STUDY PROTOCOL

Date	26 September 2017 - version 1
Study Type	*Clinical*
Study title	***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***

Investigator details

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Regulatory framework

Ethical Considerations and compliance With Good Clinical Practice (GCP)
This study will be conducted in compliance with Institutional Review Board/ Independent Ethics Committee (IRB/IEC) and privacy regulations. In addition, all local regulatory requirements will be adhered to, in particular those which afford greater protection to the safety of the trial participants. This study will be conducted in general according to the Declaration of Helsinki and with local laws and regulations relevant to the use of new therapeutic agents in the country of conduct.

Informed Consent
The investigator, or a person designated by the investigator, will explain the benefits and risks of participation in the study to each subject, subject's legally acceptable representative or impartial witness and obtain written informed consent prior to the subject entering the study (before initiation of protocol-specified procedures). The informed consent document must be approved by IRB/IEC and must be in compliance with ICHGCP and in accordance with local regulatory and legal requirements, in language readily understood by the subject. Each subject's original consent form, signed and dated by the subject or by the subject's legally acceptable representative, and a witness to the informed consent discussion, will be retained by the investigator.

Insurance
The sponsor of the clinical trial shall submit to the Ethics Committee an insurance certificate in Italian, duly executed by the insurance company under a valid insurance policy, which is to make explicit reference to the proposed interventional study and describe its essential aspects as provided by the Italian Law.
The insurance policy is to grant specific cover in connection with the reimbursement of damages caused to the subjects by the clinical trial activities throughout the entire duration thereof, thus covering any civil liability of investigator and sponsor of the clinical trial, without excluding any damage which may be unintentionally caused by accident and/or be attributed to negligence, imprudence or inexperience.

1. SCIENTIFIC INFORMATION

Background & Rationale

Cigarette smoke contains a mixture of over 7000 chemicals many of which harm the human body causing a broad range of diseases (1). Smoking is the leading cause of preventable premature mortality in the world; total tobacco attributable deaths are projected to increase from approximately 5 million per year today to over 8 million annually by 2030 (2). Death is mainly caused by ischemic heart disease, stroke, lung cancer and the catastrophic complications of advanced stage chronic obstructive pulmonary disease (COPD) and quitting smoking is known to reduce the risk of developing these diseases (1-3). But while smoking cessation may be the most desirable final outcome from a health point of view (4), many smokers are unable or unwilling to quit. A realistic alternative is to encourage these smokers to switch to less harmful sources of nicotine and select the ones that give the greatest probability of eliminating or substantially reducing exposure to combustible toxicants from tobacco smoking (5).

Amongst the available nicotine-containing reduced risk products, the **electronic cigarette** (EC) has been rapidly gaining on conventional cigarettes (6). The growing popularity of ECs appears to be associated with several factors including efficiency at reducing cigarette consumption whilst to continue having a 'smoking' experience, competitive

prices, and the perception of a much less harmful smoking alternative (7,8) given that vapour toxicology is by far less problematic than tobacco cigarette toxicology (9).

Although the high rate of ECs trials demonstrates the strong latent demand for less harmful nicotine-containing products, at present, there is low rate of conversion from trial to usage of these products as shown in survey and clinical trials (10,11). This is indication that the current generation of ECs are not yet fit to bring about a fulfilling smoking experience.

Consequently, better performing conventional cigarette substitutes are required to meet the demand of adult smokers for reduced risk products. Second-generation ECs (or personal vaporizers) seem to assent to a more fulfilling sensorial experience, because nicotine delivery to the bloodstream has improved compared to first-generation ECs (12,13), and is approaching that of conventional cigarettes.

More recently, products that electrically heat tobacco have been introduced as an alternative to combustible tobacco cigarettes. By heating tobacco, the temperature reached is lower than that reached in the burning cone of a conventional lit-end cigarette. These new products, known as **Heat-not-Burn** (HnB), may potentially provide a more gratifying smoking experience with reduced exposure to tobacco toxicants (14,15).

With this in mind, we have designed 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), as better detailed below.

