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# Electronic cigarette for smoking cessation. A randomized, placebo controlled, double blind, double dummy, multicenter trial comparing electronic cigarettes with nicotine to varenicline and to electronic cigarettes without nicotine. The ECSMOKE trial.

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**Trial registration and approvals**

Research code number: P150952J - EUDRACT No.: 2017 – 003588 – 37

Ethics Committee (Comité de protection des personnes, CPP Ouest II-Angers) approved this protocol on 17 April 2018.

The Agence National de Sécurité du Médicament et des Produits de Santé (ANSM) approved this protocol on 9 May 2018.

**Roles and responsibilities**

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**Role of the Funder/Sponsor:**

The funder: Ministry of Health, had no role in the conception, design, redaction of the research protocol. The sponsor of the trial is Assistance publique-Hôpitaux. According to existing French rules, laws and regulations, the sponsor's role includes a) the submission of the research protocol to the ethics committee, to the French drug agency: Agence National de Sécurité du Médicament et des Produits de Santé (ANSM) authorizing all clinical research; b) to contribute to the data collection and c) organisation of the regulatory and technical aspects of conducting and monitoring the study. It is the sponsor's role to report adverse events to national and European Union regulatory drug agencies.

All authors contributed to conception, design, and redaction of the research protocol and will intervene in the data analysis, interpretation of the data, preparation, review and approval of the manuscript and decision to submit the manuscript for publication."

## Abstract

### Introduction

Electronic cigarettes (EC) mainly with nicotine content are widely used worldwide. Although the number of publications about its use is increasing exponentially, evidence based, unbiased, conclusive, head-to-head comparisons about its efficacy and safety as an aid for smoking cessation are lacking.

### Methods and analysis

*Design:* Randomized, placebo and reference treatment-controlled, multicenter, double blind, double dummy, parallel group trial.

*Participants:* Smokers smoking at least 10 cigarettes/day in the past year and motivated to quit, aged 18 to 70 years.

*Interventions:*

A) EC without nicotine (ECwoN) plus placebo tablets of varenicline administered by oral route: **placebo condition**

B) EC with nicotine (ECwN) plus placebo tablets of varenicline: **ECwN condition**

Voltage regulated electronic cigarettes will be used with liquid containing 12 mg/ml of nicotine for *ad libitum* use. Flavour: blond tobacco.

C) Reference: ECwoN plus 0.5 mg varenicline tablets: **varenicline condition.** Varenicline administered according to the marketing autorisation.

Treatment duration: 1 week + 3 months.

*Primary outcome:* Continuous smoking abstinence rate (CAR) (abstinence from conventional/combustible cigarettes) during the last 4 weeks (weeks 9 to 12) of the treatment period defined as self-report of no smoking during the previous 2 weeks and expired air CO ≤ 8 at Visit 4 at Week 10 after target quit date (TQD) i.e. 11 weeks after treatment initiation AND at Visit 5, Week 12 after TQD i.e. 13 weeks after treatment initiation.

*Secondary outcomes*: Safety profile; point prevalence abstinence rate; CAR confirmed by urinary anabasine concentration; changes in cigarettes/day consumption, craving for tobacco and withdrawal symptoms with respect of baseline.

### Ethics and dissemination

The ethics committee approval was obtained on 17 April 2018. All data collected about the study participants will be anonymised. Investigators will communicate trial results to participants, health authorities, healthcare professionals, the public, and other relevant groups without any publication restrictions.

## Article Summary

*Strength and limitations*

*Strengths*

- Randomized, head-to-head comparison, reference and placebo controlled double blind, double dummy smoking cessation efficacy and safety trial.
- Power sufficient to conclude about superiority of electronic cigarette with nicotine over electronic cigarette without nicotine and non-inferiority of electronic cigarette with nicotine to varenicline.
- Ad libitum electronic cigarette use mimicking conventional cigarette use.

*Limitations*

- Only one, fixed dose e-liquid nicotine concentration and one e-liquid flavour are used.
- A rigorous RCT is prioritised over a pragmatic, everyday life trial, more likely to demonstrate convincingly efficacy and safety. However this can reduce the generalizability of the results to everyday population use.

## Introduction

Tobacco use kills more than 5 million people per year worldwide. Among the five greatest risk factors for mortality, it is the single most preventable cause of death (1). It reduces life expectancy by 9 to 15 years (2, 3, 4). Implementation of tobacco control strategies, including smoking cessation behavioral and pharmacological treatments, avoided 8 million premature deaths in the United States between 1964 and 2012 (5). Smoking cessation before the age of 40 reduces the risk of death compared to continued smoking by 90 % (3).

Tobacco is used in its combustible forms: cigarettes, cigarillos, pipes, cigars, shisha, or as smokeless tobacco: oral snuff, snus. The most widely used form is cigarettes. As of today, alternative nicotine delivery systems (ANDS) such as electronic cigarettes (EC) and Juul and heat-not-burn systems containing tobacco. These ANDS are used either for recreational purposes or with the intent to quit smoking.

Among ANDS, the most studied are EC. However as of today, their benefit/risk ratio as an aid for smoking cessation is not established with confidence.

Electronic cigarettes are diverse battery-powered devices to produce an aerosol. The battery heats a resistance that allows aerosolisation of the liquid called “e-liquid” which contains humectants (propylene glycol and/or glycerin) along with flavorants and may or may not contain nicotine. The European Union Tobacco Product Directive limited the nicotine content to 20 mg/mL; requires products to be child and tamper proof; requires health warnings, instructions for use, information on addictiveness and toxicity to appear on the packaging; bans promotional elements on packaging; requires all substances contained in the product and information on the product’s nicotine content to be listed (6).

The EU Directive has been transposed in France on May 19, 2016 (7).

As of today, ECs are consumer products and sold outside the health care system. In France pharmacies are prohibited to sell them.

Exposure to tobacco-related carcinogens and toxins are substantially lower among long-term EC users than among cigarette smokers or dual (EC+cigarettes) users and similar to that found among long-term nicotine replacement therapy NRT users (8). Substantial evidence shows that during EC use exposure to potentially toxic substances is lower compared with combustible/conventional cigarette smoking (9).

Last generation EC deliver more nicotine than first and second generation EC, venous plasma nicotine concentrations after 65 minutes’ use are up to 48.1 ng/mL in experienced and 31.4 ng/mL in naïve users and the mean venous plasma nicotine concentrations are close to those observed with conventional cigarettes (9, 10, 11, 12).

To the best of our knowledge, there is no published report on arterial plasma nicotine concentration with EC or nicotinic acetyl choline receptor (NAchR) occupancy in the brain while using EC with nicotine.

EC reduce desire/craving to smoke and withdrawal symptoms (13, 14, 15) main predictors of successful quit.

*EC as an aid to quit smoking conventional cigarettes*

Observational cohorts provided conflicting results as an aid to quit smoking (17, 18,19) and will not be mentioned further.

Two randomized trials assessing the electronic cigarettes for smoking cessation (20, 21) and 2 meta-analyses of these two trials (22, 23) have been published. Caponetto et al. (21) (ECLAT trial) randomized 300 smokers, not intended to quit into 3 groups: EC disposable cartridge containing 7.2 mg (n=100), 5.4 mg (n=100) and no nicotine (n=100). Intent-to-treat analysis of the main outcome did not show significant differences between groups. Bullen et al. (20) (ASCEND trial) randomized smokers wanting to quit: 289 to receive nicotine containing EC, 295 to receive 21 mg/24h nicotine patches and 73 to receive EC without nicotine. Cartridges of nicotine EC contained 10 to 16 mg nicotine/mL. The treatment duration was 12 weeks and the main outcome measure was continuous abstinence at 6 months after quit date defined as "self-reported abstinence over the whole follow-up period, allowing ≤5 cigarettes in total" and verified at 6 months by a measure of expired air CO (<10 ppm). All participants were referred to a quit line for support. The main outcome measure did not show statistically significant difference: 7.3 %, 5.8 %, 4.1 %, in the nicotine EC, nicotine patch groups, and placebo EC respectively (ITT analysis). This is the only trial that reports on serious (SAE) and non-serious adverse (AE) events with straightforward definitions. 19.7 % of the participants in the nicotine EC, 11.3 % in the nicotine patch group and 13.9 % in the placebo EC had a SAE, respectively.

A Cochrane review of EC for smoking cessation and reduction has been published in 2014 (22) and updated in 2016 (23). The quality of evidence (GRADE system) rated the evidence as low or very low because of the low (N=2) number of trials. Pooling data of these 2 trials, the authors report a relative risk (RR) of 2.29, 95% CI 1.05-4.96 for abstinence rate at 6 months. Analysis of the same 2 trials (20, 21) did not confirm these results (17).

There is a general consensus that high-quality, large-scale randomized studies are needed (9, 24). The current trial is intended to fulfil this requirement.

**Objectives**

*Primary objective*: To assess the therapeutic efficacy and safety of EC with nicotine for smoking cessation. EC containing nicotine with EC not containing nicotine (placebo) and with varenicline, as a reference drug for smoking cessation will be compared.

*Trial design*

This will be a randomized, placebo controlled, multicenter, double blind, double dummy, parallel groups, phase III trial.

Included participants will be randomly assigned to one of the 3 groups:

A) Control group: EC without nicotine (ECwoN) plus placebo tablets of varenicline: **placebo condition**
B) Experimental group: EC with nicotine (ECwN) plus placebo tablets of varenicline: **ECwN condition**
C) Reference group : ECwoN plus varenicline tablets : **varenicline condition**
with a randomisation ratio of A:B:C= 1:3:3.
Each participant will use an EC and takes 2 tablets twice per day.

*Setting*

This national trial will involve smoking cessation clinics of both academic and community hospitals. Twelve study sites and 16 co-investigators agreed to participate and committed to recruit and follow up smokers for the trial. Individuals are eligible to be a co-investigator if they are medical doctors, having obtained a post-graduate diploma in addictive and/or tobacco related disorders. The list of study sites can be obtained from the principal investigator.

## Participants

*Eligibility criteria*

Inclusion criteria

1. Smokers smoking at least 10 cigarettes/day (factory made or roll-your-own) in the past year
2. Aged 18 to 70 years
3. Motivated to quit, defined as a score > 5 on a visual rating scale ranging from 0 (not motivated at all) to 10 (extremely motivated)
4. Signed written informed consent
5. Understanding and speaking French
6. Women of childbearing age can be included if they use an effective contraceptive method: either hormonal contraception or an intrauterine device started at least one month before the first research visit
7. Individual affiliated to a health insurance system
8. Previous failure of nicotine replacement therapy for smoking cessation

Exclusion criteria

1. Any unstable disease condition within the last 3 months defined by the investigator as major change in symptoms or treatments such as recent myocardial infarction, unstable or worsening angina, severe cardiac arrhythmia, unstable or uncontrolled arterial hypertension, recent stroke, cerebrovascular disease, obliterative peripheral arterial disease, cardiac insufficiency, diabetes, hyperthyroidism, pheochromocytoma, severe hepatic insufficiency, history of seizures, severe depression, chronic obstructive pulmonary disease (COPD);
2. Any life threatening condition with life-expectancy of less than 3 months;
3. Alcohol use disorder defined as a score ≥ 10 on the AUDIT-C questionnaire (see below)
4. Abuse of or dependence on illegal drugs in the last 6 months revealed by medical history;
5. Regular use of tobacco products other than cigarettes;
6. Current or previous (last 6 months) use of EC;
7. Pregnant women;
8. Breastfeeding women;

9. Protected adults;
10. Current or past 3 months participation in another interventional research;
11. Current or past 3 months' use of smoking cessation medication such as varenicline, bupropion, nicotine replacement therapies;
12. Known lactose intolerance (placebo tablets contain lactose);
13. Hypersensitivity to the active substance or to any of the excipients;
14. Known severe renal failure.

*Patient and Public Involvement*

Patients or public were not involved in the conception and writing of this protocol. Study results will be disseminated individually to all study participants if requested.

**Interventions**

*Investigational product 1: EC with nicotine or EC placebo*

EC exists in two forms: liquid containing nicotine or with liquid not containing nicotine. Nicotine content in EC can vary in the European Union between 0 and 19.9 mg/mL. Third and fourth generation EC allow the user to change voltage leading to individualised nicotine delivery and dose adaptation.

A call for application by EC companies has been launched by the sponsor twice in 2017 and 2018 (no candidate in 2017).
Some major requirements for applications are listed here:

- EC liquid containing 0 and 12 mg/mL of nicotine
- Regular and reported control of nicotine's concentration in EC liquid by batches
- Tobacco flavour
- Long shelf life
- Detailed information about constituents
- Highly purified nicotine

Packaging: active or placebo bottles of e-liquid are provided blinded as unidentifiable bottles. Each blinded box package contains ten 10 mL bottles of e-liquids for 1 months.

In the current study the ECwN group will use EC liquids containing 12 mg/mL of nicotine. E-liquids will be allowed to be used *ad libitum* and because nicotine delivery can be adjusted according to the user's need, all participants would adjust their individual nicotine dose by varying the voltage of their EC, by varying puff frequency, puff volume and depth of inhalation similarly as they are doing (or used to do) with conventional cigarettes. A recent paper by Soar et al. (25) demonstrates that over a 12 months period EC users maintained their nicotine intake, as measured by saliva cotinine concentration, possibly through self-titration.
*Justification of the nicotine concentration*
We consider, based on previous studies, that one cigarette contains approximately 1 mg of nicotine, thus 10 cigarettes contain approximately 10 mg of nicotine (26, 27). Nicotine's bioavailability when inhaled in cigarette smoke is 90 to 95 %; it is plausible that the bioavailability of nicotine of the aerosol delivered by an EC is lower. In the current research protocol the use of e-liquid of 12 mg/mL of nicotine may, thus, correspond approximately to 10 cigarettes. The only randomized, placebo controlled study (nicotine – placebo: double blind) against nicotine patch (open label) used in the nicotine EC arm 10-16 mg/mL e-liquid concentration (20). Abstinence rate was not different between EC with nicotine vs EC with

placebo (double blind comparison) on the main outcome measure. It was raised that this negative result is due to the low bioavailability of nicotine delivered by the EC used dating back to 2012. More recent studies using tank system EC provide plasma nicotine concentrations higher than earlier studies using EC of 2012 to 2014 (12).

Dawkins et al. (28) assessed 6 mg/mL and 24 mg/mL nicotine e-liquid concentrations in a self-titration/self-administration design. Plasma nicotine concentrations were higher with the 24 mg/mL nicotine liquid than with the 6 mg/mL nicotine liquid. However, reduction in craving for cigarettes were similar. Compensatory puffing occurred with the 6 mg/mL nicotine concentration, puff number, puff duration and liquid consumption were higher with the low than with the high nicotine concentration liquid. There were no statistically significant differences between conditions in self-reported craving, withdrawal symptoms, satisfaction, throat hit or adverse effects. However, the blood nicotine concentration was higher at 60 minutes with the 24 mg/mL than with the 6 mg/mL liquid: 43.57 (SD 34.78) 22.03 (SD 16.19) ng/mL. Thus EC users compensate low nicotine liquid concentration by increasing puff topography characteristics to increase nicotine uptake. This compensatory puffing is similar as with conventional cigarettes.

We can, thus, conclude that an intermediary concentration of nicotine would be optimal: plasma nicotine concentrations sufficiently high leading to a sufficient craving reduction. The chosen e-liquid concentration of 12 mg/mL takes also into account the standard dose-response relationship (6-12-24 mg/mL).

