	XX.X/XXXX	XXXXXXX	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XXXX	XX.XX
			XXXXXXX	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XXXX	XX.XX
			XXXXXXX	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XXXX	XX.XX
			XXXXXXX	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XXXX	XX.XX
XXXXXX	XXXXXX	XX.X/XXXX	XXXXXXX	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XXXX	XX.XX
			XXXXXXX	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XXXX	XX.XX
			XXXXXXX	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XXXX	XX.XX
			XXXXXXX	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XXXX	XX.XX
XXXXXX	XXXXXX	XX.X/XXXX	XXXXXXX	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XXXX	XX.XX
			XXXXXXX	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XXXX	XX.XX
			XXXXXXX	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XXXX	XX.XX
			XXXXXXX	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XXXX	XX.XX
XXXXXX	XXXXXX	XX.X/XXXX	XXXXXXX	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XXXX	XX.XX
			XXXXXXX	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XXXX	XX.XX
			XXXXXXX	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XXXX	XX.XX
			XXXXXXX	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XXXX	XX.XX

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<Ordered by: Screening Number>
<Stratified by: Group>

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Listing D.9 Device consignment < Group HnB / Group EC >

Screening Number	Random. Number	Age/Gender	Visit	Has the device been tested and does it work?	Has the subject been trained for the allocated device?	<see > footnote>	<see footnote>
XXXXXX	XXXXXX	XX/XXXX	XXXXXX	XXX	XXXXXXXXXXXX	XXXXX	XXXXXXXXXX
			XXXXXX	XXX	XXXXXXXXXXXX	XXXXX	XXXXXXXXXX
			XXXXXX	XXX	XXXXXXXXXXXX	XXXXX	XXXXXXXXXX
			XXXXXX	XXX	XXXXXXXXXXXX	XXXXX	XXXXXXXXXX
XXXXXX	XXXXXX	XX/XXXX	XXXXXX	XXX	XXXXXXXXXXXX	XXXXX	XXXXXXXXXX
			XXXXXX	XXX	XXXXXXXXXXXX	XXXXX	XXXXXXXXXX
			XXXXXX	XXX	XXXXXXXXXXXX	XXXXX	XXXXXXXXXX
			XXXXXX	XXX	XXXXXXXXXXXX	XXXXX	XXXXXXXXXX
XXXXXX	XXXXXX	XX/XXXX	XXXXXX	XXX	XXXXXXXXXXXX	XXXXX	XXXXXXXXXX
			XXXXXX	XXX	XXXXXXXXXXXX	XXXXX	XXXXXXXXXX
			XXXXXX	XXX	XXXXXXXXXXXX	XXXXX	XXXXXXXXXX
			XXXXXX	XXX	XXXXXXXXXXXX	XXXXX	XXXXXXXXXX
XXXXXX	XXXXXX	XX/XXXX	XXXXXX	XXX	XXXXXXXXXXXX	XXXXX	XXXXXXXXXX
			XXXXXX	XXX	XXXXXXXXXXXX	XXXXX	XXXXXXXXXX
			XXXXXX	XXX	XXXXXXXXXXXX	XXXXX	XXXXXXXXXX
			XXXXXX	XXX	XXXXXXXXXXXX	XXXXX	XXXXXXXXXX

<File: [..]\\Work_In_Progress\[..]\Statistica\Programmi\xxxxx.sas>
<Source: [..]\\Work_In_Progress\[..]\Gestione Dati\Dati SAS\xxxxx.sas7bdat> Generated on XXXXXXXXX XX:XX

<Ordered by: Screening Number>
<Stratified by: Group>
<No. of sticks delivered - Preferred flavor@of heatstick / Quantity in mg/ml of e-liquid bottles - Preferred flavor@of e-liquid>

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Listing D.10 Device supply and accountability < Group HnB / Group EC >

Screening Number	Random. Number	Age/Gender	Visit	<see footnote>
XXXXXX	XXXXXX	XX/XXXX	XXXXXXX	XXX
			XXXXXXX	XXX
			XXXXXXX	XXX
			XXXXXXX	XXX
			XXXXXXX	XXX
XXXXXX	XXXXXX	XX/XXXX	XXXXXXX	XXX
			XXXXXXX	XXX
			XXXXXXX	XXX
			XXXXXXX	XXX
			XXXXXXX	XXX
XXXXXX	XXXXXX	XX/XXXX	XXXXXXX	XXX
			XXXXXXX	XXX
			XXXXXXX	XXX
			XXXXXXX	XXX
			XXXXXXX	XXX
XXXXXX	XXXXXX	XX/XXXX	XXXXXXX	XXX
			XXXXXXX	XXX
			XXXXXXX	XXX
			XXXXXXX	XXX
			XXXXXXX	XXX

<File: [..]\\Work_In_Progress\[..]\Statistica\Programmi\xxxxx.sas>
<Source: [..]\\Work_In_Progress\[..]\Gestione Dati\Dati SAS\xxxxx.sas7bdat>   Generated on XXXXXXXXX XX:XX

<Ordered by: Screening Number>
<Stratified by: Group>
< Average sticks consumed per day / No. of empty e-liquid refill bottles returned>

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Listing D.11 Product use recording < Group HnB / Group EC >