References

1. US Department of Health and Human Services. The Health Consequences of Smoking: 50 Years of Progress: a Report of the Surgeon General. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014.
2. World Health Organization. WHO Report on the Global Tobacco Epidemic, 2008 – The MPOWER package. Geneva: World Health Organization; 2008.
3. Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 yearobservations on male British doctors. BMJ. 2004;328:1519-28.
4. Polosa R, Benowitz NL: Treatment of nicotine addiction: present therapeutic options and pipeline developments. Trends PharmacolSci 2011, 32(5):281-289.
5. Polosa, R.; Rodu, B.; Caponnetto, P.; Maglia, M.; Raciti, C. A fresh look at tobacco harm reduction: The case for the electronic cigarette. Harm Reduct. J. 2013, 10.
6. Adelman DJ, Grainger M, Ayala V, Paxton K. Tobacco: New Years' Resolutions + E-Cigs = Weaker Volumes? New York: Morgan Stanley Research North America, March 7, 2013.
7. FarsalinosKE, Romagna G, Tsiapras D, Kyrzopoulos S, Voudris V. Characteristics, perceived side effects and benefits of electronic cigarette use: a worldwide survey of more than 19,000 consumers. International Journal of Environmental Research and Public Health. 2014;11(4):4356-4373.
8. EtterJF, Bullen C. Electronic cigarette: users profile, utilization, satisfaction and perceived efficacy. Addiction, 2011; 106(11):2017-2028.
9. FarsalinosKE, Polosa, R. Safety evaluation and risk assessment of electronic cigarettes as tobacco cigarettes substitutes: A systematic review. Therapeutic Advances in Drug Safety. 2014, 5: 67-86.
10. Dockrell M, Morrison R, Bauld L, McNeill A. E-cigarettes: prevalence and attitudes in Great Britain. Nicotine Tob Res. 2013 Oct;15(10):1737-44.
11, Caponnetto P, Campagna D, Cibella F, et al. (2013a) EffiCiency and Safety of an eLectroniccigAreTte (ECLAT) as Tobacco Cigarettes Substitute: A Prospective 12-Month Randomized Control Design Study. PLoS One, 8(6):e66317.
12. Dawkins L, Corcoran O: Acute electronic cigarette use: nicotine delivery and subjective effects in regular users. Psychopharmacology (Berl) 2014, 231(2):401-407.
13. FarsalinosKE, Spyrou A, Tsimopoulou K, Stefopoulos C, Romagna G, Voudris V: Nicotine absorption from electronic cigarette use: comparison between first and new-generation devices. Sci Rep 2014, 4:4133.
14. Frost-Pineda, K., Zedler, B.K., Oliveri, D., Liang, Q., Feng, S., Roethig, H.J., 2008c. 12-Week clinical exposure evaluation of a third-generation electrically heated cigarette smoking system (EHCSS) in adult smokers. Regul. Toxicol. Pharmacol. 52, 111–117.
15. Roethig, H.J., Koval, T., Muhammad-Kah, R., Jin, Y., Mendes, P., Unverdorben, M., 2010. Short term effects of reduced exposure to cigarette smoke on white blood cells, platelets and red blood cells in adult cigarette smokers. Regul. Toxicol. Pharmacol. 57, 333–337.

Scientific hypothesis, objective(s) & intended methodologies

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), as better detailed below.

Minimum Glossary

Efficacy: the quit rate derived from the use of the product (HnB or EC)
Adoption rate: the daily product use (HnB or EC), measured independently from tobacco cigarette consumption
Tolerability: the incidence of adverse or serious adverse events derived from the use of the product (HnB or EC)
Tobacco harm reduction: reduction of selected biomarkers of exposure in spot urine and improvement in some biological parameters.

Hyphotesis:
Expected quit rate based on most recent EC literature is about 20-25% and our hyphotesis is that differences in quit rates between products under investigation should not exceed 10-15% (as per non-inferiority definition).

Objectives:

Primary endpoint:
1) 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)]

Secondary endpoints:

2) 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;
3) 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];
4) 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.
5) 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.
6) 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-5D questionnaire);
7) to compare the **reliability** of HnB and EC, in terms of incidence and kind of malfunctioning events, through self-reporting.

Study Design and Study Plan

STUDY DESIGN: 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 220 healthy smokers, not motivated to quit, **randomized** (1:1) to switch to one of these products.

Before the baseline visit, a face to face screening (V0) for pre-eligibility will be conducted, and selected participants will be instructed on how to collect and store their morning urine before bringing it to the hospital on the day established for Baseline/Visit 1.