Only one flavour will be used to reduce variability of treatment response according to a preferred flavour. We chose the blond tobacco flavour with which all smokers can be familiar, which is less likely to be aversive in adults and the most sold when initiating EC use.

*EC device:*
Mini iStick kit (20 W) Eleaf, clearomiser: GS Air M with resistance of 1.5 ohm. To keep the blinding, the clearomiser's Pyrex window is of gray colour not allowing distinguishing coloration of the e-liquid containing nicotine.

*Liquid for EC* is manufactured by GAIATREND SARL (https://www.gaiatrend.fr/fr/).

*Counselling about the use of EC*
All participants will be delivered a short manual and a video specifically developed for this study explaining the use of EC. At each visit participants receive also verbal counselling about the use of the EC device and answers to their questions about handling the EC device. Investigators are trained at the first Investigators' meeting to provide straightforward counselling about EC use.

*Investigational product 2 (reference drug): varenicline 0.50 mg and its placebo*

Varenicline and not nicotine replacement therapies (NRT) has been chosen for this study as the reference drug because:
i) Varenicline is associated with the highest level of abstinence rate among the 3 available smoking cessation medications with marketing authorization (bupropion, NRT, varenicline) (29), therefore a better comparator for a new therapeutic intervention for which we aim to demonstrate a therapeutic efficacy as high as the best available medication.
ii) Identical placebo tablets for varenicline can easily be manufactured and none of the placebo NRT forms are available. Manufacturers of NRT products do not have any more

corresponding placebos and manufacturing identical placebos by an external company may increase the likelihood of non-identical placebos. Moreover, purchasing both identical placebos along with active NRT products manufactured by a company that do not have the marketing license for NRT may introduce a major uncertainty by raising the question: Does the NRT product have the same bioavailability as the original, licensed NRT product? Uncertainty about the active NRT product's bioavailability may compromise the validity of the trial's results.

iii) Blinding of tablets administered by oral route is more convenient than blinding of NRT such as transdermal patches, gums, lozenges, inhaler or buccal spray;

Varenicline (Champix®) 0.5 mg is presented as a capsular-shaped, biconvex, white film-coated tablet. The tablets are held under a vial of 56 tablets.

Varenicline has been purchased at Pfizer France.

*List of excipients:*

Core tablets: Cellulose, Microcrystalline, Calcium Hydrogen Phosphate Anhydrous, Croscarmellose Sodium Silica, Colloidal Anhydrous, Magnesium Stearate

Film coating : Hypromellose Titanium Dioxide (E171) Macrogols Triacetin.

Placebo and active tablets are strictly similar. Placebo tablets of varenicline have been manufactured, packaged and labeled by a pharmaceutical sub-contractor according to the Good Manufacturing Practices and under the responsibility and supervision of AGEPS.

The dose regiment of varenicline/placebo follows varenicline's monograph:

Day 1 to Day 3 : one tablet of 0.5 mg/placebo in the morning

Day 4 to Day 7 : 1 tablet of 0.5 mg/placebo morning and the evening

From Day 8 until end of treatment: 1 mg morning and evening i.e. two 0.5 mg/placebo tablets morning and evening

EC and tablets are started one week before the target quit date (TQD) to stop smoking and followed up for 3 months after TQD.

**Behavioral counselling for smoking cessation**

Brief behavioural smoking cessation counselling for all participants is administered at all visits by the investigators specialised in smoking cessation. It is based on the national guidelines for smoking cessation (30).

**Criteria for discontinuing or modifying allocated interventions**

Any participant can withdraw from participating in the research at any time and for any reason.

- The investigator can end a subject's participation in the research for any reason that affects the participant's safety or which would be in the participant's best interests but not because of non-abstinence from cigarettes after TQD.
- In case of loss to follow-up, the investigator should make all efforts to reach the participant and collect the reason of loss to follow-up and information about his/her safety data.
- In case of pregnancy during the study, the participant will exit the trial and will be followed up until delivery.

The case report form must list the various reasons for ending participation in the research:

- Adverse event/reaction
- Other medical problem
- Participant's personal reasons

- Explicit withdrawal of consent

If a participant leaves the research prematurely or withdraws consent, any data collected prior to the date of premature exit can be used.

**Methods for monitoring compliance with the treatments**

Study medication compliance at Visits 1 through 5 will be assessed with the questions:

A) Did you use the electronic cigarette
- Every day
- Approximately every other day
- Twice a week
- Less than twice a week.

B) Did you take your tablets
- Every day
- Approximately every other day
- Twice a week
- Less than twice a week.

Accountability of returned EC bottles and tablet vials will allow approximating EC liquid's and tablets' use.

**Guess test to control efficacy of the blinding**

At Visit 2 (Week 4 after TQD i.e. 5 weeks after treatment initiation) and at Visit 5 (Week 12 after TQD i.e. 13 weeks after treatment initiation) a guess test will be run. It consists of the following question:
"Do you think you received:
- Placebo tablets and electronic cigarettes without nicotine? Yes/No
- Placebo tablets and electronic cigarettes with nicotine? Yes/No
- Varenicline (Champix©) tablets and electronic cigarettes without nicotine? Yes/No

**Concomitant care and interventions**

All previously introduced medications will be permitted to be continued. The following concomitant medications per NRT's licence in France, by extrapolation to nicotine containing e-liquids, and according to the requirement of the French drug agency (ANSM) will be prohibited: theophylline, clozapine, olanzapine, méthadone, ropinirole, pharmaceutical caffeine (dose adaptation when quit smoking).

As of today, varenicline has no known clinically significant drug-drug interaction.

To the best of our knowledge, there is no available information about drug interaction of EC with or without nicotine.

NRT use is not permitted during the study but its over-the-counter purchase cannot be controlled for. At each post-quit day visit we will check its use as a control variable. Positive

answer will result asking the participant to stop NRT use. If he/she does not comply, the participant will be excluded for noncompliance with the study protocol.

**Primary outcome**

Continuous smoking abstinence rate (CAR) (abstinence from conventional/combustible cigarettes) during the last 4 weeks (weeks 9 to 12) of the treatment period of 3 months.
Definition: Self-report of no smoking during the previous 2 weeks and expired air CO ≤ 8 ppm. at Visit 4 at Week 10 after TQD i.e. 11 weeks after treatment initiation AND at Visit 5, Week 12 after TQD i.e. 13 weeks after treatment initiation.

**Secondary outcomes**

- Safety profile of EC containing nicotine comparatively to its placebo and varenicline.
- Point prevalence abstinence: 7-day abstinence at Visit 1, 2, 3 and 14 days of abstinence at Visit 4 and 5 (see timeline below) associated with expired air CO ≤ 8 ppm.
- Time to relapse to smoking after TQD
- CAR confirmed by urinary anabasine concentration ≤ 3 ng/mL
- Change in cigarettes/day consumption with respect of baseline
- Change in craving for tobacco as assessed by the French 12-item Tobacco Craving Questionnaire (31) with respect of baseline
- Change in withdrawal symptoms as assessed by the modified Minnesota Nicotine Withdrawal Scale (32) with respect of baseline

Control variables:

- Study medication compliance recorded at each visit
- Baseline level of tobacco dependence
- Urinary concentration of anabasine, anatabine (both alkaloids found only in tobacco, control for tobacco smoking) and cotinine (main metabolite of nicotine, control for nicotine intake) at Visit 4 and 5 (33). Analysis laboratory: Swiss Laboratory for Doping Analyses, Epalinges, Switzerland.
- Results of the "guess test" i.e. correct identification of the treatments by participants

**Participant timeline (Figure 1)**

Randomisation visit = Visit 0 - Dispensing of the treatment

Treatment initiation within the 7 days following randomization.

Target quit date (TQD) should occur between 7 and 15 days after randomization and after 7 days of treatment intake.

The first post-target quit date visit (Visit 1) is at Week 2 after TQD i.e. 3 weeks after treatment initiation.
Visit 2 is at Week 4 after TQD i.e. 5 weeks after treatment initiation.
Visit 3 is at Week 8 after TQD i.e. 9 weeks after treatment initiation.
Visit 4 is at Week 10 after TQD i.e. 11 weeks after treatment initiation.
Visit 5 is at Week 12 after TQD i.e. 13 weeks after treatment initiation.
Visit 6 is at Week 24 after TQD i.e. 25 weeks after treatment initiation.

*Assessments at Visit 0*

– *Demographic characteristics*

- Age
- Gender
- Professional situation
  Employed/Housewife/Unemployed/Student/Retired
- Education level: Number of years after age 7 years.
- Marital status:
  Cohabiting/ Married/Separated/Divorced/Single/Widowed
- Annual household income (euros)
  < 12 000/12 001 – 30 000/30 001 – 100 000/> 100 000
- Self-reported ethnic origin
  European/African/Asian/Other

– *Previous medical history :*
  - any unstable disease condition within the last 3 months defined by the investigator as major change in symptoms or treatments
  - any life threatening condition with life-expectancy of less than 3 months
  - alcohol use disorder defined as a score ≥ 10 on the AUDIT-C questionnaire
  - abuse of or dependence on illegal drugs in the last 3 months revealed by the medical history
  - regular use of tobacco products other than cigarettes
  - current or previous (last 6 months) use of electronic cigarette
  - pregnant women
  - breastfeeding women
  - current or past 3 months participation in another interventional research
  - current or past (last 3 months) use of smoking cessation medication such as varenicline, bupropion, nicotine replacement therapies
  - known lactose intolerance (placebo tablets contain lactose)
  - hypersensitivity to the active substance or to any of the excipients
  - known severe renal failure
– *Previous mental health history (**before** the last 6 months):*
  - Treatment for major depression
  - Treatment for psychosis
  - Treatment for bipolar disorder
  - Treatment for substance use disorder:
  - Cannabis, alcohol, cocaine, opioid, psychostimulant use
  - Treatment for smoking cessation by NRT, varenicline, bupropion
– *Current, past 6 months, medical history:*
  - Cardiovascular disorders (yes/no); stable on treatment: yes/no
  - Myocardial infarction/unstable angina (yes/no); stable on treatment: yes/no
  - Arterial hypertension (yes/no); stable on treatment: yes/no
  - Malignancy disorder (yes/no); stable on treatment: yes/no
  - Pulmonary disorder (other than COPD) (yes/no); stable on treatment: yes/no
  - COPD (yes/no); stable on treatment: yes/no
  - Type 1 or type 2 diabetes mellitus (yes/no); stable on treatment: yes/no
  - Other (yes/no); stable on treatment: yes/no
– *Current, past 6 months, mental health history:*
  - Treatment for major depression (yes/no);; stable on treatment: yes/no
  - Treatment for psychosis (yes/no); ; stable on treatment: yes/no
  - Treatment for bipolar disorder (yes/no); stable on treatment: yes/no

- Treatment for substance use disorder (yes/no);
- Cannabis, alcohol, cocaine, opioid, psychostimulant use disorder (exclusion if any)
- Treatment for smoking cessation by NRT, varenicline, bupropion (exclusion if any)

– Smoking characteristics
  - Age of the first cigarette (years)
  - Age of regular smoking (years)
  - Number of previous attempt(s) to quit
  - Longest duration of abstinence if any
  - Fagerström Test for Cigarette Dependence score
  - Spouse/partner smokes (yes/no)
  - Other smoker in the household (yes/no)
  - Secondhand smoke exposure at home/work/leisure (yes/no) :
  - Current self-reported number of cigarettes smoked per day
– Clinical measures
  - Systolic and diastolic blood pressure in sitting position
  - Height
  - Body weight
  - Expired air CO along with time (minutes) since last cigarette smoked
  - Craving for tobacco using the FTCQ-12 (30)
  - Withdrawal symptoms using the Minnesota Tobacco Withdrawal Scale (31)
– Substance use
  - Cannabis use in the last 30 days
  - Alcohol use

The AUDIT (Alcohol Use Disorders Identification Test) will be used to screen for alcohol problems. It has been identified as the most effective instrument identifying individuals at-risk, hazardous or harmful drinking (34). Its sensitivity ranges from 51 % to 97 % and specificity from 78 to 96 % according to a systematic review. The corresponding values for the CAGE questionnaire (35) are: 43 % to 94 % and 70 % to 97 % (36).
The short French language form, AUDIT-C of the questionnaire will be used as recommended by recent French guidelines (37).

*At each visit will be measured:*

- Systolic and diastolic blood pressure in sitting position.
- Body weight
- Cannabis use since the last visit
- Alcohol use since the last visit (more than 1 drink per day/less than one drink per day)
- Expired air CO along with time (minutes) since last cigarette
- Current self-reported number of cigarette smoked per day in the last 7 days
- Craving for tobacco using the FTCQ-12 (30)
- Withdrawal symptoms using the Minnesota Tobacco Withdrawal Scale (31)

Expired air CO will be measured with a Smokerlyzer (Bedfont Scientific Ltd, Kent, UK) a value of less than or equal to 8 ppm will be required to support the self-report of abstinence.
The FTCQ-12 and MNWS are paper and pencil self-report questionnaires.

*At each further visit adverse reactions/events* are inquired with the following question:
“Did you experience since the last visit a health symptom or event which is unusual?”

If the answer is "Yes", the adverse reaction/event will be recorded.

**Sample size**

According to the EAGLES study (29) with N=8144 smokers, the percent abstinent at the main efficacy criterion – similar to that used in the current study – was 33.5 %. Taking this percentage as reference, with an OR=1/0.60=1.664 and a power of 80 % we would need at least 272 participants in each of the varenicline (reference) and the ECwN group (38). We would randomize 1/3 of the participants to the group ECwoN, that is 91 smokers. These numbers would allow to show a significant difference between varenicline and ECwN with an alpha=0.05. The total number needed to be randomized will, thus, be of 2*272+91= 635 smokers. To take into account lost to follow up, we plan to randomize *at least* 650 smokers: 280 in each of the ECwN and varenicline arm and 90 (rounded) in the ECwoN arm.

*Justification to randomize only 90 participants in the placebo-placebo condition (ECwoN)*
The main research question is the superiority of ECwN and varenicline (reference) – justifying of testing of non-inferiority between these groups including 280 participants/group.
If the superiority testing is non-significant, we propose to switch to non-interiority testing.
We conclude on the non-inferiority if and:

- ECwN is non-inferior to varenicline
- ECwN superior to ECwoN
- Varenicline is superior to ECwoN

Thus the comparison involving ECwoN will be run "after" the comparisons between ECwN and varenicline.

We considered the following percent of abstinence: p(varenicline)=33.5 % and p(ECwoN)=15 %. Thus with 280 participants in the varenicline and 90 participants in the ECwoN group we will have sufficient power to conclude.

**Decision rules**

We will conclude that ECwN is superior to varenicline if the two tailed superiority test at 5 % on the main outcome measure (percent abstinent (p)) will be significative such as p(ECwN) > p(varenicline).
Would this test show a p value higher than 0.05, we would switch to non-inferiority. We will conclude that ECwN is non-inferior to varenicline if:

- the two-tailed superiority test is non-significant at the 5 % level
- the test of non-inferiority at 5 % one-tailed with a delta=5% is significant
- the two-tailed superiority test of p(ECwN) versus p(ECwoN) is significative at 5%;
- the two-tailed superiority test of p(varenicline) versus p(ECwoN) is significative at 5%.

In any case we will conclude that ECwN is superior to ECwoN, if the test of superiority at 5 % (two-tailed) is significant such as p(ECwN) > p(ECwoN).