Screening Number	Random. Number	Age/Gender	Q1	If yes, specify type and amount of daily use	Q2	If yes, average <sticks/e-liquid in ml consumed> per day
XXXXXX	XXXXXX	XX/XXXX	XXX	XXXXXXXXXXXXXXXXXXXXXXXXX	XXX	XXXXXXXXXX
XXXXXX	XXXXXX	XX/XXXX	XXX	XXXXXXXXXXXXXXXXXXXXXXXXX	XXX	XXXXXXXXXX
XXXXXX	XXXXXX	XX/XXXX	XXX	XXXXXXXXXXXXXXXXXXXXXXXXX	XXX	XXXXXXXXXX
XXXXXX	XXXXXX	XX/XXXX	XXX	XXXXXXXXXXXXXXXXXXXXXXXXX	XXX	XXXXXXXXXX
XXXXXX	XXXXXX	XX/XXXX	XXX	XXXXXXXXXXXXXXXXXXXXXXXXX	XXX	XXXXXXXXXX
XXXXXX	XXXXXX	XX/XXXX	XXX	XXXXXXXXXXXXXXXXXXXXXXXXX	XXX	XXXXXXXXXX
XXXXXX	XXXXXX	XX/XXXX	XXX	XXXXXXXXXXXXXXXXXXXXXXXXX	XXX	XXXXXXXXXX
XXXXXX	XXXXXX	XX/XXXX	XXX	XXXXXXXXXXXXXXXXXXXXXXXXX	XXX	XXXXXXXXXX
XXXXXX	XXXXXX	XX/XXXX	XXX	XXXXXXXXXXXXXXXXXXXXXXXXX	XXX	XXXXXXXXXX
XXXXXX	XXXXXX	XX/XXXX	XXX	XXXXXXXXXXXXXXXXXXXXXXXXX	XXX	XXXXXXXXXX

<File: [..]\\Work_In_Progress\[..]\Statistica\Programmi\xxxxx.sas>
<Source: [..]\\Work_In_Progress\[..]\Gestione Dati\Dati SAS\xxxxx.sas7bdat> Generated on XXXXXXXXX XX:XX

Q1: Did the subject use different RRP or other anti-smoking products during the last three months?
Q2: If no, are you using the products delivered by this study?

<Ordered by: Screening Number>
<Stratified by: Group>

EFFICACY DATA

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Listing E.1 EQ-5D <Group HnB / Group EC >

Screening Number	Random. Number	Age/Gender	Visit	Q1	Q2	Q3	Q4	Q5	Q6
XXXXXX	XXXXXX	XX.X/XXXX	XXXXXXX	X	X	X	X	X	XXX
			XXXXXXX	X	X	X	X	X	XXX
			XXXXXXX	X	X	X	X	X	XXX
			XXXXXXX	X	X	X	X	X	XXX
XXXXXX	XXXXXX	XX.X/XXXX	XXXXXXX	X	X	X	X	X	XXX
			XXXXXXX	X	X	X	X	X	XXX
			XXXXXXX	X	X	X	X	X	XXX
			XXXXXXX	X	X	X	X	X	XXX
XXXXXX	XXXXXX	XX.X/XXXX	XXXXXXX	X	X	X	X	X	XXX
			XXXXXXX	X	X	X	X	X	XXX
			XXXXXXX	X	X	X	X	X	XXX
			XXXXXXX	X	X	X	X	X	XXX
XXXXXX	XXXXXX	XX.X/XXXX	XXXXXXX	X	X	X	X	X	XXX
			XXXXXXX	X	X	X	X	X	XXX
			XXXXXXX	X	X	X	X	X	XXX
			XXXXXXX	X	X	X	X	X	XXX

<File: [..]\\Work_In_Progress\[..]\Statistica\Programmi\xxxxx.sas>
<Source: [..]\\Work_In_Progress\[..]\Gestione Dati\Dati SAS\xxxxx.sas7bdat>   Generated on XXXXXXXXX XX:XX

<Ordered by: Screening Number>
<Stratified by: Group>

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Listing E.2 MCEQ <Group HnB / Group EC >

Screening Number	Random. Number	Age/Gender	Visit	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12
XXXXXX	XXXXXX	XX.X/XXXX	XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X
XXXXXX	XXXXXX	XX.X/XXXX	XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X
XXXXXX	XXXXXX	XX.X/XXXX	XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X
XXXXXX	XXXXXX	XX.X/XXXX	XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X

<File: [..]\\Work_In_Progress\[..]\Statistica\Programmi\xxxxx.sas>
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<Ordered by: Screening Number>
<Stratified by: Group>

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Listing E.3 Smoking cue appeal <Group HnB / Group EC >

Screening Number	Random. Number	Age/Gender	Visit	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
XXXXXX	XXXXXX	XX.X/XXXX	XXXXXXX	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X
XXXXXX	XXXXXX	XX.X/XXXX	XXXXXXX	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X
XXXXXX	XXXXXX	XX.X/XXXX	XXXXXXX	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X
XXXXXX	XXXXXX	XX.X/XXXX	XXXXXXX	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X

<File: [..]\\Work_In_Progress\[..]\Statistica\Programmi\xxxxx.sas>
<Source: [..]\\Work_In_Progress\[..]\Gestione Dati\Dati SAS\xxxxx.sas7bdat> Generated on XXXXXXXXX XX:XX

<Ordered by: Screening Number>
<Stratified by: Group>

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Listing E.4 ITUQ <Group HnB / Group EC >

Screening Number	Random. Number	Age/Gender	Visit	Q4	Q5	Q6
XXXXXX	XXXXXX	XX.X/XXXX	XXXXXXX	X	X	X
			XXXXXXX	X	X	X
			XXXXXXX	X	X	X
			XXXXXXX	X	X	X
XXXXXX	XXXXXX	XX.X/XXXX	XXXXXXX	X	X	X
			XXXXXXX	X	X	X
			XXXXXXX	X	X	X
			XXXXXXX	X	X	X
XXXXXX	XXXXXX	XX.X/XXXX	XXXXXXX	X	X	X
			XXXXXXX	X	X	X
			XXXXXXX	X	X	X
			XXXXXXX	X	X	X
XXXXXX	XXXXXX	XX.X/XXXX	XXXXXXX	X	X	X
			XXXXXXX	X	X	X
			XXXXXXX	X	X	X
			XXXXXXX	X	X	X