At baseline, participants will be randomized in two separate study groups. The randomization sequence will be computer generated by using blocks size of 4, with an allocation ratio of 1:1 for each of the study conditions (A, B). 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. A prospective evaluation of efficacy, adoption rates, acceptability and tolerability will be also recorded at 24-weeks, through a follow-up visit, as better detailed below.

SUBJECT POPULATION: 220 healthy smokers, not motivated to quit, will be randomized in two treatment groups in a 1:1 ratio. Sample size determination (better detailed below, in the relevant section) 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). According to these hypotheses the required number of participants per study arm is 104. Hence we intend to include 220 participants, 110 per group.

Inclusion criteria:

Subjects must meet all of the following inclusion criteria to be eligible for enrolment into the study:

1. Able to comply with the study procedures

2. Male or female healthy smokers aged ≥19

3. Smoking at least 10 cigarettes a day

4. Smoking for at least one year

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?’’)

6. Female smokers not planning to become pregnant are using an acceptable form of contraception.

Exclusion criteria:

The presence of any of the following will exclude a subject from study enrolment:

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.

2. Use of nicotine replacement therapy or other smoking cessation therapies within the last 3 months and at baseline.

3. Self-reported pregnancy, planned pregnancy or breastfeeding.

4. Tobacco industry employees and 1st degree relatives will be excluded in order to safeguard independence of the study.

PRODUCTS UNDER INVESTIGATION:

-Heat-not-Burn (HnB) = We will use **P.M.I. Platform 1**, a heat-not-burn tobacco product that does not involve combustion, generating a nicotine-containing aerosol. Its commercial name is iQOS, and it is composed by: 1) a tobacco stick – a novel patent-pending tobacco product with unique processed tobacco made from tobacco powder; 2) an electronic holder into which the tobacco stick is inserted and which heats the tobacco by means of an electronically controlled heating blade; 3) a charger that is used to recharge the holder after each use. We will use the three kind of **heatsticks** normally sold in Italy: Marlboro Blue, Marlboro Silver, and Marlboro White.

-Electronic cigarette (EC) = We will use the **Justfog Q16 Starter Kit,** one of the most sold in Italy for its high performance and quality, at an affordable price, and very easy-to-use especially for beginners; **and three kind of e-liquid tastes:** Riserva Country 16 mg; Riserva Toscana 16 mg; Artic 16 mg (2 tobacco-flavours and one menthol flavour, among the most sold in Italy, to be compared to the HnB heatsticks).

STUDY PLAN:

It is anticipated that it will take about 6 months to accomplish with all regulatory requirements (Ethics Committee review and approval, Legal Department review and approval, fully executed Agreement in place, call for tender procedures to select the CRO and the external lab). The clinical study, from the enrollment to the study close out for all the patients, will then have a total duration of 12 months. The planned start date for the clinical study is January 2018 and ending date is planned for December 2018.

Enrollment period will last 6 months with the support of a multi-channel advertising method. This will include location-based advertising on social networks, advertising in local media, information days organized within the city.

After that, the 12-week (3 months) randomized treatment period will follow. This will include 6 study visits, which will be performed at our Center for Tobacco Research, Cessation and Prevention. A follow-up visit will be performed at week 24 (V7). We remark that the free provision of the products will be given to the participants from baseline (V1) to visit 6 (V6) at week 12.

The last 4 months of the study will be dedicated to data cleaning, data analysis and writing of the draft interim and final report.

Dissemination activities will be performed after clinical study close out, as better described in the relevant section.

Study Procedures and Methods

Procedures

We will record data from every subject on an electronic CRF, provided by a CRO, named FULLCRO S.r.l (Rome, Italy).
The selected CRO is GCP compliant, 21 CFR Part 11 FDA compliant, listed in AIFA list of operating CRO.

Efficacy assessment:

The **efficacy** of HnB and EC, in terms of quit rates, will be assessed by self-reporting abstinence from classic cigarette [validated by an Exhaled breath Carbon monoxide (eCO) measurement ≤10ppm)]. Abstinence from smoking, defined as complete self-reported abstinence from tobacco smoking - not even a puff (together with an eCO concentration of ≤10ppm ppm) since the previous study visit[1], will be calculated at each study visit (‘‘quitters’’), including at week 24. Primary endpoint is, however, fixed at week 12.

1. Caponnetto P, Campagna D, Cibella F, et al. (2013a) EffiCiency and Safety of an eLectronic cigAreTte (ECLAT) as Tobacco Cigarettes Substitute: A Prospective 12-Month Randomized Control Design Study. PLoS One, 8(6):e66317.