A Pearson's two-tailed Khi square test at 5 % will be used to test the superiority. A Dunnet & Gent Chi square test at 5 %, one-tailed, will be used for testing the non-inferiority (39).

Some simulations
1. If p(Varenicline) = 33.5 %, p(ECwN)=33.5% and p(ECwoN)=15% then
a. the probability that ECwN is superior to varenicline is of 2.5 %

b. the probability that ECwN is non-inferior to varenicline is of 31.5%.
c. the probability that ECwN is superior to varenicline is of 2.5%+31.5%=34%.
d. the probability that ECwN is superior to ECwoN is of 95%.

2. If p(Varenicline)=33.5%, p(ECwN)=40% and p(ECwoN)=15% then
a. the probability that ECwN is superior to varenicline is of 33.6 %
b. the probability that ECwN is non-inferior to varenicline is of 52.7 %.
c. the probability that ECwN is superior to varenicline is of 33.6%+52.7%=86.3 %.
d. the probability that ECwN is superior to ECwoN is of 99.8 %.

3. If p(Varenicline)=33.5 %, p(ECwN)=45 % and p(ECwoN)=15 % then
a. the probability that ECwN is superior to varenicline is of 80.1 %
b. the probability that ECwN is non-inferior to varenicline is of 19 %.
c. the probability that ECwN is superior to varenicline is of 80.1%+19.0%=99.1 %.
d. the probability that ECwN is superior to ECwoN is of 99.9 %.

The estimate of an abstinence rate of around 40 % with the two active treatments and a 15 % abstinence rate in the placebo condition seems reasonable and clinically significant.

There is no justification to run first a global comparison. Either the ECwN arm is better than the varenicline arm and we have answered the main research question or the ECwN is non-inferior to the varenicline arm and there will be a necessity to run two separate comparisons against ECwoN (i.e.ECwN against ECwoN; varenicline against ECwoN).

**Recruitment**

Recruitment is either local (a) directly by the centres or centralized (b) using a web page and a centralised study specific phone number and email address.
a) Smokers intending to quit smoking are recruited by advertisement in pharmacies, physicians' offices situated in the catchment area of each investigator's centre, by local newspapers and in public places of the centres' health care facilities.
b) Candidates to participate can register by the study's website, unique email address and phone number. Registration is followed by a phone screening before dispatching to the study centres.
Only one person by household will be recruited.

**Assignment of interventions and blinding**

To assure allocation concealment, computer generated randomization list (allocation ratio: 1:3:3) involving blocks, stratified by age (<45 versus ≥ 45 years) and centre, will be prepared and is kept blinded to all participants to the trial. The randomization list is incorporated into the eCRF, and a treatment number is attributed automatically upon completion of the randomization visit. The random, computer generated allocation sequence is prepared by a statistician of the Clinical Reseach Unit of Pitié Salpêtrière Charles Foix.

The randomization list is being kept in a secured place by the sponsor and a copy of the randomization code is being kept separately in the Poison Centre of Fernand Widal Hospital, Paris, in case of a serious adverse event necessitating the opening of the participant's group assignment (see below). Investigators, members of the coordination centre, hospital

pharmacists, and the sponsor's clinical research assistants in charge of monitoring will be kept blinded.

*Blinding methods and measures to protect the blinding*

Varenicline and its placebo are administered as non-identifiable tablets.
Because nicotine solutions tend to become yellow with time, the following provisions have been taken to make EC liquids non-identifiable:
Liquids of EC will be delivered to the participants in white, non-transparent vials of 10 mL specifically manufactured for the study. Both nicotine and no nicotine containing liquids will have a tobacco flavour and smell (blond tobacco). The EC's clearomiser' Pyrex walls will be transparent but of grey colour allowing the user to see the level of the liquid but not its colour.

*Unblinding procedures*

Unblinding is the sponsor's decision. However, the investigating physician may request unblinding if he/she considers essential in the participant's interest/care.

**Data collection and management**

Data will be collected through the study's eCRF. Data entry is carried out on electronic media via a web browser by co-investigators. The source documents are any original document or item that proves the existence or accuracy of a data-point or fact recorded during the trial. Source documents are kept by the investigator, or by the hospital in the case of hospital medical records, for the statutory period. During and after the clinical study, all data collected about the study participants and sent to the sponsor by the investigators (or any other specialized collaborators) will be anonymised. CNIL, the French Data Protection Authority implemented the "Méthodologie de référence" (MR-001) according to the provisions of Article 54, paragraph 5 of modified Law No. 78-17 of 6 January 1978. The sponsor, Assitance publique-Hôpitaux de Paris has signed a commitment to comply with it.

**Data analysis**

**Populations submitted to the analyses**

1. The *intent-to-treat* (ITT) efficacy analysis will include all participants who were randomized and having received at least one dose of any study treatment.
2. *Safety population*: All participants who were randomized and having received at least one dose of any study treatment.
3. *Full analysis set* (FAS) population: All participants who were randomized and having received at least one dose of study treatment except those who had no data at all post-randomisation.
4. *Per-protocol* population: All participants who are followed up to Week 12 and for whom the main efficacy criterion (CAR week 9 to 12) is available and who received at least one dose of treatment.

*Handling of missing data*
Participants who miss a visit will receive at least 2 phone calls as a reminder.

Missed visits are not a criterion for discontinuation. All participants will bestrongly encouraged to stay in the trial up to the end of the research that is up to week 24.
Smoking (lapse: some puffs or relapse: relapse to regular conventional cigarette consumption) will not be a reason for discontinuation.

**Primary analysis**

We want to demonstrate the effectiveness of ECwN over varenicline. For that we will compare the percentage of success (CAR) between the two arms with a two-tailed Chi square test. If this test is not significant (i.e. p>5%), we will perform a non-inferiority test (switch) for ECwN over varenicline with a unilateral Dunnet and Gent test at 5% and a non-inferiority bound of $\Delta_L = 5\%$.
In parallel with the non-inferiority test, we will perform two tests of superiority, one comparing the ECwN to ECwoN on the one hand, and one comparing varenicline to ECwoN on the other hand to ensure that the non-inferiority is not obtained by lack of efficacy in both ECwN and varenicline arms. Thus non-inferiority will be achieved if the non-inferiority test is significant as well as the two superiority tests described above.
For the superiority tests, the analysis will focus on the ITT population and will be confirmed on the per protocol population. The non-inferiority test will be done on the per protocol population and will be confirmed on the ITT population. (See details in Decision rules)

**Secondary analyses**

Comparisons will be made between ECwN and varenicline arms but may be done between the 3 treatment arms. Qualitative variables will be analyzed with a Chi2 test. Quantitative variables will be compared with Student's t test (or non-parametric tests as appropriate). Censored variables, such as the time to relapse will be analyzed by the log rank test.
These three tests will be generalized with a logistic model, ANOVA or a Cox model if adequate. Variables collected at different visits will be analysed in longitudinal, linear or logistic random effect models. In the same way the absolute variation or the relative variation can be studied there also with linear models with random effect.

Missing secondary endpoints will be imputed in both ITT and per protocol populations. The primary endpoint will be imputed by a multiple imputation method EF?). The other criteria will not be imputed, since most of these criteria will be analyzed in longitudinal analysis.We will perform a sensitivity analysis by rerunning the population analysis of subjects whose primary endpoint is non-missing.

**Monitoring**

Clinical Research Associates (CRAs) appointed by the sponsor are responsible for the proper running of the study, for collecting, documenting, recording and reporting all handwritten data, in accordance with the Standard Operating Procedures applied within the DRCI and in accordance with Good Clinical Practice as well as with the statutory and regulatory requirements.
The investigator and the members of the investigator's team agree to make themselves available during regular Quality Control visits by the Clinical Research Associate. During these visits, the following elements will be reviewed:

- written consent

- compliance with the study protocol and its procedures
- quality of the data collected in the case report forms: accuracy, missing data, consistency of the data with the "source" documents (medical files, appointment books, original copies of laboratory results, etc.)
- management of the treatments used.

**Safety assessment**

Safety will be assessed at each visit during the treatment period. However, the safety assessment will also be conducted at Visit 6 (end of research) even if no adverse event/reaction has previously been reported. Rational: one cannot exclude occurrence of adverse events/reactions even 3 months after stopping study medications.

*Safety endpoints*

- AE diagnosis/description
- The date when the AE started and stopped
- CTCAE grade maximum intensity (Comon Terminology Criteria for Advesre Events (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf)
- Whether the AE is serious or not
- Reason why the SAE was serious (e.g. hospitalisation)
- Investigator causality rating against the investigational product (yes or no)
- Action taken with regard to investigational product
- Outcome

*Anticipated methods and timetable for measuring, collecting and analysing the safety endpoints*

Safety and tolerance are recorded as follows:
- adverse events will be recorded in the "adverse event" section of the case report form;
- adverse effects' declaration by the participant will be collected at each visit or anytime when the participant establishes a contact with his/her investigator. Investigators reports to the Sponsor the participants' declaration and/or examinations' results linked to any adverse reaction/event along with its estimated severity and imputability. The Data Safety Monitoring Board (DSMB) monitors safety data to avoid continuing the trial if it estimates that the risk prevails the benefit.

*Recording and reporting adverse events*

*Definitions* (40)

**Adverse event**

Any untoward medical occurrence in a trial subject, which does not necessarily have a causal relationship with the clinical trial or with the investigational product.

- **Adverse reaction to an investigational medicinal product**

Any adverse event occurred in a trial subject, which has a causal relationship with the clinical trial or with the investigational medicinal product

- **Serious adverse event or reaction**

Any adverse event or reaction that at any dose of medication, results in death, threatens the life of the research subject, requires hospitalisation or prolongs hospitalisation, causes a severe or long-term disability or handicap, or results in a congenital abnormality or deformity.

- **Unexpected adverse reaction to an investigational medicinal product**

Any adverse reaction to the product, whose nature, severity, frequency or outcome is inconsistent with the safety information described in the Reference Safety Information (summary of product characteristics, or the investigator's brochure if the product is not authorised).

- **Emerging safety issue**

Any new safety information that may lead to a reassessment of the risk/benefit ratio of the trial or the investigational medicinal product, modifications in the investigational medicinal product use, the conduct of the clinical trial, or the clinical trial documents, or a suspension, interruption or modification of the protocol of the clinical trial or other similar trials..
Examples:
a) any clinically significant increase in the frequency of an expected serious adverse reaction
b) suspected unexpected serious adverse reactions in patients who have terminated their participation in the clinical trial that are notified by the investigator to the sponsor together with follow-up reports
c) any new safety issue relating to the conduct of the clinical trial or the development of the investigational medicinal product, that may impact the safety of the trial subjects.
d) recommendations from the DSMB that may affect the safety of the trial subjects
e) any suspected unexpected serious adverse reaction (SUSAR) reported to the sponsor by another sponsor of a trial carried out in a different country but relating to the same medication.

**Data Safety Monitoring Board (DSMB)** (39)

A Data Safety Monitoring Board has been set up for this trial. Its primary mission is to serve as a committee for monitoring safety data. The sponsor is responsible for justifying the creation the DSMB to the Competent Authority (ANSM) and to the Ethics committee (CPP).

The DSMB's preliminary meeting took place on 12 December 2017, before the protocol submission to competent health authority (ANSM) and Ethics committee (CPP). DSMB's operating methods and the meeting schedule have been defined during this first meeting. All missions as well as the precise operating methods of the DSMB are described in the DSMB's charter for the research.

The members of the DSMB are:
- Pr Eric Bellissant, President, clinical pharmacologist with expertise in public health and social medicine, Centre Hospitalier Universitaire de Rennes, Rennes, France
- Pr. Daniel Thomas, cardiologist, previous head of the Department of Cardiology, Hôpitaux Universitaires Pitié-Salpêtrière, Paris, France
- Pr Laurence Galanti, physician, smoking cessation specialist, CHU Mont-Godinne, Belgium.

General information about the DSMB
The DSMB makes recommendations to the sponsor about the continuation, modification or termination of the research. The recommendations that the DSMB can make are:

- to continue the research with no modifications
- to continue the research with a modification to the protocol and/or to the monitoring of subjects
- to temporarily halt inclusions
- to permanently terminate the research in light of safety data: serious adverse reactions

## Ethics and dissemination

The ethics committee (Comité de protection des personnes, CPP Ouest II-Angers, France, approved this protocol on 17 April 2018.

The potential participant is granted a reflection period of one week between the time when the subject receives the information and the time when he or she signs the consent form. Informed consent is obtained before the inclusion by the investigator physician as required for this type of study by French regulations. The form is available in French on request.

The persons responsible for the quality control of clinical studies (41) take all necessary precautions to ensure the confidentiality of information relating to the investigational medicinal products, the study, the study participants and in particular the identity of the participants and the results obtained. These persons, as well as the investigators themselves, are bound by professional secrecy (42, 43).

During and after the clinical study, all data collected about the study participants and sent to the sponsor by the investigators (or any other specialised collaborators) will be anonymised. The principal investigator, the Unité de Recherche Clinique (Clinical Research Unit) and the sponsor will have access to the final trial dataset without limitation.

Investigators will communicate trial results to participants, health authorities, healthcare professionals, the public, and other relevant groups without any publication restrictions.

Main authorship eligibility for publication in medical journals will follow International committee of Medical Journal Editors ICMJE criteria (45).



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## Author Contributions

Concept and design: I. Berlin, B. Dautzenberg

Drafting of the manuscript: I. Berlin

Critical revision of the manuscript for important intellectual content: B. Dautzenberg, B. Lehmann, Y. de Rycke, F. Tubach, J. Palmyre, E. Liégey

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Conflict of Interest Disclosure: I. Berlin reports occasional honoraria from Pfizer in the last 3 years for counseling and presentations at meetings

F. Tubach is head of the clinical research unit of Pitié-Salpêtrière and Charles Foix hospitals and the pharmacoepidemiology center of Assistance Publique Hôpitaux de Paris, that have received research funding, grants and fees for consultant activities from a large number of pharmaceutical companies, that have contributed indiscriminately to the salaries of its employees. She didn't receive any personal remuneration from these companies.

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Figure 1. The trial's outline.

| | | |
|---|---|---|
| | Phone screening | |
| Visit 0 | Inclusion/ Randomisation to Placebo Condition or Nicotine Condition or Varenicline Condition | |
| | Treatment initiation Day -7 | Electronic cigarette + Tablets |
| | Target quit day (TQD) Day 0 | x |
| Visit 1 | Week 2/TQD | x |
| Visit 2 | Week 4/TQD | x |
| Visit 3 | Week 8/TQD | x |
| Visit 4 | Week 10/TQD | x |
| Visit 5 | Week 12/TQD | End of treatment |
| Visit 6 Follow up visit | Week 24/TQD | End of study |

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BMJ Open

# A randomized, placebo controlled, double blind, double dummy, multicenter trial comparing electronic cigarettes with nicotine to varenicline and to electronic cigarettes without nicotine; the ECSMOKE trial protocol.

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| Primary Subject Heading: | Smoking and tobacco |
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| Keywords: | electronic cigarettes, varenicline, smoking cessation, randomised, controlled, double dummy trial |
| | |

# A randomized, placebo controlled, double blind, double dummy, multicenter trial comparing electronic cigarettes with nicotine to varenicline and to electronic cigarettes without nicotine; the ECSMOKE trial protocol.

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**Trial registration and approvals**

Research code number: P150952J - EUDRACT No.: 2017 – 003588 – 37

Ethics Committee (Comité de protection des personnes, CPP Ouest II-Angers) approved this protocol on 17 April 2018.