<File: [..]\\Work_In_Progress\[..]\Statistica\Programmi\xxxxx.sas>
<Source: [..]\\Work_In_Progress\[..]\Gestione Dati\Dati SAS\xxxxx.sas7bdat>   Generated on XXXXXXXXX XX:XX

<Ordered by: Screening Number>
<Stratified by: Group>

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Listing E.5 Risk perception CC <Group HnB / Group EC >

Screening Number	Random. Number	Age/Gender	Visit	Screen 1/3 Q1	Q2	Q3	Q4	Q5	Q6	Screen 2/3 Q1	Q2	Q3	Q4	Q5	Q6	Screen 3/3 Q1	Q2	Q3	Q4	Q5	Q6
XXXXXX	XXXXXX	XX.X/XXXX	XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
XXXXXX	XXXXXX	XX.X/XXXX	XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
XXXXXX	XXXXXX	XX.X/XXXX	XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
XXXXXX	XXXXXX	XX.X/XXXX	XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

<File: [..]\\Work_In_Progress\[..]\Statistica\Programmi\xxxxx.sas>
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<Ordered by: Screening Number>
<Stratified by: Group>

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Listing E.6 Risk perception RRP <Group HnB / Group EC >

Screening Number	Random. Number	Age/Gender	Visit	Screen 1/3 Q1	Q2	Q3	Q4	Q5	Q6	Screen 2/3 Q1	Q2	Q3	Q4	Q5	Q6	Screen 3/3 Q1	Q2	Q3	Q4	Q5	Q6
XXXXXX	XXXXXX	XX.X/XXXX	XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
XXXXXX	XXXXXX	XX.X/XXXX	XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
XXXXXX	XXXXXX	XX.X/XXXX	XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
XXXXXX	XXXXXX	XX.X/XXXX	XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			XXXXXXX	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

<File: [..]\\Work_In_Progress\[..]\Statistica\Programmi\xxxxx.sas>
<Source: [..]\\Work_In_Progress\[..]\Gestione Dati\Dati SAS\xxxxx.sas7bdat>   Generated on XXXXXXXXX XX:XX

<Ordered by: Screening Number>
<Stratified by: Group>

SAFETY DATA

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Listing S.1 Extent of Exposure and Study Duration <Group HnB / Group EC >

Screening Number	Random. Number	Age/Sex	Visit	Start Date	End Date	Days of Exposure
XXXXXX	XXXXXX	XX.X/XXXX	XX	XX/XX/XXXX	XX/XX/XXXX	XXX
XXXXXX	XXXXXX	XX.X/XXXX	XX	XX/XX/XXXX	XX/XX/XXXX	XXX
XXXXXX	XXXXXX	XX.X/XXXX	XX	XX/XX/XXXX	XX/XX/XXXX	XXX
XXXXXX	XXXXXX	XX.X/XXXX	XX	XX/XX/XXXX	XX/XX/XXXX	XXX
XXXXXX	XXXXXX	XX.X/XXXX	XX	XX/XX/XXXX	XX/XX/XXXX	XXX
XXXXXX	XXXXXX	XX.X/XXXX	XX	XX/XX/XXXX	XX/XX/XXXX	XXX
XXXXXX	XXXXXX	XX.X/XXXX	XX	XX/XX/XXXX	XX/XX/XXXX	XXX
XXXXXX	XXXXXX	XX.X/XXXX	XX	XX/XX/XXXX	XX/XX/XXXX	XXX
XXXXXX	XXXXXX	XX.X/XXXX	XX	XX/XX/XXXX	XX/XX/XXXX	XXX
XXXXXX	XXXXXX	XX.X/XXXX	XX	XX/XX/XXXX	XX/XX/XXXX	XXX
XXXXXX	XXXXXX	XX.X/XXXX	XX	XX/XX/XXXX	XX/XX/XXXX	XXX

<File: [..]\\Work_In_Progress\[..]\Statistica\Programmi\xxxxx.sas>
<Source: [..]\\Work_In_Progress\[..]\Gestiona Dati\Dati SAS\xxxxx.satd7sas> Generated on XXXXXXXXX XX:XX

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Listing S.2 Adverse Events <Group HnB / Group EC >