Smoking reduction assessment:
A ≥ 50% reduction in the number of cig/day since baseline, defined as self-reported reduction in the number of cig/day compared to baseline, will be calculated at each study visit (‘‘reducers’’).

Adoption rates and adherence to product use assessments:
To compare the adoption rate, and adherence to product use in the two groups, we will collect (empty) e-liquid refill bottles and used heathsticks from V2 to V6, verified by a study diary filled daily by the subject, and their average consumption will be calculated on a daily basis. Final data source will be the study diary, in order to avoid underestimation of product usage due to forgetfulness in returning products, but we will evaluate also subjects' reliability comparing the data reported in the diary and the returned product counting.

Acceptability assessment:
Product satisfaction, effects on craving and nicotine withdrawal, product preferences, risk perception, subjective and sensorial effects to compare the acceptability of HnB and of EC, wiil be evaluated at wk 4, wk 8, wk 12 (+ follow-up at wk 24), by using:

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.

Safety and tolerability assessment:
Adverse and serious adverse events, symptoms thought to be related to tobacco smoking, EC or HnB use, and to withdrawal from nicotine will be recorded at baseline and at each subsequent study visit on the adverse event page of the eCRF. This procedure is better detailed in the relevant “Safety reporting” section below. Vital signs (BP, HR) will be recorded at each study visit. Body weight and height will be measured at baseline and wk 12 (+ follow-up at wk 24).

Tobacco Harm Reduction assessment:

a) we will record changes in Biomarkers of Biological Effects (BoBE) such as: eCO in the exhaled breath (i.e. eCO) will be assessed at each study visit (+ follow-up at wk 24); step test values at baseline, wk 4, wk 12 (+ follow-up at wk 24).

b) measurement of 14 selected Biomarkers of Exposure (BoE) in spot urine samples of study participants, at baseline (V1) and wk 4 (V4):
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.
Lab analysis: urine samples will be collected at baseline and wk 4, and sent to an external laboratory to search for any modifications in the above mentioned Biomarkers of Exposure (BoE); the lab selected is ABF GmbH: SOPs for urine collection and lab procedures are available and briefly described in the quotation attached.

c) Self-perception of “Tobacco Harm Reduction process**”** will be assessed by changes in quality of life score at baseline, wk 4, wk 8, wk 12 (+ follow-up at wk 24). The quality of life will be assessed by a validated visual analogic scale specifically designed to measure this topic and named “EQ-5D”;

Product Reliability assessment:

- Type and frequency of malfunctioning events (through participants self-reporting in the study diary) will be recorded in the eCRF at each study visits from wk 1 to wk 12 (+ follow-up at wk 24).

VISIT SCHEDULE

	V0 **(screening)**	Visit 1 (**baseline**)	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7 **Follow-up**
Assessment		**≤ 7 days after V0**	**1 week after visit +/-3 days**	**2 weeks after visit 1 +/-3 days**	**4 weeks after visit 1 +/-3days**	**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 self-reporting		X	X	X	X	X	X	X
Device and supply accountability (collection of empty e-liquid refill bottles			X	X	X	X	X	

and used heathsticks; eventual substitution of malfunctioning devices)								
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 PRI-P 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 monitoring/reporting		X	X	X	X	X	X	X

Visit schedule description:

V0: Screening visit for eligibility criteria. Recording of the medical history and smoking behavior of the participant. Selected participants will sign an Informed Consent. Selected participants will be instructed on how to collect and store their first morning urine (containers for urine collection will be delivered to them during the screening) before bringing it to the hospital on the day established for Baseline/Visit 1. (SOPs are available).

Visit 1 (V1) (to be programmed within 1 week from V0): Eligibility criteria confirmation, All Baseline assessments, Self-reported daily conventional cigarette consumption recording (baseline measurement), Randomisation, HnB or EC free supply for 1 week and familiarization period to choose the preferred flavor* (30 min to 2h, as specified below), training on product use, spot urine samples collection and storage.

Visit 2 (V2): Week 1 from V1 (with a tolerance of +/- 3 days): vital signs measurement, smoking abstinence/reduction assessment (self-reporting + eCO measurement), adoption rates assessment, HnB or EC free supply for 1 week.