The Agence National de Sécurité du Médicament et des Produits de Santé (ANSM) approved this protocol on 9 May 2018.

**Roles and responsibilities**

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**Role of the Funder/Sponsor:**

The funder: Ministry of Health, had no role in the conception, design, redaction of the research protocol. The sponsor of the trial is Assistance publique-Hôpitaux de Paris. According to existing French rules, laws and regulations, the sponsor's role includes a) the submission of the research protocol to the ethics committee, to the French drug agency: Agence National de Sécurité du Médicament et des Produits de Santé (ANSM) authorizing all clinical research; b) contributing to the data collection; c) organising the regulatory and technical aspects of conducting and monitoring the study; contracting the mandatory insurance. It is the sponsor's role to report adverse events to national and European Union regulatory drug agencies.

All authors contributed to the conception, design, and redaction of the research protocol and will intervene in the data analysis, interpretation of the data, preparation, review and approval of the manuscript and decision to submit the manuscript for publication.

## Abstract

### Introduction

Electronic cigarettes (EC) mainly with nicotine content are widely used worldwide. Although the number of publications about its use is increasing exponentially, evidence based, unbiased, conclusive, head-to-head comparisons about its efficacy and safety as an aid for smoking cessation are lacking.

### Methods and analysis

*Design:* Randomized, placebo and reference treatment-controlled, multicenter, double blind, double dummy, parallel group trial.

*Participants:* Smokers smoking at least 10 cigarettes/day in the past year and motivated to quit, aged 18 to 70 years.

*Interventions:*

A) EC without nicotine (ECwoN) plus placebo tablets of varenicline administered by oral route: **placebo condition**

B) EC with nicotine (ECwN) plus placebo tablets of varenicline: **ECwN condition**

Voltage regulated electronic cigarettes will be used with liquid containing 12 mg/ml of nicotine for *ad libitum* use. Flavour: blond tobacco.

C) Reference: ECwoN plus 0.5 mg varenicline tablets: **varenicline condition.** Varenicline administered according to the marketing autorisation.

Treatment duration: 1 week + 3 months.

*Primary outcome:* Continuous smoking abstinence rate (CAR) (abstinence from conventional/combustible cigarettes) during the last 4 weeks (weeks 9 to 12) of the treatment period defined as self-report of no smoking during the previous 2 weeks and expired air CO ≤ 8 at Visit 4 at Week 10 after target quit date (TQD) i.e. 11 weeks after treatment initiation AND at Visit 5, Week 12 after TQD i.e. 13 weeks after treatment initiation.

*Secondary outcomes*: Safety profile; point prevalence abstinence rate; CAR confirmed by urinary anabasine concentration; changes in cigarettes/day consumption; craving for tobacco and withdrawal symptoms with respect of baseline.

### Ethics and dissemination

The ethics committee approval was obtained on 17 April 2018. All data collected about the study participants will be anonymised. Investigators will communicate trial results to participants, health authorities, healthcare professionals, the public, and other relevant groups without any publication restrictions.

## Article Summary

*Strength and limitations*

*Strengths*

- Randomized, head-to-head comparison, reference and placebo controlled double blind, double dummy smoking cessation efficacy and safety trial.
- Power sufficient to conclude about superiority of electronic cigarette with nicotine over electronic cigarette without nicotine and non-inferiority of electronic cigarette with nicotine compared to varenicline.
- Ad libitum electronic cigarette use mimicking conventional cigarette use.

*Limitations*

- Only one, fixed dose e-liquid nicotine concentration and one e-liquid flavour are used.
- A rigorous RCT is prioritised over a pragmatic, everyday life trial, more likely to demonstrate convincingly efficacy and safety. However, this can reduce the generalizability of the results to everyday population use.

## Introduction

Tobacco use kills more than 5 million people per year worldwide. Among the five greatest risk factors for mortality, it is the single most preventable cause of death (1). It reduces life expectancy by 9 to 15 years (2, 3, 4). Implementation of tobacco control strategies, including smoking cessation behavioral and pharmacological treatments, avoided 8 million premature deaths in the United States between 1964 and 2012 (5). Smoking cessation before the age of 40 reduces the risk of death compared to continued smoking by 90 % (3).

Tobacco is used in its combustible forms: cigarettes, cigarillos, pipes, cigars, shisha, or as smokeless tobacco: oral snuff, snus. The most widely used form is cigarettes. As of today, alternative nicotine delivery systems (ANDS) such as electronic cigarettes (EC), Juul and heat-not-burn/heated tobacco systems containing tobacco. These ANDS are used either for recreational purposes or with the intent to quit smoking.

Among ANDS, the most studied are EC. However as of today, their benefit/risk ratio as an aid for smoking cessation is not established with confidence.

Electronic cigarettes are diverse battery-powered devices to produce an aerosol. The battery heats a resistance that allows aerosolisation of the liquid called “e-liquid” which contains humectants (propylene glycol and/or glycerin) along with flavorants and may or may not contain nicotine. The European Union Tobacco Product Directive limits the nicotine content to 20 mg/mL; requires products to be child and tamper proof; requires health warnings, instructions for use, information on addictiveness and toxicity to appear on the packaging; bans promotional elements on packaging; requires all substances contained in the product and information on the product’s nicotine content to be listed (6).

The EU Directive has been transposed in France on May 19, 2016 (7).

As of today, ECs are consumer products and sold outside the health care system. In France pharmacies are prohibited to sell them.

Exposure to tobacco-related carcinogens and toxins are substantially lower among long-term EC users than among cigarette smokers or dual (EC+cigarettes) users and similar to that found among long-term nicotine replacement therapy NRT users (8). Substantial evidence shows that during EC use exposure to potentially toxic substances is lower compared with combustible/conventional cigarette smoking (9).

Last generation EC deliver more nicotine than first and second generation EC.Venous plasma nicotine concentrations after 65 minutes’ use are up to 48.1 ng/mL in experienced and 31.4 ng/mL in naïve users and the mean venous plasma nicotine concentrations are close to those observed with conventional cigarettes (9, 10, 11, 12).

To the best of our knowledge, there is no published report on arterial plasma nicotine concentration with EC or nicotinic acetyl choline receptor (NAchR) occupancy in the brain while using EC with nicotine.

EC reduce desire/craving to smoke and withdrawal symptoms (13, 14, 15, 16) main predictors of successful quit.

*EC as an aid to quit smoking conventional cigarettes*

Observational cohorts provided conflicting results as an aid to quit smoking (17, 18,19) and will not be mentioned further. Observational studies provide lower level of evidence (for various reasons) than randomised, controlled, double blind trials, therefore results are difficult to compare adequately.

Two randomized trials assessing the electronic cigarettes for smoking cessation (20, 21) and 2 meta-analyses of these two trials (22, 23) have been published. Caponetto et al. (21) (ECLAT trial) randomized 300 smokers, not intended to quit into 3 groups: EC disposable cartridge containing 7.2 mg (n=100), 5.4 mg (n=100) and no nicotine (n=100) were used. Intent-to-treat analysis of the main outcome did not show significant differences between groups. Bullen et al. (20) (ASCEND trial) randomized smokers wanting to quit: 289 to receive nicotine containing EC, 295 to receive 21 mg/24h nicotine patches and 73 to receive EC without nicotine. Cartridges of nicotine EC contained 10 to 16 mg nicotine/mL. The treatment duration was 12 weeks and the main outcome measure was continuous abstinence at 6 months after quit date defined as "self-reported abstinence over the whole follow-up period, allowing ≤5 cigarettes in total" and verified at 6 months by a measure of expired air CO (<10 ppm). All participants were referred to a quit line for support. The main outcome measure did not show statistically significant difference: 7.3 %, 5.8 %, 4.1 %, in the nicotine EC, nicotine patch groups, and placebo EC respectively (ITT analysis). 19.7 % of the participants in the nicotine EC, 11.3 % in the nicotine patch and 13.9 % in the placebo EC group had a serious adverse event (SAE), respectively.

A Cochrane review of EC for smoking cessation and reduction has been published in 2014 (22) and updated in 2016 (23). The quality of evidence (GRADE system) rated the evidence as low or very low because of the low (N=2) number of trials. Pooling data of these 2 trials, the authors report a relative risk (RR) of 2.29, 95% CI 1.05-4.96 for abstinence rate at 6 months. Analysis of the same 2 trials (20, 21) did not confirm these results (17).

A major randomised pragmatic but open trial has recently been published (January 30, 2019) (24). Smokers attending U.K. National Service stop-smoking services (N=886) were randomised to receive NRT for 3-months or a one month EC pack with liquid containing 18 mg/mL of nicotine. Both treatments could be used further at the discretion of the participants. The primary outcome measure of sustained abstinence at 1 year showed 18 % in the EC and 9.9 % abstinence in the NRT group (RR: 1.82, 95 % CI: 1.30 to 2.58). More respiratory SAE were observed in the EC than in the NRT group (5 *versus* 1). Incidence of cough and phlegm were lower in the EC than in the NRT group.

There is a general consensus that high-quality, large-scale randomized studies are needed (9, 25). The current trial is intended to fulfil this requirement.

**Objectives**

*Primary objective*: To assess the therapeutic efficacy and safety of EC with nicotine for smoking cessation. EC containing nicotine to EC not containing nicotine (placebo) and to varenicline, as a reference drug for smoking cessation, will be compared.

*Trial design*

This will be a randomized, placebo controlled, multicenter, double blind, double dummy, parallel groups, phase III type trial.

Included participants will be randomly assigned to one of the 3 groups:
A) Control group: EC without nicotine (ECwoN) plus placebo tablets of varenicline: **placebo condition**
B) Experimental group: EC with nicotine (ECwN) plus placebo tablets of varenicline: **ECwN condition**
C) Reference group : ECwoN plus varenicline tablets : **varenicline condition**
with a randomisation ratio of A:B:C= 1:3:3.
Each participant will use an EC and takes 2 tablets twice per day.

*Setting*

This national trial will involve smoking cessation clinics of both academic and community hospitals. Twelve study sites and 16 co-investigators agreed to participate and committed to recruit and follow up smokers for the trial. Individuals are eligible to be a co-investigator if they are medical doctors, having obtained a post-graduate diploma in addictive and/or tobacco related disorders. The list of study sites can be obtained from the principal investigator.

**Participants**

*Eligibility criteria*

Inclusion criteria

1. Smokers smoking at least 10 cigarettes/day (factory made or roll-your-own) in the past year
2. Aged 18 to 70 years
3. Motivated to quit, defined as a score > 5 on a visual rating scale ranging from 0 (not motivated at all) to 10 (extremely motivated)
4. Signed written informed consent
5. Understanding and speaking French
6. Women of childbearing age can be included if they use an effective contraceptive method: either hormonal contraception or an intrauterine device started at least one month before the first research visit
7. Individual affiliated to a health insurance system
8. Previous failure of nicotine replacement therapy for smoking cessation.

Exclusion criteria

1. Any unstable disease condition within the last 3 months defined by the investigator as major change in symptoms or treatments such as recent myocardial infarction, unstable or worsening angina, severe cardiac arrhythmia, unstable or uncontrolled arterial

hypertension, recent stroke, cerebrovascular disease, obliterative peripheral arterial disease, cardiac insufficiency, diabetes, hyperthyroidism, pheochromocytoma, severe hepatic insufficiency, history of seizures, severe depression, chronic obstructive pulmonary disease (COPD)
2. Any life threatening condition with life-expectancy of less than 3 months
3. Alcohol use disorder defined as a score $\geq 10$ on the AUDIT-C questionnaire (see below)
4. Abuse of or dependence on illegal drugs in the last 6 months revealed by medical history
5. Regular use of tobacco products other than cigarettes
6. Current or previous (last 6 months) use of EC
7. Pregnant women
8. Breastfeeding women
9. Protected adults
10. Current or past 3 months participation in another interventional research
11. Current or past 3 months' use of smoking cessation medication such as varenicline, bupropion, nicotine replacement therapies
12. Known lactose intolerance (placebo tablets contain lactose)
13. Hypersensitivity to the active substance or to any of the excipients
14. Known severe renal failure.

*Patient and Public Involvement*

Patients or public were not involved in the conception and writing of this protocol. Study results will be disseminated individually to all study participants if requested.

**Interventions**

*Investigational product 1: EC with nicotine or EC placebo*

EC exists in two forms: liquid containing nicotine or with liquid not containing nicotine. Nicotine content in EC can vary in the European Union between 0 and 19.9 mg/mL. Third and fourth generation EC allow the user to change voltage and airflow leading to individualised nicotine delivery and dose adaptation.

A call for application by EC companies has been launched by the sponsor twice in 2017 and 2018 (no candidate in 2017).
Some major requirements for applications are listed here:

- EC liquid containing 0 and 12 mg/mL of nicotine
- Regular and reported control of nicotine's concentration in EC liquid by batches
- Tobacco flavour
- Long shelf life
- Detailed information about constituents
- Highly purified nicotine

Packaging: active or placebo bottles of e-liquid will be provided blinded as unidentifiable bottles. Each blinded box package will contain ten 10 mL bottles of e-liquids for 1 months.

In the current study the ECwN group will use EC liquids containing 12 mg/mL of nicotine. E-liquids will be allowed to be used *ad libitum* and because nicotine delivery can be adjusted according to the user's need, all participants would adjust their individual nicotine dose by varying the voltage of their EC, by varying puff frequency, puff volume and depth of inhalation similarly as they are doing (or used to do) with conventional cigarettes. A recent

paper by Soar et al. (26) demonstrates that over a 12 months period EC users maintained their nicotine intake, as measured by saliva cotinine concentration, possibly through self-titration.

*Justification of the nicotine concentration*

We consider, based on previous studies, that one cigarette contains approximately 1 mg of nicotine, thus 10 cigarettes contain approximately 10 mg of nicotine (27, 28). Nicotine's bioavailability when inhaled in cigarette smoke is 90 to 95 %; it is plausible that the bioavailability of nicotine of the aerosol delivered by an EC is lower. In the current research protocol the use of e-liquid of 12 mg/mL of nicotine may, thus, correspond approximately to 10 cigarettes. The randomized, placebo controlled study (nicotine – placebo: double blind) against nicotine patch (open label) used in the nicotine EC arm 10-16 mg/mL e-liquid concentration (20). Abstinence rate was not different between EC with nicotine *versus* EC with placebo (double blind comparison) on the main outcome measure. It was raised that this negative result is due to the low bioavailability of nicotine delivered by the EC used dating back to 2012. More recent studies using tank system EC provide plasma nicotine concentrations higher than earlier studies using EC of 2012 to 2014 (12).

Dawkins et al. (29) assessed 6 mg/mL and 24 mg/mL nicotine e-liquid concentrations in a self-titration/self-administration design. Plasma nicotine concentrations were higher with the 24 mg/mL nicotine liquid than with the 6 mg/mL nicotine liquid. However, reduction in craving for cigarettes were similar. Compensatory puffing occurred with the 6 mg/mL nicotine concentration, puff number, puff duration and liquid consumption were higher with the low than with the high nicotine concentration liquid. There were no statistically significant differences between conditions in self-reported craving, withdrawal symptoms, satisfaction, throat hit or adverse effects. However, the blood nicotine concentration was higher at 60 minutes with the 24 mg/mL than with the 6 mg/mL liquid: 43.57 (SD 34.78) 22.03 (SD 16.19) ng/mL. Thus EC users compensate low nicotine liquid concentration by increasing puff topography characteristics to increase nicotine uptake. This compensatory puffing is similar as with conventional cigarettes.