Screen. Number	Random. Number	Age/Sex	N. AE	AE Description	If other specify	AE Severity	Is the AE Serious?	If Serious	If Death Specify date	If death autopsy?	If hospitalization Start Date	End Date	Outcome	If recovery, recovery date	Relations with products?	Action Taken
XXXXXX	XXXXXX	X.X/XXXX	XX	XXXXXXXXXX	XXXXXXXX	XXX	XXX	XXXXXXXXXX	XX/XX/XXXX	XXX	XX/XX/XXXX	XX/XX/XXXX	XXXXXXX	XX/XX/XXXX	XXX	XXXXXXX
XXXXXX	XXXXXX	X.X/XXXX	XX	XXXXXXXXXX	XXXXXXXX	XXX	XXX	XXXXXXXXXX	XX/XX/XXXX	XXX	XX/XX/XXXX	XX/XX/XXXX	XXXXXXX	XX/XX/XXXX	XXX	XXXXXXX
XXXXXX	XXXXXX	X.X/XXXX	XX	XXXXXXXXXX	XXXXXXXX	XXX	XXX	XXXXXXXXXX	XX/XX/XXXX	XXX	XX/XX/XXXX	XX/XX/XXXX	XXXXXXX	XX/XX/XXXX	XXX	XXXXXXX
XXXXXX	XXXXXX	X.X/XXXX	XX	XXXXXXXXXX	XXXXXXXX	XXX	XXX	XXXXXXXXXX	XX/XX/XXXX	XXX	XX/XX/XXXX	XX/XX/XXXX	XXXXXXX	XX/XX/XXXX	XXX	XXXXXXX
XXXXXX	XXXXXX	X.X/XXXX	XX	XXXXXXXXXX	XXXXXXXX	XXX	XXX	XXXXXXXXXX	XX/XX/XXXX	XXX	XX/XX/XXXX	XX/XX/XXXX	XXXXXXX	XX/XX/XXXX	XXX	XXXXXXX
XXXXXX	XXXXXX	X.X/XXXX	XX	XXXXXXXXXX	XXXXXXXX	XXX	XXX	XXXXXXXXXX	XX/XX/XXXX	XXX	XX/XX/XXXX	XX/XX/XXXX	XXXXXXX	XX/XX/XXXX	XXX	XXXXXXX
XXXXXX	XXXXXX	X.X/XXXX	XX	XXXXXXXXXX	XXXXXXXX	XXX	XXX	XXXXXXXXXX	XX/XX/XXXX	XXX	XX/XX/XXXX	XX/XX/XXXX	XXXXXXX	XX/XX/XXXX	XXX	XXXXXXX
XXXXXX	XXXXXX	X.X/XXXX	XX	XXXXXXXXXX	XXXXXXXX	XXX	XXX	XXXXXXXXXX	XX/XX/XXXX	XXX	XX/XX/XXXX	XX/XX/XXXX	XXXXXXX	XX/XX/XXXX	XXX	XXXXXXX
XXXXXX	XXXXXX	X.X/XXXX	XX	XXXXXXXXXX	XXXXXXXX	XXX	XXX	XXXXXXXXXX	XX/XX/XXXX	XXX	XX/XX/XXXX	XX/XX/XXXX	XXXXXXX	XX/XX/XXXX	XXX	XXXXXXX
XXXXXX	XXXXXX	X.X/XXXX	XX	XXXXXXXXXX	XXXXXXXX	XXX	XXX	XXXXXXXXXX	XX/XX/XXXX	XXX	XX/XX/XXXX	XX/XX/XXXX	XXXXXXX	XX/XX/XXXX	XXX	XXXXXXX

<File: [..]\\Work_In_Progress\[..]\Statistica\Programmi\xxxxx.sas>
<Source: [..]\\Work_In_Progress\[..]\Gestione Dati\Dati SAS\xxxxx.satd7sas> Generated on XXXXXXXXX XX:XX

AE Severity: 0=Mild ; 1=Moderate ; 2=Severe
AE Serious: 0=Death ; 1=Life threatening ; 2=Hospitalization or prolonged hospitalization ; 3=Permanent significant disability
4=Congenital anomaly/birth deficit ; 5=Medical important event
Outcome: 1=Recovered without Sequelae ; 2=Recovered with Sequelae ; 3=Ongoing ; 4=Persisting ; 5=Unknown
Relationship: 0=Not Related ; 1=Unlikely ; 2=Possible ; 1=Probably ; 2=Definitive
Action Taken: 0=No action taken ; 1=Study product dosage adjusted ; 2=Study product temporarily interrupted

Sponsor: Center for Tobacco Research, Cessation and Prevention, Via S. Sofia 78, 95123, Catania (CT) - Italy
Protocol: Progetto e-cig vs IQOS

Listing S.3 Vital Signs <Group HnB / Group EC >

Screening Number	Random. Number	Age/Gender	Visit	Date of Visit	Parameter #1 <u.m.>	Parameter #2 <u.m.>	. . . .	Parameter #n <u.m.>
XXXXXX	XXXXXX	XX.X/XXXX	XX	XX/XX/XXXX	XXX.X	XXX.X	XXX.X	XXX.X
			XX	XX/XX/XXXX	XXX.X	XXX.X	XXX.X	XXX.X
			XX	XX/XX/XXXX	XXX.X	XXX.X	XXX.X	XXX.X
			XX	XX/XX/XXXX	XXX.X	XXX.X	XXX.X	XXX.X
			XX	XX/XX/XXXX	XXX.X	XXX.X	XXX.X	XXX.X
XXXXXX	XXXXXX	XX.X/XXXX	XX	XX/XX/XXXX	XXX.X	XXX.X	XXX.X	XXX.X
			XX	XX/XX/XXXX	XXX.X	XXX.X	XXX.X	XXX.X
			XX	XX/XX/XXXX	XXX.X	XXX.X	XXX.X	XXX.X
			XX	XX/XX/XXXX	XXX.X	XXX.X	XXX.X	XXX.X
			XX	XX/XX/XXXX	XXX.X	XXX.X	XXX.X	XXX.X
XXXXXX	XXXXXX	XX.X/XXXX	XX	XX/XX/XXXX	XXX.X	XXX.X	XXX.X	XXX.X
			XX	XX/XX/XXXX	XXX.X	XXX.X	XXX.X	XXX.X
			XX	XX/XX/XXXX	XXX.X	XXX.X	XXX.X	XXX.X
			XX	XX/XX/XXXX	XXX.X	XXX.X	XXX.X	XXX.X
			XX	XX/XX/XXXX	XXX.X	XXX.X	XXX.X	XXX.X
XXXXXX	XXXXXX	XX.X/XXXX	XX	XX/XX/XXXX	XXX.X	XXX.X	XXX.X	XXX.X
			XX	XX/XX/XXXX	XXX.X	XXX.X	XXX.X	XXX.X
			XX	XX/XX/XXXX	XXX.X	XXX.X	XXX.X	XXX.X
			XX	XX/XX/XXXX	XXX.X	XXX.X	XXX.X	XXX.X
			XX	XX/XX/XXXX	XXX.X	XXX.X	XXX.X	XXX.X

<File: [..]\\Work_In_Progress\[..]\Statistica\Programmi\xxxxx.sas>
<Source: [..]\\Work_In_Progress\[..]\Gestione Dati\Dati SAS\xxxxx.satd7sas> Generated on XXXXXXXXX XX:XX