Visit 3 (V3): Week 2 from V1 (with a tolerance of +/- 3 days): vital signs measurement, smoking abstinence/reduction assessment, adoption rates assessment, HnB or EC free supply for 2 weeks, repeat instructions for first morning urine collection and storage at V4 and delivery of containers.

Visit 4 (V4): Week 4 from V1 (with a tolerance of +/- 3 days): Second hand over of spot urine samples, vital signs measurement, smoking abstinence/reduction assessment, adoption rates assessment, quality of life perception assessment, HnB or EC free supply for 4 weeks, step test, acceptability assessment.

Visit 5 (V5): Week 8 from V1 (with a tolerance of +/- 7 days): vital signs measurement, smoking abstinence/reduction assessment, adoption rates assessment, quality of life perception assessment, HnB or EC free supply for 4 weeks, acceptability assessment.

Visit 6 (V6): Week 12 from V1 (with a tolerance of +/- 7 days): vital signs and weight/height measurement, smoking abstinence/reduction assessment, adoption rates assessment, quality of life perception assessment, acceptability assessment. End of product free provision.

Follow-up Visit (V7): Week 24 from V1 (with a tolerance of +/- 7 days): After 3 months from V6, a follow-up visit will be performed to assess the product usage and tolerability, medical/smoking/vaping/NGP behaviour, vital signs and weight/height measurement, step test, smoking abstinence/reduction assessment, quality of life perception assessment, acceptability assessment. It is remarked that the product free provision is stopped at V6.

Safety assessment (adverse and serious adverse events) and product reliability (eventual malfunctioning) will be monitored throughout the whole study and recorded in the eCFR.

***Remark**: At Baseline, during a period from 30 minutes to 2 hours, subjects will use and familiarize with their allocated product, as per randomization. In the same period, they will have the option to try and choose the preferred flavor of either e-liquid or heatstick, depending on the allocated arm. The choice must be maintained and cannot be changed for the 12-weeks study.

The subjects will be appropriately trained and counseled on the products, at baseline and during the whole study. Oral explanation, practical demonstration, brochures and direct help line with the investigators will be used for this objective. As specified in the exclusion criteria, the subjects will be alerted that, apart from using their allocated product and their own brand conventional cigarettes as they wish, they cannot use any other tobacco products during the 12-weeks study.

Discontinuation Criteria

Recruitment at the center may be stopped for reasons of particularly low recruitment, protocol violation, and unadequate data recording. Premature termination of this clinical trial may occur because of a regulatory authority

decision, or a change in opinion of the IRB.
The reason for a subject discontinuing from the study will be recorded in the case report form. A discontinuation occurs when an enrolled subject ceases participation in the study, regardless of the circumstances, prior to completion of the protocol. The investigator must determine the primary reason for discontinuation. Withdrawal due to adverse event should be distinguished from withdrawal due to insufficient response. A discontinuation must be reported immediately to the clinical monitor or his/her designated representative if it is due to a serious adverse event. The final evaluation required by the protocol will be performed at the time of study discontinuation. The investigator will record the reason for study discontinuation, provide or arrange for appropriate follow-up (if required) for such subjects, and document the course of the subject's condition. Subjects who discontinue product under study may continue participation in the study. Subjects will be required to maintain the visit schedule and may be eligible to continue participation in the nontreatment phase of the study.

Safety Reporting

Adverse Events

All observed or volunteered adverse events, or suspected causal relationship to study product, will be recorded on the adverse event page(s) of the eCRF. Adverse and serious adverse events, symptoms thought to be related to tobacco smoking, EC or HnB use, and to withdrawal from nicotine will be recorded and presented as per randomization arm. For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification. For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event (i.e., study product or other illness). The investigator is required to assess causality and indicate that assessment on the eCRF. Follow-up of the adverse event, after the date of study discontinuation, is required if the adverse event or its sequelae persist.

Serious Adverse Events

All serious adverse events (as defined below) regardless of study group or suspected relationship to study product must be reported immediately. A serious adverse event is any adverse experience that:
1. Results in death;
2. Is life-threatening;
3. Results in subject hospitalization;
4. Results in a persistent or significant disability/incapacity.

Statistical Analysis Plan

Sample size calculation

We assume that:

- current e-vapor products provide a 25% quitting rate in clinical trials (1,2)
- non-inferiority in quit rates means that the proportion of subjects successfully quitting smoking using the test product is not worse than the proportion of subjects quitting smoking using the alternative or reference product, this difference is allowed a tolerance of 15% (3,4).