We can, thus, conclude that an intermediary concentration of nicotine would be optimal: plasma nicotine concentrations sufficiently high leading to a sufficient craving reduction. The chosen e-liquid concentration of 12 mg/mL takes also into account the standard dose-response relationship (6-12-24 mg/mL).

Only one flavour will be used to reduce variability of treatment response according to a preferred flavour. We chose the blond tobacco flavour with which all smokers can be familiar, which is less likely to be aversive in adults and the most sold when initiating EC use.

*EC device:*

Mini iStick kit (20 W) Eleaf, clearomiser: GS Air M with resistance of 1.5 ohm. To keep the blinding, the clearomiser's Pyrex window is of gray colour not allowing distinguishing coloration of the e-liquid containing nicotine.

*Liquid for EC* is manufactured by GAIATREND SARL (https://www.gaiatrend.fr/fr/).

*Counselling about the use of EC*

All participants will be delivered a short manual and a video specifically developed for this study explaining the use of EC. At each visit participants receive also verbal counselling about the use of the EC device and answers to their questions about handling the EC device.

Investigators are trained at the first Investigators' meeting to provide straightforward counselling about EC use.

*Investigational product 2 (reference drug): varenicline 0.50 mg and its placebo*

Varenicline and not nicotine replacement therapies (NRT) has been chosen for this study as the reference drug because:
i) Varenicline is associated with the highest level of abstinence rate among the 3 available smoking cessation medications with marketing authorization (bupropion, NRT, varenicline) (30, 31) (but its efficacy is similar to that of combined (short + long acting) NRT (32)). Varenicline is, therefore, a better comparator for a new therapeutic intervention for which we aim to demonstrate a therapeutic efficacy as high as the best available single medication treatment.
ii) Identical placebo tablets for varenicline can easily be manufactured and none of the placebo NRT forms are available. Manufacturers of NRT products do not have any more corresponding placebos and manufacturing identical placebos by an external company may increase the likelihood of non-identical placebos. Moreover, purchasing both identical placebos along with active NRT products manufactured by a company that do not have the marketing license for NRT may introduce a major uncertainty by raising the question: Does the NRT product have the same bioavailability as the original, licensed NRT product? Uncertainty about the active NRT product's bioavailability may compromise the validity of the trial's results.
iii) Blinding of tablets administered by oral route is more convenient than blinding of NRT such as transdermal patches, gums, lozenges, inhaler or buccal spray.

Varenicline (Champix®) 0.5 mg is presented as a capsular-shaped, biconvex, white film-coated tablet. The tablets are held under a vial of 56 tablets.
Varenicline has been purchased at Pfizer France.
*List of excipients:*
Core tablets: Cellulose, Microcrystalline, Calcium Hydrogen Phosphate Anhydrous, Croscarmellose Sodium Silica, Colloidal Anhydrous, Magnesium Stearate
Film coating : Hypromellose Titanium Dioxide (E171) Macrogols Triacetin.
Placebo and active tablets are strictly similar. Placebo tablets of varenicline have been manufactured, packaged and labeled by a pharmaceutical sub-contractor according to the Good Manufacturing Practices and under the responsibility and supervision of AGEPS.
The dose regiment of varenicline/placebo follows varenicline's monograph:
Day 1 to Day 3 : one tablet of 0.5 mg/placebo in the morning
Day 4 to Day 7 : 1 tablet of 0.5 mg/placebo morning and the evening
From Day 8 until end of treatment: 1 mg morning and evening i.e. two 0.5 mg/placebo tablets morning and evening. The number of tablets per day can be modified at the discretion of the investigator if a better control of adverse effects is needed.

EC and tablets are started one week before the target quit date (TQD) to stop smoking and followed up for 3 months after TQD.

**Behavioral counselling for smoking cessation**
Brief behavioural smoking cessation counselling for all participants is administered at all visits by the investigators specialised in smoking cessation. It is based on the national guidelines for smoking cessation (33).

**Criteria for discontinuing or modifying allocated interventions**

Any participant can withdraw from participating in the research at any time and for any reason.

- The investigator can end a subject's participation in the research for any reason that affects the participant's safety or which would be in the participant's best interests but not because of non-abstinence from cigarettes after TQD.
- In case of loss to follow-up, the investigator should make all efforts to reach the participant and collect the reason of loss to follow-up and information about his/her safety data.
- In case of pregnancy, despite the mandatory contraception, the participant will exit the trial and will be followed up until delivery.

The case report form must list the various reasons for ending participation in the research:

- Adverse event/reaction
- Other medical problem
- Participant's personal reasons
- Explicit withdrawal of consent

If a participant leaves the research prematurely or withdraws consent, any data collected prior to the date of premature exit can be used.

**Methods for monitoring compliance with the treatments**

Study medication compliance at Visits 1 through 5 will be assessed with the questions:

A) Did you use the electronic cigarette

- Every day
- Approximately every other day
- Twice a week
- Less than twice a week.

B) Did you take your tablets

- Every day
- Approximately every other day
- Twice a week
- Less than twice a week.

Accountability of returned EC bottles and tablet vials will allow approximating EC liquid's and tablets' use.

**Guess test to control efficacy of the blinding**

At Visit 2 (Week 4 after TQD i.e. 5 weeks after treatment initiation) and at Visit 5 (Week 12 after TQD i.e. 13 weeks after treatment initiation) a guess test will be run. It consists of the following question:

"Do you think you received:

- Placebo tablets and electronic cigarettes without nicotine? Yes/No
- Placebo tablets and electronic cigarettes with nicotine? Yes/No
- Varenicline (Champix©) tablets and electronic cigarettes without nicotine? Yes/No

**Concomitant care and interventions**

All previously introduced medications will be permitted to be continued. The following concomitant medications per NRT's licence in France, by extrapolation to nicotine containing e-liquids, and according to the requirement of the French drug agency (ANSM) will be prohibited: theophylline, clozapine, olanzapine, méthadone, ropinirole, pharmaceutical caffeine (dose adaptation when quit smoking).

As of today, varenicline has no known clinically significant drug-drug interaction.

To the best of our knowledge, there is no available information about drug interaction of EC with or without nicotine.

NRT use is not permitted during the study but its over-the-counter purchase cannot be controlled for. At each post-quit day visit we will check its use as a control variable. Positive answer will result asking the participant to stop NRT use. If he/she does not comply, the participant will be excluded for noncompliance with the study protocol.

**Primary outcome**

Continuous smoking abstinence rate (CAR) (abstinence from conventional/combustible cigarettes) during the last 4 weeks (weeks 9 to 12) of the treatment period of 3 months.
Definition: Self-report of no smoking during the previous 2 weeks and expired air CO ≤ 8 ppm. at Visit 4 at Week 10 after TQD i.e. 11 weeks after treatment initiation AND at Visit 5, Week 12 after TQD i.e. 13 weeks after treatment initiation.

**Secondary outcomes**

- Safety profile of EC containing nicotine comparatively to its placebo and varenicline.
- Point prevalence abstinence: 7-day abstinence at Visit 1, 2, 3, 6 and 14 days of abstinence at Visit 4 and 5 (see timeline below) associated with expired air CO ≤ 8 ppm.
- Time to relapse to smoking after TQD
- CAR confirmed by urinary anabasine concentration ≤ 3 ng/mL
- Change in cigarettes/day consumption with respect of baseline
- Change in craving for tobacco as assessed by the French 12-item Tobacco Craving Questionnaire (34) with respect of baseline
- Change in withdrawal symptoms as assessed by the modified Minnesota Nicotine Withdrawal Scale (35) with respect of baseline

Control variables:

- Study medication compliance recorded at each visit
- Baseline level of tobacco dependence
- Urinary concentration of anabasine, anatabine (both alkaloids found only in tobacco, control for tobacco smoking) and cotinine (main metabolite of nicotine, control for nicotine intake) at Visit 4 and 5 (36). Analysis laboratory: Swiss Laboratory for Doping Analyses, Epalinges, Switzerland.
- Results of the "guess test" i.e. correct identification of the treatments by participants

**Participant timeline**

Randomisation visit = Visit 0 - Dispensing of the treatment

Treatment initiation within the 7 days following randomization.

Target quit date (TQD) should occur between 7 and 15 days after randomization and after 7 days of treatment intake (Figure 1).

The first post-target quit date visit (Visit 1) is at Week 2 after TQD i.e. 3 weeks after treatment initiation.
Visit 2 is at Week 4 after TQD i.e. 5 weeks after treatment initiation.
Visit 3 is at Week 8 after TQD i.e. 9 weeks after treatment initiation.
Visit 4 is at Week 10 after TQD i.e. 11 weeks after treatment initiation.
Visit 5 is at Week 12 after TQD i.e. 13 weeks after treatment initiation.
Visit 6 is at Week 24 after TQD i.e. 25 weeks after treatment initiation.

*Assessments at Visit 0*

- *Demographic characteristics*
  - Age
  - Gender
  - Professional situation
    Employed/Housewife/Unemployed/Student/Retired
  - Education level: Number of years after age 7 years.
  - Marital status:
    Cohabiting/ Married/Separated/Divorced/Single/Widowed
  - Annual household income (euros)
    < 12 000/12 001 – 30 000/30 001 – 100 000/> 100 000
  - Self-reported ethnic origin
    European/African/Asian/Other
- *Previous medical history :*
  - any unstable disease condition within the last 3 months defined by the investigator as major change in symptoms or treatments
  - any life threatening condition with life-expectancy of less than 3 months
  - alcohol use disorder defined as a score ≥ 10 on the AUDIT-C questionnaire
  - abuse of or dependence on illegal drugs in the last 3 months revealed by the medical history
  - regular use of tobacco products other than cigarettes
  - current or previous (last 6 months) use of electronic cigarette
  - pregnant women
  - breastfeeding women
  - current or past 3 months participation in another interventional research
  - current or past (last 3 months) use of smoking cessation medication such as varenicline, bupropion, nicotine replacement therapies
  - known lactose intolerance (placebo tablets contain lactose)
  - hypersensitivity to the active substance or to any of the excipients
  - known severe renal failure
- *Previous mental health history (**before** the last 6 months):*
  - Treatment for major depression
  - Treatment for psychosis

- Treatment for bipolar disorder
- Treatment for substance use disorder:
- Cannabis, alcohol, cocaine, opioid, psychostimulant use
- Treatment for smoking cessation by NRT, varenicline, bupropion

– *Current, past 6 months, medical history:*
- Cardiovascular disorders (yes/no); stable on treatment: yes/no
- Myocardial infarction/unstable angina (yes/no); stable on treatment: yes/no
- Arterial hypertension (yes/no); stable on treatment: yes/no
- Malignancy disorder (yes/no); stable on treatment: yes/no
- Pulmonary disorder (other than COPD) (yes/no); stable on treatment: yes/no
- COPD (yes/no); stable on treatment: yes/no
- Type 1 or type 2 diabetes mellitus (yes/no); stable on treatment: yes/no
- Other (yes/no); stable on treatment: yes/no

– *Current, past 6 months, mental health history:*
- Treatment for major depression (yes/no);; stable on treatment: yes/no
- Treatment for psychosis (yes/no); ; stable on treatment: yes/no
- Treatment for bipolar disorder (yes/no); stable on treatment: yes/no
- Treatment for substance use disorder (yes/no);
- Cannabis, alcohol, cocaine, opioid, psychostimulant use disorder (exclusion if any)
- Treatment for smoking cessation by NRT, varenicline, bupropion (exclusion if any)

– Smoking characteristics
- Age of the first cigarette (years)
- Age of regular smoking (years)
- Number of previous attempt(s) to quit
- Longest duration of abstinence if any
- Fagerström Test for Cigarette Dependence score
- Spouse/partner smokes (yes/no)
- Other smoker in the household (yes/no)
- Secondhand smoke exposure at home/work/leisure (yes/no)
- Current self-reported number of cigarettes smoked per day

– Clinical measures
- Systolic and diastolic blood pressure in sitting position
- Height
- Body weight
- Expired air CO along with time (minutes) since last cigarette smoked
- Craving for tobacco using the FTCQ-12 (34)
- Withdrawal symptoms using the Minnesota Tobacco Withdrawal Scale (35)

– Substance use
- Cannabis use in the last 30 days
- Alcohol use

The AUDIT (Alcohol Use Disorders Identification Test) will be used to screen for alcohol problems. It has been suggested as the most effective instrument identifying individuals at-risk, hazardous or harmful drinking (37). Its sensitivity ranges from 51 % to 97 % and specificity from 78 to 96 % according to a systematic review (38). The corresponding values for the CAGE questionnaire (39) are: 43 % to 94 % and 70 % to 97 %.

The short French language form, AUDIT-C of the questionnaire will be used as recommended by recent French guidelines (40).

*At each visit will be measured:*

- Systolic and diastolic blood pressure in sitting position.
- Body weight
- Cannabis use since the last visit
- Alcohol use since the last visit (more than 1 drink per day/less than one drink per day)
- Expired air CO along with time since last cigarette
- Current self-reported number of cigarette smoked per day in the last 7 days
- Craving for tobacco using the FTCQ-12 (34)
- Withdrawal symptoms using the Minnesota Tobacco Withdrawal Scale (35)

Expired air CO will be measured with a Smokerlyzer (Bedfont Scientific Ltd, Kent, UK) a value of less than or equal to 8 ppm will be required to support the self-report of abstinence. The FTCQ-12 and MNWS are paper and pencil self-report questionnaires.

*At each further visit adverse reactions/events* are inquired with the following question: "Did you experience since the last visit a health symptom or event which is unusual?" If the answer is "Yes", the adverse reaction/event will be recorded.

**Sample size**

According to the EAGLES study (30) with N=8144 smokers, the percent abstinent at the main efficacy criterion – similar to that used in the current study – was 33.5 %. Taking this percentage as reference, with an OR=1/0.60=1.664 and a power of 80 % we would need at least 272 participants in each of the varenicline (reference) and the ECwN group (41). We would randomize 1/3 of the participants to the group ECwoN, that is 91 smokers. These numbers would allow to show a significant difference between varenicline and ECwN with an alpha=0.05. The total number needed to be randomized will, thus, be of 2*272+91= 635 smokers. To take into account lost to follow up, we plan to randomize *at least* 650 smokers: 280 in each of the ECwN and varenicline arm and 90 (rounded) in the ECwoN arm.

*Justification to randomize only 90 participants in the placebo-placebo condition (ECwoN)*
The main research question is the superiority of ECwN and varenicline (reference) – justifying of testing of non-inferiority between these groups including 280 participants/group. If the superiority testing is non-significant, we propose to switch to non-interiority testing. We conclude on the non-inferiority if and:

- ECwN is non-inferior to varenicline
- ECwN superior to ECwoN
- Varenicline is superior to ECwoN

Thus, the comparison involving ECwoN will be run "after" the comparisons between ECwN and varenicline.

We considered the following percent of abstinence: p(varenicline)=33.5 % and p(ECwoN)=15 %. Thus with 280 participants in the varenicline and 90 participants in the ECwoN group we will have sufficient power to conclude.

**Decision rules**

We will conclude that ECwN is superior to varenicline if the two tailed superiority test at 5 % on the main outcome measure (percent abstinent (p)) will be significative such as p(ECwN) > p(varenicline).
Would this test show a p value higher than 0.05, we would switch to non-inferiority. We will conclude that ECwN is non-inferior to varenicline if:

- the two-tailed superiority test is non-significant at the 5 % level
- the test of non-inferiority at 5 % one-tailed with a delta=5% is significant
- the two-tailed superiority test of p(ECwN) versus p(ECwoN) is significative at 5%;
- the two-tailed superiority test of p(varenicline) versus p(ECwoN) is significative at 5%.