APPENDIX 4
Flow Chart

	V0 screening	V1 baseline	V2	V3	V4	V5	V6	V7 follow-up
Assessment		≤ 7 days after V0	1 week after visit 1 +/-3 days	2 weeks after visit 1 +/-3 days	4 weeks after visit 1 +/-3 days	8 weeks after visit 1 +/-7 days	12 weeks after visit 1 +/-7 days	24 weeks after visit 1 +/-7 days
Medical/smoking/vaping/new generation product use history	X							X
Instructions for urine collection and storage; delivery of containers	X			X				
Eligibility criteria verification and confirmation	X							
Informed consent	X							
Vital Signs (BP, HR)		X	X	X	X	X	X	X
Weight and Height		X					X	X
Urine sample pick up		X			X			
Randomization		X						
Training for the allocated device (from 30min to 2 hours)		X						
Device delivery (included 1 week supply heatsticks for iQOS or eliquid for JustFog)		X						
Providing 1 week supply of heatsticks for iQOS or eliquid for JustFog			X					
Providing 2 weeks supply of heatsticks for iQOS or eliquid for JustFog				X				

Providing 4 weeks supply of heatsticks for iQOS or eliquid for JustFog					X	X		
Smoking consumption/abstinence/reduction recording through subject selfreporting		X	X	X	X	X	X	X
Device and supply accountability (collection of empty e-liquid refill bottles and used heathsticks; eventual substitution of malfunctioning devices)			X	X	X	X	X	X
mCEQ					X	X	X	X
Smoking Cue Appeal (8 items)					X	X	X	X
ITUQ – items 4-6					X	X	X	X
Risk perception (PRI-P CC e PRIP RRP)					X	X	X	X
EQ-5D		X			X	X	X	X
eCO		X	X	X	X	X	X	X
Step test		X			X		X	X
Safety and product reliability onitoring reporting		X	X	X	X	X	X	X

APPENDIX 5
DRM Minute

Titolo del Protocollo: A 12-weeks open label, non-inferiority trial comparing HnB products vs ECs in terms of efficacy and adoption rates, acceptability, tolerability, and tobacco harm reduction in healthy smokers, not motivated to quit.	**Versione**: 1.0 26 Settembre 2017
Prodotto: Sigaretta elettronica/HnB (Heat-not-Burn)	**Sponsor**: AOU Policlinico Vittorio Emanuele - University of Catania Centro per la cura e la prevenzione del tabagismo
Contatti:Pasquale Caponnetto - AOU Policlinico Vittorio Emanuele University of Catania Email: p.caponnetto@unict.it - Phone number: (+39) 095.3781537	

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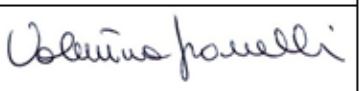
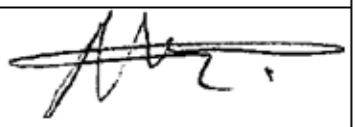
PARTECIPANTI			
Nome	**Qualifica**	**Data**	**Firma**
Riccardo Polosa	Direttore	01/07/2020	
Pasquale Caponnetto	Co-sperimentatore	01/07/2020	
Fabio Cibella	Consulente Statistico	01/07/2020	
Caruso Massimo	Responsabile Laboratorio	01/07/2020	
Marilena Maglia	Sub-sperimentatore	01/07/2020	
Rosalia Emma	Co-responasabile laboratorio	01/07/2020	
Valentina Granelli	Project Manager Fullcro		
Adrian Shallvari	Data Manager Fullcro		

NON PARTECIPANTI			
Nome	**Qualifica**	**Data**	**Firma**
Maria Signorelli	Sperimentatore Principale	01/07/2020	
Daniela Saitta	Project Manager	01/07/2020	

PARTECIPANTI			
Nome	**Qualifica**	**Data**	**Firma**
Riccardo Polosa	Direttore		
Pasquale Caponnetto	Co-sperimentatore		
Fabio Cibella	Consulente Statistico		
Caruso Massimo	Responsabile Laboratorio		
Marilena Maglia	Sub-sperimentatore		
Rosalia Emma	Co-responasabile laboratorio		
Valentina Granelli	Project Manager Fullcro	01/07/2020	
Adrian Shallvari	Data Manager Fullcro	01/07/2020	

STORIA DELLE VERSIONI

Versione	Data	Descrizione dei cambiamenti
Draft 0.1	12 Giugno 2020	Prima versione per la revisione del Team
Draft 0.2	23 Giugno 2020	Nuova versione successiva ad una call di chiarimento dopo il DRM
Finale 1.0	08 Luglio 2020	Versione finale dopo la revisione del team

INDICE

1 INTRODUZIONE

In data 10 Giugno 2020, sulla piattaforma zoom meeting, si è tenuto il "Data Review Meeting" (DRM) dello studio in oggetto. I partecipanti alla riunione sono elencati nella pagina firme. Il DRM si è svolto seguendo le indicazioni delle SOP di Fullcro Srl (CRO incaricata della gestine dello studio) e seguendo le indicazioni del Piano di Analisi Statistica (Statistical Analysis Plan) Versione 1.1 del 4 Giugno 2020.

Gli obiettivi del DRM erano definiti nell'Agenda inviata al Team il 5 Giugno 2020 che si riporta nell'Allegato 1.

Questo documento è strutturato sulla base dei punti elencati nell'Agenda. In particolare, per la definizione delle popolazioni in studio, in Allegato 2 è riportato l'elenco completo. Questa lista sarà inclusa dallo Statistico dello studio in un dataset derivato che farà parte integrante del database clinico.