For sample size definition, we used the Farrington-Manning Score Test for Proportion Difference, 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

Consequently, a total of 220 smokers not intending to quit (110 per each arm) will be recruited.

Statistics

Primary study endpoint:

Quit rate at 3 months in the experimental (study) group – with respect to reference group – by means a non-inferiority threshold of 15%.

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.

Secondary study endpoints:

Different urinary metabolites will be evaluated at week 4 by means of a descriptive analysis using 95% confidence intervals, adjusted for confounding variables and for the baseline log-transformed level of the biomarker.

Safety assessments:

Descriptive statistics will be used to summarize the number and percentage of subjects experiencing adverse events

and adverse reactions by study group. Parametric and non-parametric data will be expressed as mean (±SD) and median (and interquartile range [IQR]) respectively. Within-group (from baseline) and between-group differences were evaluated by means of parametric and non parametric statistical tests, for paired and unpaired data, as appropriate. Significance of differences in frequency distribution of categorical variables will be tested by $\chi 2$ test.

References

1. Polosa R, Caponnetto P, Maglia M, Morjaria JB, Russo C. Success rates with nicotine personal vaporizers: a prospective a prospective 6-month pilot study of smokers not intending to quit. BMC Public Health 2014;14:1159.
2. Polosa R, Caponnetto P, Morjaria JB, Papale G, Campagna D, et al Effect of an electronic nicotine delivery device (E-cigarette) on smoking cessation and reduction: a prospective pilot study. BMC Public Health 2011, 11: 786
3. Tulloch HE, Pipe AL, Els C, Clyde MJ, Reid RD. Flexible, dual-form nicotine replacement therapy or varenicline in comparison with nicotine patch for smoking cessation: a randomized controlled trial. BMC Med. 2016 Jun 7;14:80
4. Baker TB, Piper ME, Stein JH, Smith SS, Bolt DM, Fraser DL, Fiore MC. Effects of Nicotine Patch vs Varenicline vs Combination Nicotine Replacement Therapy on Smoking Cessation at 26 Weeks: A Randomized Clinical Trial. JAMA. 2016 Jan 26;315(4):371-9

Data Management Plan

For this study, a web-based Electronic Case Report Form (eCRF), provided by a CRO with expertise in tobacco research studies. This CRO will be used for collecting the data. All the Data Management activities will be carried forward according to the CRO SOPs. Before the study start, the Investigator will be trained on the use of the eCRF functions. He/She will be provided with specific access rights (which can be changed in any time), which allow him/her to enter the system, and a dedicated user's manual. The source data, recorded in the appropriate source documentation at site, will be reported by the Investigator or a designee into the eCRF Database. The data cleaning will be performed by the CRO Data Management team, who will provide the Investigator with all the inconsistencies found through a specific function implemented in the eCRF. The validation of the inconsistencies (change or acceptance) will be made by the Investigator by using the cited function. All the activities related to the data managing will be described in the Data Management Plan (DMP) that will be prepared and maintained for the whole study duration by the Data Management of the CRO. The DMP will also include all the edit check implemented into the eCRF or to be run in batch on the Database.
Before the data freezing, the CRO will code the medical terms. All the activities related to the Database freezing will be described in the DMP. After having frozen the Database, the CRO Data Manager will send it to the Biostatistics Unit for the Statistical Analyses. This activity will also be described in the DMP.

Publication & Presentation Strategy

Dissemination activities will be performed after clinical study close out.

The study results will be disseminated principally throuh peer reviewed academic publications, and by way of dissemination events. We will prioritise the use of open access channels in the course of dissemination activities.

At least **3 peer-reviewed open access academic publications** will be submitted within the end of 2018 to high impact scientific journals (indexed on PubMed), about:
- success (efficacy and reduction) rates and tolerability, comparing EC vs HnB;
- tobacco harm reduction values, comparing EC vs HnB;
- product satisfaction, effects on craving and nicotine withdrawal, product preferences, risk perception, subjective and sensorial effects, comparing EC vs HnB.

First of the **dissemination events** will take place after study close out as an international conference held in Catania where final results will be presented. Participation of at least 30 experts from relevant backgrounds, and of international media/journalists is foreseen.
Second and third dissemination events will take place as oral and/or poster presentations on the preliminary and final data to two international congresses/conferences, to present the results to the scientific community and to the general public.