In any case we will conclude that ECwN is superior to ECwoN, if the test of superiority at 5 % (two-tailed) is significant such as p(ECwN) > p(ECwoN).

A Pearson's two-tailed Chi square test at 5 % will be used to test the superiority. A Dunnet & Gent Chi square test at 5 %, one-tailed, will be used for testing the non-inferiority (42).

Some simulations

1. If p(Varenicline) = 33.5 %, p(ECwN)=33.5% and p(ECwoN)=15% then
   a. the probability that ECwN is superior to varenicline is of 2.5 %
   b. the probability that ECwN is non-inferior to varenicline is of 31.5%.
   c. the probability that ECwN is superior to varenicline is of 2.5%+31.5%=34%.
   d. the probability that ECwN is superior to ECwoN is of 95%.

2. If p(Varenicline)=33.5%, p(ECwN)=40% and p(ECwoN)=15% then
   a. the probability that ECwN is superior to varenicline is of 33.6 %
   b. the probability that ECwN is non-inferior to varenicline is of 52.7 %.
   c. the probability that ECwN is superior to varenicline is of 33.6%+52.7%=86.3 %.
   d. the probability that ECwN is superior to ECwoN is of 99.8 %.

3. If p(Varenicline)=33.5 %, p(ECwN)=45 % and p(ECwoN)=15 % then
   a. the probability that ECwN is superior to varenicline is of 80.1 %
   b. the probability that ECwN is non-inferior to varenicline is of 19 %.
   c. the probability that ECwN is superior to varenicline is of 80.1%+19.0%=99.1 %.
   d. the probability that ECwN is superior to ECwoN is of 99.9 %.

The estimate of an abstinence rate of around 40 % with the two active treatments and a 15 % abstinence rate in the placebo condition seems reasonable and clinically significant.

There is no justification to run first a global comparison. Either the ECwN arm is better than the varenicline arm and we have answered the main research question or the ECwN is non-inferior to the varenicline arm and there will be a necessity to run two separate comparisons against ECwoN (i.e.ECwN against ECwoN; varenicline against ECwoN).

**Recruitment**

Recruitment is either local (a) directly by the centres or centralized (b) using a web page and a centralised study specific phone number and email address.

a) Smokers intending to quit smoking are recruited by advertisement in pharmacies, physicians' offices situated in the catchment area of each investigator's centre, by local newspapers and in public places of the centres' health care facilities.
b) Candidates to participate can register by the study's website, unique email address and phone number. Registration is followed by a phone screening before dispatching to the study centres.
Only one person by household will be recruited.

**Assignment of interventions and blinding**

To assure allocation concealment, computer generated randomization list (allocation ratio: 1:3:3) involving blocks, stratified by age (<45 versus ≥ 45 years) and centre, will be prepared and is kept blinded to all participants to the trial. The randomization list is incorporated into the eCRF, and a treatment number is attributed automatically upon completion of the randomization visit. The random, computer generated allocation sequence is prepared by a statistician of the Clinical Reseach Unit of Pitié Salpêtrière Charles Foix.

The randomization list is being kept in a secured place by the sponsor and a copy of the randomization code is being kept separately in the Poison Centre of Fernand Widal Hospital, Paris, in case of a serious adverse event necessitating the opening of the participant's group assignment (see below). Investigators, members of the coordination centre, hospital pharmacists, and the sponsor's clinical research assistants in charge of monitoring will be kept blinded.

*Blinding methods and measures to protect the blinding*

Varenicline and its placebo are administered as non-identifiable tablets.
Because nicotine solutions tend to become yellow with time, the following provisions have been taken to make EC liquids non-identifiable:
Liquids of EC will be delivered to the participants in white, non-transparent vials of 10 mL specifically manufactured for the study. Both nicotine and no nicotine containing liquids will have a tobacco flavour and smell (blond tobacco). The EC's clearomiser' Pyrex walls will be transparent but of grey colour allowing the user to see the level of the liquid but not its colour.

*Unblinding procedures*

Unblinding is the sponsor's decision. However, the investigating physician may request unblinding if he/she considers essential in the participant's interest/care.

**Data collection and management**

Data will be collected through the study's eCRF. Data entry is carried out on electronic media via a web browser by co-investigators. The source documents are any original document or item that proves the existence or accuracy of a data-point or fact recorded during the trial. Source documents are kept by the investigator, or by the hospital in the case of hospital medical records, for the statutory period. During and after the clinical study, all data collected about the study participants and sent to the sponsor by the investigators (or any other specialised collaborators) will be anonymised. CNIL, the French Data Protection Authority implemented the "Méthodologie de référence" (MR-001) according to the provisions of

Article 54, paragraph 5 of modified Law No. 78-17 of 6 January 1978. The sponsor, Assitance publique-Hôpitaux de Paris has signed a commitment to comply with it.

**Data analysis**

**Populations submitted to the analyses**

1. The *intent-to-treat* (ITT) efficacy analysis will include all participants who were randomized and having received at least one dose of any study treatment.
2. *Safety population*: All participants who were randomized and having received at least one dose of any study treatment.
3. *Full analysis set* (FAS) population: All participants who were randomized and having received at least one dose of study treatment except those who had no data at all post-randomisation.
4. *Per-protocol* population: All participants who are followed up to Week 12 and for whom the main efficacy criterion (CAR week 9 to 12) is available and who received at least one dose of treatment.

*Handling of missing data*
Participants who miss a visit will receive at least 2 phone calls as a reminder.
Missed visits are not a criterion for discontinuation. All participants will be strongly encouraged to stay in the trial up to the end of the research that is up to week 25.
Smoking (lapse: some puffs or relapse: relapse to regular conventional cigarette consumption) will not be a reason for discontinuation.

**Primary analysis**

We want to demonstrate the effectiveness of ECwN over varenicline. For that we will compare the percentage of success (CAR) between the two arms with a two-tailed Chi square test. If this test is not significant (i.e. p>5%), we will perform a non-inferiority test (switch) for ECwN over varenicline with a unilateral Dunnet and Gent test at 5% and a non-inferiority bound of $\Delta_L = 5\%$.
In parallel with the non-inferiority test, we will perform two tests of superiority, one comparing the ECwN to ECwoN on the one hand, and one comparing varenicline to ECwoN on the other hand to ensure that the non-inferiority is not obtained by lack of efficacy in both ECwN and varenicline arms. Thus, non-inferiority will be achieved if the non-inferiority test is significant as well as the two superiority tests described above.
For the superiority tests, the analysis will focus on the ITT population and will be confirmed on the per protocol population. The non-inferiority test will be done on the per protocol population and will be confirmed on the ITT population. (See details in Decision rules)

**Secondary analyses**

Comparisons will be made between ECwN and varenicline arms but may be done between the 3 treatment arms. Qualitative variables will be analyzed with a Chi2 test. Quantitative variables will be compared with Student's t test (or non-parametric tests as appropriate). Censored variables, such as the time to relapse will be analyzed by the log rank test.
These three tests will be generalized with a logistic model, ANOVA or a Cox model if adequate. Variables collected at different visits will be analysed in longitudinal, linear or

logistic random effect models. In the same way the absolute variation or the relative variation can be studied there also with linear models with random effect.

Missing secondary endpoints will be imputed in both ITT and per protocol populations. The primary endpoint will be imputed by a multiple imputation method. The other criteria will not be imputed, since most of these criteria will be analyzed in longitudinal analysis.We will perform a sensitivity analysis by rerunning the population analysis of subjects whose primary endpoint is non-missing.

**Monitoring**

Clinical Research Associates (CRAs) appointed by the sponsor are responsible for the proper running of the study, for collecting, documenting, recording and reporting all handwritten data, in accordance with the Standard Operating Procedures applied within the DRCI and in accordance with Good Clinical Practice as well as with the statutory and regulatory requirements.
The investigator and the members of the investigator's team agree to make themselves available during regular Quality Control visits by the Clinical Research Associate. During these visits, the following elements will be reviewed:

- written consent
- compliance with the study protocol and its procedures
- quality of the data collected in the case report forms: accuracy, missing data, consistency of the data with the "source" documents (medical files, appointment books, original copies of laboratory results, etc.)
- management of the treatments used.

**Safety assessment**

Safety will be assessed at each visit during the treatment period. However, the safety assessment will also be conducted at Visit 6 (end of research) even if no adverse event/reaction has previously been reported. Rational: one cannot exclude occurrence of adverse events/reactions even 3 months after stopping study medications.

*Safety endpoints*

- AE diagnosis/description
- The date when the AE started and stopped
- CTCAE grade maximum intensity (Comon Terminology Criteria for Advesre Events (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf)
- Whether the AE is serious or not
- Reason why the SAE was serious (e.g. hospitalisation)
- Investigator causality rating against the investigational product (yes or no)
- Action taken with regard to investigational product
- Outcome

*Anticipated methods and timetable for measuring, collecting and analysing the safety endpoints*

Safety and tolerance are recorded as follows:

- adverse events will be recorded in the "adverse event" section of the case report form;
- adverse effects' declaration by the participant will be collected at each visit or anytime when the participant establishes a contact with his/her investigator. Investigators reports to the Sponsor the participants' declaration and/or examinations' results linked to any adverse reaction/event along with its estimated severity and imputability. The Data Safety Monitoring Board (DSMB) will monitor safety data to avoid continuing the trial if it estimates that the risk prevails the benefit.

*Recording and reporting adverse events*

*Definitions*

**Adverse event**

Any untoward medical occurrence in a trial subject, which does not necessarily have a causal relationship with the clinical trial or with the investigational product (43).

- **Adverse reaction to an investigational medicinal product**

Any adverse event occurred in a trial subject, which has a causal relationship with the clinical trial or with the investigational medicinal product.

- **Serious adverse event or reaction**

Any adverse event or reaction that at any dose of medication, results in death, threatens the life of the research subject, requires hospitalisation or prolongs hospitalisation, causes a severe or long-term disability or handicap, or results in a congenital abnormality or deformity.

- **Unexpected adverse reaction to an investigational medicinal product**

Any adverse reaction to the product, whose nature, severity, frequency or outcome is inconsistent with the safety information described in the Reference Safety Information (summary of product characteristics, or the investigator's brochure if the product is not authorised).

- **Emerging safety issue**

Any new safety information that may lead to a reassessment of the risk/benefit ratio of the trial or the investigational medicinal product, modifications in the investigational medicinal product use, the conduct of the clinical trial, or the clinical trial documents, or a suspension, interruption or modification of the protocol of the clinical trial or other similar trials..
Examples:
a) any clinically significant increase in the frequency of an expected serious adverse reaction
b) suspected unexpected serious adverse reactions in patients who have terminated their participation in the clinical trial that are notified by the investigator to the sponsor together with follow-up reports
c) any new safety issue relating to the conduct of the clinical trial or the development of the investigational medicinal product, that may impact the safety of the trial subjects.
d) recommendations from the DSMB that may affect the safety of the trial subjects
e) any suspected unexpected serious adverse reaction (SUSAR) reported to the sponsor by another sponsor of a trial carried out in a different country but relating to the same medication.

## Data Safety Monitoring Board (DSMB)

A Data Safety Monitoring Board has been set up for this trial. Its primary mission is to serve as a committee for monitoring safety data. The sponsor is responsible for justifying the creation the DSMB to the Competent Authority (ANSM) and to the Ethics committee (CPP).

The DSMB's preliminary meeting took place on 12 December 2017, before the protocol submission to competent health authority (ANSM) and Ethics committee (CPP). DSMB's operating methods and the meeting schedule have been defined during this first meeting. All missions as well as the precise operating methods of the DSMB are described in the DSMB's charter for the research.

The members of the DSMB are:

- Pr Eric Bellissant, President, clinical pharmacologist with expertise in public health and social medicine, Centre Hospitalier Universitaire de Rennes, Rennes, France
- Pr. Daniel Thomas, cardiologist, previous head of the Department of Cardiology, Hôpitaux Universitaires Pitié-Salpêtrière, Paris, France
- Pr Laurence Galanti, physician, smoking cessation specialist, CHU Mont-Godinne, Belgium.

General information about the DSMB

The DSMB makes recommendations to the sponsor about the continuation, modification or termination of the research. The recommendations that the DSMB can make are:

- to continue the research with no modifications
- to continue the research with a modification to the protocol and/or to the monitoring of subjects
- to temporarily halt inclusions
- to permanently terminate the research in light of safety data: serious adverse reactions.

## Ethics and dissemination

The ethics committee (Comité de protection des personnes, CPP Ouest II-Angers, France, approved this protocol on 17 April 2018.

The potential participant is granted a reflection period of one week between the time when the subject receives the information and the time when he or she signs the consent form. Informed consent is obtained before the inclusion by the investigator physician as required for this type of study by French regulations. The form is available in French on request.

The persons responsible for the quality control of clinical studies (44) take all necessary precautions to ensure the confidentiality of information relating to the investigational medicinal products, the study, the study participants and in particular the identity of the participants and the results obtained. These persons, as well as the investigators themselves, are bound by professional secrecy (45, 46).

During and after the clinical study, all data collected about the study participants and sent to the sponsor by the investigators (or any other specialised collaborators) will be anonymised. The principal investigator, the Unité de Recherche Clinique (Clinical Research Unit) and the sponsor will have access to the final trial dataset without limitation.

Investigators will communicate trial results to participants, health authorities, healthcare professionals, the public, and other relevant groups without any publication restrictions. The Service Presse of Assistance publique-Hôpitaux de Paris will help prepare a dissemination plan about participant and public involvement in the research.

Main authorship eligibility for publication in medical journals will follow International Committee of Medical Journal Editors ICMJE criteria (47).

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**Author Contributions**

Concept and design: I. Berlin, B. Dautzenberg

Drafting of the manuscript: I. Berlin

Critical revision of the manuscript for important intellectual content: B. Dautzenberg, B. Lehmann, Y. de Rycke, F. Tubach, J. Palmyre, E. Liégey

Administrative, technical, material support: B. Lehmann, J. Palmyre, E. Liégey

Conflict of Interest Disclosure: I. Berlin reports occasional honoraria from Pfizer in the last 3 years for counseling and presentations at meetings

F. Tubach is head of the clinical research unit of Pitié-Salpêtrière and Charles Foix hospitals and the pharmacoepidemiology center of Assistance Publique Hôpitaux de Paris, that have received research funding, grants and fees for consultant activities from a large number of pharmaceutical companies, that have contributed indiscriminately to the salaries of its employees. She didn't receive any personal remuneration from these companies.