In ogni sezione del presente documento saranno elencate le decisioni prese dal Team sui vari argomenti. La firma del presente documento certificherà l'accettazione a maggioranza delle decisioni prese.

La minuta del DRM sarà inclusa come allegato del SAP Versione 2.0.

Il giorno 22 Giugno è stata fatta una call, sempre su piattaforma zoom meeting, al fine chiarire alcuni punti emersi durante la revisione della Minuta del DRM. Le decisioni vanno ad integrare il presente documento nella sua versione draft 0.2. Una volta approvato da tutto il team, verrà prodotta la versione finale che sarà inserita nel SAP.

2 ARGOMENTI IN AGENDA

2.1 Problemi non risolti sui dati

Il primo congelamento del Database è stato fatto in data 5 Giugno 2020. Il System Administrator (SA) della eCRF (electronic Case Report Form) di Fullcro ha revocato tutti I diritti di accesso in scrittura. A seguire è stato fatto un "cleaning" dei dati. Sul Database è emersa una sola inconsistenza:

Tabella: Eventi Avversi

Soggetto: 121

Num. evento: 3

Campo inconsistente: Descrizione

Contunuto: "OARLIC VOICE"

Decisione del Team

Una volta finalizzata la presente minuta, il PM dello studio richiederà lo scongelamento del Database seguendo le indicazioni della SOP Fullcro dedicata. Il SA rilascerà le credenziali in scrittura al PI per la modifica del dato.

2.2 Identificazione dei violatori

Utilizzando un listato per soggetto, preparato dallo Statistico dello studio, il Team ha esaminato tutte le possibili violazioni al protocollo. Il listato era strutturato per tipologia di violazione:

1. Criteri di selezione
2. Aderenza
3. Uscita prematura dallo studio
4. Finestre di accettabilità sulle date visita

Nel corso della riunione sono stati identificati quattro "screening failure", soggetti che, arruolati (visita 0 – screening) non sono stati randomizzati. Questa è la lista:

Soggetti n.: 055 – 113 – 118 – 195

Questi soggetti sono stati esclusi da tutte le popolazioni di analisi.

Di seguito sono riportati i risultati e le decisioni del Team su ognuna delle quattro categorie.

1 - Criteri di selezione

Non è stata osservata nessuna violazione.

Decisione del Team

N.A.

2 - Aderenza

Per "aderenza" il Team ha confermato la definizione riportata nel SAP:

considerando il totale dei giorni di studio da V1 a V6 al denominatore e il totale dei giorni di effettivo uso del prodotto oggetto dello studio (derivati dal diario del soggetto) al numeratore per lo stesso nel periodo (es. 45 gg di utilizzo/90 gg da V1 a V6 = 0,50); il soggetto è considerato "aderente" se il risultato è maggiore/uguale a 0,90.

Decisione del Team

Fissata la soglia del 90%, il Team ha deciso che nel range 70%-90% la violazione del soggetto era MINORE. Sotto la soglia del 70% il soggetto era da considerarsi violatore MAGGIORE.

Nella call del 22 Giugno è stato introdotto un ulteriore criterio per l'identificazione dei violatori. Non sarà considerato violatore MAGGIORE il soggetto che, nonostante abbia aderenza sotto la soglie del 70%, sia un "Continuous Quitter", cioè, non abbia consumeto sigarette convenzionali da Visita 4 a Visita 6. Due soggetti non aderenti sono stati considerati nella popolazione Per-Protocol in quanto da Visita 4 hanno smesso di fumare sigarette convenzionali:

064 ; 119

Lista delle violazioni MAGGIORI

Soggetti numero:

004 011 012 015 018 032 036 048 059 066 090 098 115

122 124 130 156 162 167 181 188 193 199

Lista delle violazioni MINORI

Soggetti numero:

002 039 042 080 086 135 136 140 147 149 160 179 212

3 – Uscita prematura dallo studio

Per definizione, tutti i soggetti "drop-out" a Visita 6 sono da ritenersi violatori MAGGIORI. Tutti i soggetti che escono dallo studio dopo Visita 2 sono stati esclusi solo dalla popolazione Per-Protocol. I soggetti che escono dallo studio dopo Visita 1 sono stati esclusi anche dalla popolazione ITT.

Nalla call del 22 Giugno è stato deciso di considerare una seconda popolazione PP, la "Per-Protocol V7", composta da tutti i soggetti, non violatori, che completano anche la visita di follow-up (Visita 7).

Decisione del Team

Nessuna osservazione da parte del Team.

Lista delle violazioni MAGGIORI – soggetti non inclusi nella popolazione PP

Soggetti numero:

012 015 018 048 130 137 163 183 189

Lista delle violazioni MAGGIORI – soggetti non inclusi nella popolazione PPV7

Soggetti numero:

032 090 167 180 034 071 074 077 079 091 095 103 112 115

124 129 184 194 202 206 214

Lista delle violazioni MAGGIORI – soggetti non inclusi nelle popolazioni ITT e PP

Soggetti numero:

015 163 183

4 – Finistre di accettabilità sulle date visita

Il Protocollo prevedeva una finestra di accettabilità sulle date di ogni visita. In dettaglio:

Visita 1: ≤7 giorni rispetto a Visita 0

Visite 2-3-4: ±3 giorni rispetto a Visita 1

Visite 5-6-7: ±7 giorni rispetto a Visita 1

Decisione del Team

Dopo un'attenta analisi del listato, considerando la tipologia dello studio, il Team ha ritenuto che le piccole differenze rispetto alle finestre di accettabilità osservate in alcune visite non sono da considerare violazioni.

2.3 Identificazione delle popolazioni di analisi

Utilizzando il listato citato, è stato possibile identificare i soggetti da includere nelle tre popolazioni di analisi. La numerosità delle popolazioni è la seguente:

Popolazione **Safety**: 220

Popolazione **Intention-To-Treat**: 217

Popolazione **Per-Protocol**: 193

Popolazione **Per-Protocol V7**: 177

Il dettaglio per soggetto è riportato in Allegato 2.