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**Legend for Figure 1:**

The ECSMOKE trial's outline.

| | Phone screening | |
|---|---|---|
| Visit 0 | Inclusion/<br>Randomisation to Placebo<br>Condition or Nicotine Condition or<br>Varenicline Condition | |
| | Treatment initiation<br>Day -7 | Electronic cigarette +<br>Tablets |
| | Target quit day (TQD)<br>Day 0 | x |
| Visit 1 | Week 2/TQD | x |
| Visit 2 | Week 4/TQD | x |
| Visit 3 | Week 8/TQD | x |
| Visit 4 | Week 10/TQD | x |
| Visit 5 | Week 12/TQD | |
| Visit 6<br>Follow up visit/end of<br>study | Week 24/TQD | |

254x190mm (96 x 96 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description |
|---|---|---|
| **Administrative information** | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym: *page 1* |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry: *page 2* |
| | 2b | All items from the World Health Organization Trial Registration Data Set. *Registered at ClinicalTrials.gov* |
| Protocol version | 3 | Date and version identifier: *page 2* |
| Funding | 4 | Sources and types of financial, material, and other support: *page 2* |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors: *pages 2-3* |
| | 5b | Name and contact information for the trial sponsor: *page 2* |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities: *pages 2-3* |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee): *pages 2-3* |
| **Introduction** | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention: *pages 6-7* |
| | 6b | Explanation for choice of comparators: *pages 9-11* |
| Objectives | 7 | Specific objectives or hypotheses: *pages 7-8 and 16-17* |

| | | |
|---|---|---|
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory): *pages 7-8 and 16-18* |
| **Methods: Participants, interventions, and outcomes** | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained: *page 8 and 17* |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists): *pages 8-9* |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered: *pages 9-11* |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease): *page 12* |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests): *page 12 and 19* |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial: *page 13* |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended: *pages 13-16* |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure): *page 14* |
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations: *pages 16-17* |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size: *page 17* |
| **Methods: Assignment of interventions (for controlled trials)** | | |
| Allocation: | | |

| | | |
|---|---|---|
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions: *pages 17-18* |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned: *page 18* |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions: *page 18* |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how: *page 18* |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial: *page 18* |
| **Methods: Data collection, management, and analysis** | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol: page 15-16, page 18 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols: *pages 19-20* |
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol: *page 18* |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol: *pages 19-20* |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses): *pages 19-20* |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation): *page 19* |

**Methods: Monitoring**

| | | |
|---|---|---|
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed: *page 20* |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial: *pages 16-17 and pages 21-22* |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct: *pages 20-22* |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor: NA |

**Ethics and dissemination**

| | | |
|---|---|---|
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval: *page 2, page 22* |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators): *page 22* |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32): *page 8, page 22* |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable: NA |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial: *page 18* |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site: *page 23* |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators: *page 3* |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation: *page 3* |

| | | |
|---|---|---|
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions: *pages 22-23* |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers: *page 23* |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code: NA |
| **Appendices** | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates: *page 22: available on request. The sponsor's rules exclude publication of consent form.* |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable: *page 13* |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

# A randomized, placebo controlled, double blind, double dummy, multicenter trial comparing electronic cigarettes with nicotine to varenicline and to electronic cigarettes without nicotine; the ECSMOKE trial protocol.

| | |
|---|---|
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| Date Submitted by the Author: | 06-Apr-2019 |
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| Primary Subject Heading: | Smoking and tobacco |
| Secondary Subject Heading: | Addiction, Pharmacology and therapeutics |
| Keywords: | electronic cigarettes, varenicline, smoking cessation, randomised, controlled, double dummy trial |
| | |

# A randomized, placebo controlled, double blind, double dummy, multicenter trial comparing electronic cigarettes with nicotine to varenicline and to electronic cigarettes without nicotine; the ECSMOKE trial protocol.

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Number of tables: 0

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Clinical Trials number: NCT03630614

**Protocol version:** Number 2 of 18 June 2018

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**Trial registration and approvals**

Research code number: P150952J - EUDRACT No.: 2017 – 003588 – 37

Ethics Committee (Comité de protection des personnes, CPP Ouest II-Angers) approved this protocol on 17 April 2018.

The Agence National de Sécurité du Médicament et des Produits de Santé (ANSM) approved this protocol on 9 May 2018.

**Roles and responsibilities**

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**Role of the Funder/Sponsor:**

The funder: Ministry of Health, had no role in the conception, design, redaction of the research protocol. The sponsor of the trial is Assistance publique-Hôpitaux de Paris. According to existing French rules, laws and regulations, the sponsor's role includes a) the submission of the research protocol to the ethics committee, to the French drug agency: Agence National de Sécurité du Médicament et des Produits de Santé (ANSM) authorizing all clinical research; b) contributing to the data collection; c) organising the regulatory and technical aspects of conducting and monitoring the study; contracting the mandatory insurance. It is the sponsor's role to report adverse events to national and European Union regulatory drug agencies.

All authors contributed to the conception, design, and redaction of the research protocol and will intervene in the data analysis, interpretation of the data, preparation, review and approval of the manuscript and decision to submit the manuscript for publication.

## Abstract

### Introduction

Electronic cigarettes (EC) mainly with nicotine content are widely used worldwide. Although the number of publications about its use is increasing exponentially, evidence based, unbiased, conclusive, head-to-head comparisons about its efficacy and safety as an aid for smoking cessation are lacking.

### Methods and analysis

*Design:* Randomized, placebo and reference treatment-controlled, multicenter, double blind, double dummy, parallel group trial.

*Participants:* Smokers smoking at least 10 cigarettes/day in the past year and motivated to quit, aged 18 to 70 years.

*Interventions:*

A) EC without nicotine (ECwoN) plus placebo tablets of varenicline administered by oral route: **placebo condition**

B) EC with nicotine (ECwN) plus placebo tablets of varenicline: **ECwN condition**

Voltage regulated electronic cigarettes will be used with liquid containing 12 mg/ml of nicotine for *ad libitum* use. Flavour: blond tobacco.

C) Reference: ECwoN plus 0.5 mg varenicline tablets: **varenicline condition.** Varenicline administered according to the marketing autorisation.

Treatment duration: 1 week + 3 months.

*Primary outcome:* Continuous smoking abstinence rate (CAR) (abstinence from conventional/combustible cigarettes) during the last 4 weeks (weeks 9 to 12) of the treatment period defined as self-report of no smoking during the previous 2 weeks and expired air CO ≤ 8 at Visit 4 at Week 10 after target quit date (TQD) i.e. 11 weeks after treatment initiation AND at Visit 5, Week 12 after TQD i.e. 13 weeks after treatment initiation.

*Secondary outcomes*: Safety profile; point prevalence abstinence rate; CAR confirmed by urinary anabasine concentration; changes in cigarettes/day consumption; craving for tobacco and withdrawal symptoms with respect of baseline.

### Ethics and dissemination

The ethics committee approval was obtained on 17 April 2018. All data collected about the study participants will be anonymised. Investigators will communicate trial results to participants, health authorities, healthcare professionals, the public, and other relevant groups without any publication restrictions.

## Article Summary

*Strength and limitations*

*Strengths*

- Randomized, head-to-head comparison, reference and placebo controlled double blind, double dummy smoking cessation efficacy and safety trial.
- Power sufficient to conclude about superiority of electronic cigarette with nicotine over electronic cigarette without nicotine and non-inferiority of electronic cigarette with nicotine compared to varenicline.
- Ad libitum electronic cigarette use mimicking conventional cigarette use.

*Limitations*

- Only one, fixed dose e-liquid nicotine concentration and one e-liquid flavour are used.
- A rigorous RCT is prioritised over a pragmatic, everyday life trial, more likely to demonstrate convincingly efficacy and safety. However, this can reduce the generalizability of the results to everyday population use.

## Introduction

Tobacco use kills more than 5 million people per year worldwide. Among the five greatest risk factors for mortality, it is the single most preventable cause of death (1). It reduces life expectancy by 9 to 15 years (2, 3, 4). Implementation of tobacco control strategies, including smoking cessation behavioural and pharmacological treatments, avoided 8 million premature deaths in the United States between 1964 and 2012 (5). Smoking cessation before the age of 40 reduces the risk of death compared to continued smoking by 90 % (3).

Tobacco is used in its combustible forms: cigarettes, cigarillos, pipes, cigars, shisha, or as smokeless tobacco: oral snuff, snus. The most widely used form is cigarettes. As of today, alternative nicotine delivery systems (ANDS) such as electronic cigarettes (EC), Juul and heat-not-burn/heated tobacco systems containing tobacco. These ANDS are used either for recreational purposes or with the intent to quit smoking.

Among ANDS, the most studied are EC. However as of today, their benefit/risk ratio as an aid for smoking cessation is not established with confidence.

Electronic cigarettes are diverse battery-powered devices to produce an aerosol. The battery heats a resistance that allows aerosolisation of the liquid called “e-liquid” which contains humectants (propylene glycol and/or glycerin) along with flavorings and may or may not contain nicotine. The European Union Tobacco Product Directive limits the nicotine content to 20 mg/mL; requires products to be child and tamper proof; requires health warnings, instructions for use, information on addictiveness and toxicity to appear on the packaging; bans promotional elements on packaging; requires all substances contained in the product and information on the product’s nicotine content to be listed (6).

The EU Directive has been transposed in France on May 19, 2016 (7).

As of today, ECs are consumer products and sold outside the health care system. In France pharmacies are prohibited to sell them.

Exposure to tobacco-related carcinogens and toxins are substantially lower among long-term EC users than among cigarette smokers or dual (EC+cigarettes) users and similar to that found among long-term nicotine replacement therapy NRT users (8). Substantial evidence shows that during EC use exposure to potentially toxic substances is lower compared with combustible/conventional cigarette smoking (9).

Last generation EC deliver more nicotine than first and second generation EC. Venous plasma nicotine concentrations after 65 minutes’ use are up to 48.1 ng/mL in experienced and 31.4 ng/mL in naïve users and the mean venous plasma nicotine concentrations are close to those observed with conventional cigarettes (9, 10, 11, 12).

To the best of our knowledge, there is no published report on arterial plasma nicotine concentration with EC or nicotinic acetyl choline receptor (NAchR) occupancy in the brain while using EC with nicotine.

EC reduce desire/craving to smoke and withdrawal symptoms (13, 14, 15, 16) main predictors of successful quit.

*EC as an aid to quit smoking conventional cigarettes*

Observational cohorts provided conflicting results as an aid to quit smoking (17, 18,19) and will not be mentioned further. Observational studies provide lower level of evidence (for various reasons) than randomised, controlled, double blind trials, therefore results are difficult to compare adequately.

Two randomized trials assessing the electronic cigarettes for smoking cessation (20, 21) and 2 meta-analyses of these two trials (22, 23) have been published. Caponetto et al. (21) (ECLAT trial) randomized 300 smokers, not intended to quit into 3 groups: EC disposable cartridge containing 7.2 mg (n=100), 5.4 mg (n=100) and no nicotine (n=100) were used. Intent-to-treat analysis of the main outcome did not show significant differences between groups. Bullen et al. (20) (ASCEND trial) randomized smokers wanting to quit: 289 to receive nicotine containing EC, 295 to receive 21 mg/24h nicotine patches and 73 to receive EC without nicotine. Cartridges of nicotine EC contained 10 to 16 mg nicotine/mL. The treatment duration was 12 weeks and the main outcome measure was continuous abstinence at 6 months after quit date defined as "self-reported abstinence over the whole follow-up period, allowing ≤5 cigarettes in total" and verified at 6 months by a measure of expired air CO (<10 ppm). All participants were referred to a quit line for support. The main outcome measure did not show statistically significant difference: 7.3 %, 5.8 %, 4.1 %, in the nicotine EC, nicotine patch groups, and placebo EC respectively (ITT analysis). 19.7 % of the participants in the nicotine EC, 11.3 % in the nicotine patch and 13.9 % in the placebo EC group had a serious adverse event (SAE), respectively.

A Cochrane review of EC for smoking cessation and reduction has been published in 2014 (22) and updated in 2016 (23). The quality of evidence (GRADE system) rated the evidence as low or very low because of the low (N=2) number of trials. Pooling data of these 2 trials, the authors report a relative risk (RR) of 2.29, 95% CI 1.05-4.96 for abstinence rate at 6 months. Analysis of the same 2 trials (20, 21) did not confirm these results (17).

A major randomised pragmatic but open trial has recently been published (January 30, 2019) (24). Smokers attending U.K. National Service stop-smoking services (N=886) were randomised to receive NRT for 3-months or a one month EC pack with liquid containing 18 mg/mL of nicotine. Both treatments could be used further at the discretion of the participants. The primary outcome measure of sustained abstinence at 1 year showed 18 % in the EC and 9.9 % abstinence in the NRT group (RR: 1.82, 95 % CI: 1.30 to 2.58). More respiratory SAE were observed in the EC than in the NRT group (5 *versus* 1). Incidence of cough and phlegm were lower in the EC than in the NRT group. However, no serious adverse events occurred in either arm that were considered to be related to study treatment.

There is a general consensus that high-quality, large-scale randomized studies are needed (9, 25). The current trial is intended to fulfil this requirement.

## Objectives

*Primary objective*: To assess the therapeutic efficacy and safety of EC with nicotine for smoking cessation. EC containing nicotine to EC not containing nicotine (placebo) and to varenicline, as a reference drug for smoking cessation, will be compared.

*Trial design*

This will be a randomized, placebo controlled, multicentre, double blind, double dummy, parallel groups, phase III type trial.

Included participants will be randomly assigned to one of the 3 groups:
A) Control group: EC without nicotine (ECwoN) plus placebo tablets of varenicline: **placebo condition**
B) Experimental group: EC with nicotine (ECwN) plus placebo tablets of varenicline: **ECwN condition**
C) Reference group: ECwoN plus varenicline tablets : **varenicline condition**
with a randomisation ratio of A:B:C= 1:3:3.
Each participant will use an EC and takes 2 tablets twice per day.

*Setting*

This national trial will involve smoking cessation clinics of both academic and community hospitals. Twelve study sites and 16 co-investigators agreed to participate and committed to recruit and follow up smokers for the trial. Individuals are eligible to be a co-investigator if they are medical doctors, having obtained a post-graduate diploma in addictive and/or tobacco related disorders. The list of study sites can be obtained from the principal investigator.

## Participants

*Eligibility criteria*

Inclusion criteria

1. Smokers smoking at least 10 cigarettes/day (factory made or roll-your-own) in the past year
2. Aged 18 to 70 years
3. Motivated to quit, defined as a score > 5 on a visual rating scale ranging from 0 (not motivated at all) to 10 (extremely motivated)
4. Signed written informed consent
5. Understanding and speaking French
6. Women of childbearing age can be included if they use an effective contraceptive method: either hormonal contraception or an intrauterine device started at least one month before the first research visit
7. Individual affiliated to a health insurance system
8. Previous failure of nicotine replacement therapy for smoking cessation.

Exclusion criteria

1. Any unstable disease condition within the last 3 months defined by the investigator as major change in symptoms or treatments such as recent myocardial infarction, unstable or

worsening angina, severe cardiac arrhythmia, unstable or uncontrolled arterial hypertension, recent stroke, cerebrovascular disease, obliterative peripheral arterial disease, cardiac insufficiency, diabetes, hyperthyroidism, pheochromocytoma, severe hepatic insufficiency, history of seizures, severe depression, chronic obstructive pulmonary disease (COPD)
2. Any life threatening condition with life-expectancy of less than 3 months
3. Alcohol use disorder defined as a score $\geq 10$ on the AUDIT-C questionnaire (see below)
4. Abuse of or dependence on illegal drugs in the last 6 months revealed by medical history
5. Regular use of tobacco products other than cigarettes
6. Current or previous (last 6 months) use of EC
7. Pregnant women
8. Breastfeeding women
9. Protected adults
10. Current or past 3 months participation in another interventional research
11. Current or past 3 months' use of smoking cessation medication such as varenicline, bupropion, nicotine replacement therapies
12. Known lactose intolerance (placebo tablets contain lactose)
13. Hypersensitivity to the active substance or to any of the excipients
14. Known severe renal failure.