2.4 Scelta del metodo di replicazione dei valori mancanti

Per l'analisi inferenziale degli endpoint a risposta, il soggetto drop-out è per definizione un "non Responder" (non quitter/failure). Per gli altri endpoint, come riportato nel Capitolo 5.1 del SAP, il metodo di replicazione dei dati mancanti sarà il LOCF (Last Observation Carried Forward).

2.5 Finalizzazione del SAP Vers. 2.0

Nessuna modifica del SAP Versione 1.1 è stata richiesta per cui la versione 2.0 includerà solamente la sezione "Decisioni prese durante il DRM" e l'allegato "Minuta del DRM" con i suoi allegati.

2.6 Consistenza delle codifiche dei termini medici

Il listato delle codifiche dei termini medici (solo Eventi Avversi) è stato inviato dallo Statistico al Team il 5 Giugno. A parte il termine non codificato (vedi Sezione 2.1) non è stata segnalata nessuna inconsistenza.

2.7 Riconciliazione degli Eventi Avversi Seri

N.A. (nessun Evento Avverso Serio osservato durante lo studio).

2.8 Definizione delle attività propedeutiche al congelamento del DB

Una volta finalizzata la presente minuta, il PM chiederà lo scongelamento del DB per permettere l'inserimento delle ultime query e la loro risoluzione. Quando il SA avrà verificato la completezza dei dati (data cleaning), si procederà con il secondo congelamento.

2.9 Decisione di inviare la minuta al CE

Al momento il Team ha deciso di non inviare la minuta al CE.

3 ALLEGATI

ALLEGATO 1 Agenda del DRM

ALLEGATO 2 Listato delle popolazioni di analisi

ALLEGATO 1

Agenda del DRM

DATA REVIEW MEETING

10 June 2020

(The meeting will be held by conference call)

AGENDA

1. Review of the not already solved problems on the data (pending discrepancies, missing data, other pending issues).
2. Identification of the Protocol violations (randomization, Inclusion/Exclusion Criteria, low compliance, other violations).
3. Identification of the analysis populations.
4. Values to replace the missing values (drop-out patients) for the Intention-to-treat analysis.
5. Finalization of the Statistical Analysis Plan (SAP Version 2.0).
6. Consistency check on the coding.
7. Review on the possible inconsistencies between the SAEs Data Base and the clinical Data Base still not solved.
8. Definition of all the activities necessary for the Data Base freezing.
9. Discussion on the opportunity to send the Data Review Meeting minute and the SAP to the Ethic Committee

ALLEGATO 2

Listato delle popolazioni di analisi

NumPaz	Safety	ITT	PP	PPV7
01-001	Y	Y	Y	Y
01-002	Y	Y	Y	Y
01-003	Y	Y	Y	Y
01-004	Y	Y	N	N
01-005	Y	Y	Y	Y
01-006	Y	Y	Y	Y
01-007	Y	Y	Y	Y
01-008	Y	Y	Y	Y
01-009	Y	Y	Y	Y
01-010	Y	Y	Y	Y
01-011	Y	Y	N	N
01-012	Y	Y	N	N
01-013	Y	Y	Y	Y
01-014	Y	Y	Y	Y
01-015	Y	N	N	N
01-016	Y	Y	Y	Y
01-017	Y	Y	Y	Y
01-018	Y	Y	N	N
01-019	Y	Y	Y	Y
01-020	Y	Y	Y	Y
01-021	Y	Y	Y	Y
01-022	Y	Y	Y	Y
01-023	Y	Y	Y	Y
01-024	Y	Y	Y	Y
01-025	Y	Y	Y	Y
01-026	Y	Y	Y	Y
01-027	Y	Y	Y	Y
01-028	Y	Y	Y	Y
01-029	Y	Y	Y	Y
01-030	Y	Y	Y	Y
01-031	Y	Y	Y	Y
01-032	Y	Y	N	N
01-033	Y	Y	Y	Y
01-034	Y	Y	Y	N
01-035	Y	Y	Y	Y
01-036	Y	Y	N	N
01-037	Y	Y	Y	Y
01-038	Y	Y	Y	Y
01-039	Y	Y	Y	Y
01-040	Y	Y	Y	Y

01-041	Y	Y	Y	Y
01-042	Y	Y	Y	Y
01-043	Y	Y	Y	Y
01-044	Y	Y	Y	Y
01-045	Y	Y	Y	Y
01-046	Y	Y	Y	Y
01-047	Y	Y	Y	Y
01-048	Y	Y	N	N
01-049	Y	Y	Y	Y
01-050	Y	Y	Y	Y
01-051	Y	Y	Y	Y
01-052	Y	Y	Y	Y
01-053	Y	Y	Y	Y
01-054	Y	Y	Y	Y
01-055	N	N	N	N
01-056	Y	Y	Y	Y
01-057	Y	Y	Y	Y
01-058	Y	Y	Y	Y
01-059	Y	Y	N	N
01-060	Y	Y	Y	Y
01-061	Y	Y	Y	Y
01-062	Y	Y	Y	Y
01-063	Y	Y	Y	Y
01-064	Y	Y	Y	Y
01-065	Y	Y	Y	Y
01-066	Y	Y	N	N
01-067	Y	Y	Y	Y
01-068	Y	Y	Y	Y
01-069	Y	Y	Y	Y
01-070	Y	Y	Y	Y
01-071	Y	Y	Y	N
01-072	Y	Y	Y	Y
01-073	Y	Y	Y	Y
01-074	Y	Y	Y	N
01-075	Y	Y	Y	Y
01-076	Y	Y	Y	Y
01-077	Y	Y	Y	N
01-078	Y	Y	Y	Y
01-079	Y	Y	Y	N
01-080	Y	Y	Y	Y
01-081	Y	Y	Y	Y

01-082	Y	Y	Y	Y
01-083	Y	Y	Y	Y
01-084	Y	Y	Y	Y
01-085	Y	Y	Y	Y
01-086	Y	Y	Y	Y
01-087	Y	Y	Y	Y
01-088	Y	Y	Y	Y
01-089	Y	Y	Y	Y
01-090	Y	Y	N	N
01-091	Y	Y	Y	N
01-092	Y	Y	Y	Y
01-093	Y	Y	Y	Y
01-094	Y	Y	Y	Y
01-095	Y	Y	Y	N
01-096	Y	Y	Y	Y
01-097	Y	Y	Y	Y
01-098	Y	Y	N	N
01-099	Y	Y	Y	Y
01-100	Y	Y	Y	Y
01-101	Y	Y	Y	Y
01-102	Y	Y	Y	Y
01-103	Y	Y	Y	N
01-104	Y	Y	Y	Y
01-105	Y	Y	Y	Y
01-106	Y	Y	Y	Y
01-107	Y	Y	Y	Y
01-108	Y	Y	Y	Y
01-109	Y	Y	Y	Y
01-110	Y	Y	Y	Y
01-111	Y	Y	Y	Y
01-112	Y	Y	Y	N
01-113	N	N	N	N
01-114	Y	Y	Y	Y
01-115	Y	Y	N	N
01-116	Y	Y	Y	Y
01-117	Y	Y	Y	Y
01-118	N	N	N	N
01-119	Y	Y	Y	Y
01-120	Y	Y	Y	Y
01-121	Y	Y	Y	Y
01-122	Y	Y	N	N

01-123	Y	Y	Y	Y
01-124	Y	Y	N	N
01-125	Y	Y	Y	Y
01-126	Y	Y	Y	Y
01-127	Y	Y	Y	Y
01-128	Y	Y	Y	Y
01-129	Y	Y	Y	N
01-130	Y	Y	N	N
01-131	Y	Y	Y	Y
01-132	Y	Y	Y	Y
01-133	Y	Y	Y	Y
01-134	Y	Y	Y	Y
01-135	Y	Y	Y	Y
01-136	Y	Y	Y	Y
01-137	Y	Y	N	N
01-138	Y	Y	Y	Y
01-139	Y	Y	Y	Y
01-140	Y	Y	Y	Y
01-141	Y	Y	Y	Y
01-142	Y	Y	Y	Y
01-143	Y	Y	Y	Y
01-144	Y	Y	Y	Y
01-145	Y	Y	Y	Y
01-146	Y	Y	Y	Y
01-147	Y	Y	Y	Y
01-148	Y	Y	Y	Y
01-149	Y	Y	Y	Y
01-150	Y	Y	Y	Y
01-151	Y	Y	Y	Y
01-152	Y	Y	Y	Y
01-153	Y	Y	Y	Y
01-154	Y	Y	Y	Y
01-155	Y	Y	Y	Y
01-156	Y	Y	N	N
01-157	Y	Y	Y	Y
01-158	Y	Y	Y	Y
01-159	Y	Y	Y	Y
01-160	Y	Y	Y	Y
01-161	Y	Y	Y	Y
01-162	Y	Y	N	N
01-163	Y	N	N	N

01-164	Y	Y	Y	Y
01-165	Y	Y	Y	Y
01-166	Y	Y	Y	Y
01-167	Y	Y	N	N
01-168	Y	Y	Y	Y
01-169	Y	Y	Y	Y
01-170	Y	Y	Y	Y
01-171	Y	Y	Y	Y
01-172	Y	Y	Y	Y
01-173	Y	Y	Y	Y
01-174	Y	Y	Y	Y
01-175	Y	Y	Y	Y
01-176	Y	Y	Y	Y
01-177	Y	Y	Y	Y
01-178	Y	Y	Y	Y
01-179	Y	Y	Y	Y
01-180	Y	Y	Y	N
01-181	Y	Y	N	N
01-182	Y	Y	Y	Y
01-183	Y	N	N	N
01-184	Y	Y	Y	N
01-185	Y	Y	Y	Y
01-186	Y	Y	Y	Y
01-187	Y	Y	Y	Y
01-188	Y	Y	N	N
01-189	Y	Y	N	N
01-190	Y	Y	Y	Y
01-191	Y	Y	Y	Y
01-192	Y	Y	Y	Y
01-193	Y	Y	N	N
01-194	Y	Y	Y	N
01-195	N	N	N	N
01-196	Y	Y	Y	Y
01-197	Y	Y	Y	Y
01-198	Y	Y	Y	Y
01-199	Y	Y	N	N
01-200	Y	Y	Y	Y
01-201	Y	Y	Y	Y
01-202	Y	Y	Y	N
01-203	Y	Y	Y	Y
01-204	Y	Y	Y	Y

01-205	Y	Y	Y	Y
01-206	Y	Y	Y	N
01-207	Y	Y	Y	Y
01-208	Y	Y	Y	Y
01-209	Y	Y	Y	Y
01-210	Y	Y	Y	Y
01-211	Y	Y	Y	Y
01-212	Y	Y	Y	Y
01-213	Y	Y	Y	Y
01-214	Y	Y	Y	N
01-215	Y	Y	Y	Y
01-216	Y	Y	Y	Y
01-217	Y	Y	Y	Y
01-218	Y	Y	Y	Y
01-219	Y	Y	Y	Y
01-220	Y	Y	Y	Y
01-221	Y	Y	Y	Y
01-222	Y	Y	Y	Y
01-223	Y	Y	Y	Y
01-224	Y	Y	Y	Y