*Patient and Public Involvement*

Patients or public were not involved in the conception and writing of this protocol. Study results will be disseminated individually to all study participants if requested.

**Interventions**

*Investigational product 1: EC with nicotine or EC placebo*

EC exists in two forms: liquid containing nicotine or with liquid not containing nicotine. Nicotine content in EC can vary in the European Union between 0 and 19.9 mg/mL. Third and fourth generation EC allow the user to change voltage and airflow leading to individualised nicotine delivery and dose adaptation.

A call for application by EC companies has been launched by the sponsor twice in 2017 and 2018 (no candidate in 2017).
Some major requirements for applications are listed here:

- EC liquid containing 0 and 12 mg/mL of nicotine
- Regular and reported control of nicotine's concentration in EC liquid by batches
- Tobacco flavour
- Long shelf life
- Detailed information about constituents
- Highly purified nicotine

Packaging: active or placebo bottles of e-liquid will be provided blinded as unidentifiable bottles. Each blinded box package will contain ten 10 mL bottles of e-liquids for 1 months.

In the current study the ECwN group will use EC liquids containing 12 mg/mL of nicotine. E-liquids will be allowed to be used *ad libitum* and because nicotine delivery can be adjusted according to the user's need, all participants would adjust their individual nicotine dose by varying the voltage of their EC, by varying puff frequency, puff volume and depth of inhalation

similarly as they are doing (or used to do) with conventional cigarettes. A recent paper by Soar et al. (26) demonstrates that over a 12 months period EC users maintained their nicotine intake, as measured by saliva cotinine concentration, possibly through self-titration.

*Justification of the nicotine concentration*

We consider, based on previous studies, that one cigarette contains approximately 1 mg of nicotine, thus 10 cigarettes contain approximately 10 mg of nicotine (27, 28). Nicotine's bioavailability when inhaled in cigarette smoke is 90 to 95 %; it is plausible that the bioavailability of nicotine of the aerosol delivered by an EC is lower. In the current research protocol the use of e-liquid of 12 mg/mL of nicotine may, thus, correspond approximately to 10 cigarettes. The randomized, placebo controlled study (nicotine – placebo: double blind) against nicotine patch (open label) used in the nicotine EC arm 10-16 mg/mL e-liquid concentration (20). Abstinence rate was not different between EC with nicotine *versus* EC with placebo (double blind comparison) on the main outcome measure. It was raised that this negative result is due to the low bioavailability of nicotine delivered by the EC used dating back to 2012. More recent studies using tank system EC provide plasma nicotine concentrations higher than earlier studies using EC of 2012 to 2014 (12).

Dawkins et al. (29) assessed 6 mg/mL and 24 mg/mL nicotine e-liquid concentrations in a self-titration/self-administration design. Plasma nicotine concentrations were higher with the 24 mg/mL nicotine liquid than with the 6 mg/mL nicotine liquid. However, reduction in craving for cigarettes and withdrawal symptoms were similar. Compensatory puffing occurred with the 6 mg/mL nicotine concentration, puff number, puff duration and liquid consumption were higher with the low than with the high nicotine concentration liquid. There were no statistically significant differences between conditions in self-reported craving, withdrawal symptoms, satisfaction, throat hit or adverse effects. However, the blood nicotine concentration was higher at 60 minutes with the 24 mg/mL than with the 6 mg/mL liquid: 43.57 (SD 34.78) 22.03 (SD 16.19) ng/mL. Thus, EC users compensate low nicotine liquid concentration by increasing puff topography characteristics to increase nicotine uptake. This compensatory puffing is similar as with conventional cigarettes.

We can, thus, conclude that an intermediary concentration of nicotine would be optimal: plasma nicotine concentrations sufficiently high leading to a sufficient craving reduction. The chosen e-liquid concentration of 12 mg/mL takes also into account the standard dose-response relationship (6-12-24 mg/mL).

Only one flavour will be used to reduce variability of treatment response according to a preferred flavour. We chose the blond tobacco flavour with which all smokers can be familiar, which is less likely to be aversive among adults and the most sold when initiating EC use.

*EC device:*

Mini iStick kit (20 W) Eleaf, clearomiser: GS Air M with resistance of 1.5 ohm. To keep the blinding, the clearomiser's Pyrex window is of gray colour not allowing to distinguish the coloration of the e-liquid containing nicotine.

*Liquid for EC* is manufactured by GAIATREND SARL (https://www.gaiatrend.fr/fr/).

*Counselling about the use of EC*

All participants will be delivered a short manual and a video specifically developed for this study explaining the use of EC. At each visit participants receive also verbal counselling about the use of the EC device and answers to their questions about handling the EC device.

Investigators are trained at the first Investigators' meeting to provide straightforward counselling about EC use.

*Investigational product 2 (reference drug): varenicline 0.50 mg and its placebo*

Varenicline and not nicotine replacement therapies (NRT) has been chosen for this study as the reference drug because:
i) Varenicline is associated with the highest level of abstinence rate among the 3 available smoking cessation medications with marketing authorization (bupropion, NRT, varenicline) (30, 31) (but its efficacy is similar to that of combined (short + long acting) NRT (32)). Varenicline is, therefore, a better comparator for a new therapeutic intervention for which we aim to demonstrate a therapeutic efficacy as high as the best available single medication treatment.
ii) Identical placebo tablets for varenicline can easily be manufactured and none of the placebo NRT forms are available. Manufacturers of NRT products do not have any more corresponding placebos and manufacturing identical placebos by an external company may increase the likelihood of non-identical placebos. Moreover, purchasing both identical placebos along with active NRT products manufactured by a company that do not have the marketing license for NRT may introduce a major uncertainty by raising the question: Does the NRT product have the same bioavailability as the original, licensed NRT product? Uncertainty about the active NRT product's bioavailability may compromise the validity of the trial's results.
iii) Blinding of tablets administered by oral route is more convenient than blinding of NRT such as transdermal patches, gums, lozenges, inhaler or buccal spray.

Varenicline (Champix®) 0.5 mg is presented as a capsular-shaped, biconvex, white film-coated tablet. The tablets are held under a vial of 56 tablets.
Varenicline has been purchased at Pfizer France.
*List of excipients:*
Core tablets: Cellulose, Microcrystalline, Calcium Hydrogen Phosphate Anhydrous, Croscarmellose Sodium Silica, Colloidal Anhydrous, Magnesium Stearate
Film coating : Hypromellose Titanium Dioxide (E171) Macrogols Triacetin.
Placebo and active tablets are strictly similar. Placebo tablets of varenicline have been manufactured, packaged and labeled by a pharmaceutical sub-contractor according to the Good Manufacturing Practices and under the responsibility and supervision of AGEPS.
The dose regiment of varenicline/placebo follows varenicline's monograph:
Day 1 to Day 3: one tablet of 0.5 mg/placebo in the morning
Day 4 to Day 7: 1 tablet of 0.5 mg/placebo morning and the evening
From Day 8 until end of treatment: 1 mg morning and evening i.e. two 0.5 mg/placebo tablets morning and evening. The number of tablets per day can be modified at the discretion of the investigator if a better control of adverse effects is needed.

EC and tablets are started one week before the target quit date (TQD) to stop smoking and followed up for 3 months after TQD.

**Behavioral counselling for smoking cessation**
Brief behavioural smoking cessation counselling for all participants is administered at all visits by the investigators specialised in smoking cessation. It is based on the national guidelines for smoking cessation (33).

**Criteria for discontinuing or modifying allocated interventions**

Any participant can withdraw from participating in the research at any time and for any reason.

- The investigator can end a subject's participation in the research for any reason that affects the participant's safety or which would be in the participant's best interests but not because of non-abstinence from cigarettes after TQD.
- In case of loss to follow-up, the investigator should make all efforts to reach the participant and collect the reason of loss to follow-up and information about his/her safety data.
- In case of pregnancy, despite the mandatory contraception, the participant will exit the trial and will be followed up until delivery.

The case report form must list the various reasons for ending participation in the research:

- Adverse event/reaction
- Other medical problem
- Participant's personal reasons
- Explicit withdrawal of consent

If a participant leaves the research prematurely or withdraws consent, any data collected prior to the date of premature exit can be used.

**Methods for monitoring compliance with the treatments**

Study medication compliance at Visits 1 through 5 will be assessed with the questions:

A) Did you use the electronic cigarette

- Every day
- Approximately every other day
- Twice a week
- Less than twice a week.

B) Did you take your tablets

- Every day
- Approximately every other day
- Twice a week
- Less than twice a week.

Accountability of returned EC bottles and tablet vials will allow approximating EC liquid's and tablets' use.

**Guess test to control efficacy of the blinding**

At Visit 2 (Week 4 after TQD i.e. 5 weeks after treatment initiation) and at Visit 5 (Week 12 after TQD i.e. 13 weeks after treatment initiation) a guess test will be run. It consists of the following question:

"Do you think you received:

- Placebo tablets and electronic cigarettes without nicotine? Yes/No
- Placebo tablets and electronic cigarettes with nicotine? Yes/No
- Varenicline (Champix©) tablets and electronic cigarettes without nicotine? Yes/No

**Concomitant care and interventions**

All previously introduced medications will be permitted to be continued. The following concomitant medications per NRT's licence in France, by extrapolation to nicotine containing e-liquids, and according to the requirement of the French drug agency (ANSM) will be prohibited: theophylline, clozapine, olanzapine, méthadone, ropinirole, pharmaceutical caffeine (dose adaptation when quit smoking).

As of today, varenicline has no known clinically significant drug-drug interaction.

To the best of our knowledge, there is no available information about drug interaction of EC with or without nicotine.

NRT use is not permitted during the study but its over-the-counter purchase cannot be controlled for. At each post-quit day visit we will check its use as a control variable. Positive answer will result asking the participant to stop NRT use. If he/she does not comply, the participant will be excluded for noncompliance with the study protocol.

**Primary outcome**

Continuous smoking abstinence rate (CAR) (abstinence from conventional/combustible cigarettes) during the last 4 weeks (weeks 9 to 12) of the treatment period of 3 months.
Definition: Self-report of no smoking during the previous 2 weeks and expired air CO ≤ 8 ppm. at Visit 4 at Week 10 after TQD i.e. 11 weeks after treatment initiation AND at Visit 5, Week 12 after TQD i.e. 13 weeks after treatment initiation.

**Secondary outcomes**

- Safety profile of EC containing nicotine comparatively to its placebo and varenicline.
- Point prevalence abstinence: 7-day abstinence at Visit 1, 2, 3, 6 and 14 days of abstinence at Visit 4 and 5 (see timeline below) associated with expired air CO ≤ 8 ppm.
- Time to relapse to smoking after TQD
- CAR confirmed by urinary anabasine concentration ≤ 3 ng/mL
- Change in cigarettes/day consumption with respect of baseline
- Change in craving for tobacco as assessed by the French 12-item Tobacco Craving Questionnaire (34) with respect of baseline
- Change in withdrawal symptoms as assessed by the modified Minnesota Nicotine Withdrawal Scale (35) with respect of baseline

Control variables:

- Study medication compliance recorded at each visit
- Baseline level of tobacco dependence
- Urinary concentration of anabasine, anatabine (both alkaloids found only in tobacco, control for tobacco smoking) and cotinine (main metabolite of nicotine, control for nicotine intake) at Visit 4 and 5 (36). Analysis laboratory: Swiss Laboratory for Doping Analyses, Epalinges, Switzerland.
- Results of the "guess test" i.e. correct identification of the treatments by participants

**Participant timeline**

Randomisation visit = Visit 0 - Dispensing of the treatment

Treatment initiation within the 7 days following randomization.

Target quit date (TQD) should occur between 7 and 15 days after randomization and after 7 days of treatment intake (Figure 1).

The first post-target quit date visit (Visit 1) is at Week 2 after TQD i.e. 3 weeks after treatment initiation.
Visit 2 is at Week 4 after TQD i.e. 5 weeks after treatment initiation.
Visit 3 is at Week 8 after TQD i.e. 9 weeks after treatment initiation.
Visit 4 is at Week 10 after TQD i.e. 11 weeks after treatment initiation.
Visit 5 is at Week 12 after TQD i.e. 13 weeks after treatment initiation.
Visit 6 is at Week 24 after TQD i.e. 25 weeks after treatment initiation.

*Assessments at Visit 0*

- *Demographic characteristics*
  - Age
  - Gender
  - Professional situation
    Employed/Housewife/Unemployed/Student/Retired
  - Education level: Number of years after age 7 years.
  - Marital status:
    Cohabiting/ Married/Separated/Divorced/Single/Widowed
  - Annual household income (euros)
    < 12 000/12 001 – 30 000/30 001 – 100 000/> 100 000
  - Self-reported ethnic origin
    European/African/Asian/Other
- *Previous medical history :*
  - any unstable disease condition within the last 3 months defined by the investigator as major change in symptoms or treatments
  - any life threatening condition with life-expectancy of less than 3 months
  - alcohol use disorder defined as a score ≥ 10 on the AUDIT-C questionnaire
  - abuse of or dependence on illegal drugs in the last 3 months revealed by the medical history
  - regular use of tobacco products other than cigarettes
  - current or previous (last 6 months) use of electronic cigarette
  - pregnant women
  - breastfeeding women
  - current or past 3 months participation in another interventional research
  - current or past (last 3 months) use of smoking cessation medication such as varenicline, bupropion, nicotine replacement therapies
  - known lactose intolerance (placebo tablets contain lactose)
  - hypersensitivity to the active substance or to any of the excipients
  - known severe renal failure
- *Previous mental health history (**before** the last 6 months):*
  - Treatment for major depression
  - Treatment for psychosis
  - Treatment for bipolar disorder
  - Treatment for substance use disorder:

- Cannabis, alcohol, cocaine, opioid, psychostimulant use
- Treatment for smoking cessation by NRT, varenicline, bupropion

– *Current, past 6 months, medical history:*
  - Cardiovascular disorders (yes/no); stable on treatment: yes/no
  - Myocardial infarction/unstable angina (yes/no); stable on treatment: yes/no
  - Arterial hypertension (yes/no); stable on treatment: yes/no
  - Malignancy disorder (yes/no); stable on treatment: yes/no
  - Pulmonary disorder (other than COPD) (yes/no); stable on treatment: yes/no
  - COPD (yes/no); stable on treatment: yes/no
  - Type 1 or type 2 diabetes mellitus (yes/no); stable on treatment: yes/no
  - Other (yes/no); stable on treatment: yes/no
– *Current, past 6 months, mental health history:*
  - Treatment for major depression (yes/no);; stable on treatment: yes/no
  - Treatment for psychosis (yes/no); ; stable on treatment: yes/no
  - Treatment for bipolar disorder (yes/no); stable on treatment: yes/no
  - Treatment for substance use disorder (yes/no);
  - Cannabis, alcohol, cocaine, opioid, psychostimulant use disorder (exclusion if any)
  - Treatment for smoking cessation by NRT, varenicline, bupropion (exclusion if any)
– Smoking characteristics
  - Age of the first cigarette (years)
  - Age of regular smoking (years)
  - Number of previous attempt(s) to quit
  - Longest duration of abstinence if any
  - Fagerström Test for Cigarette Dependence score
  - Spouse/partner smokes (yes/no)
  - Other smoker in the household (yes/no)
  - Secondhand smoke exposure at home/work/leisure (yes/no)
  - Current self-reported number of cigarettes smoked per day
– Clinical measures
  - Systolic and diastolic blood pressure in sitting position
  - Height
  - Body weight
  - Expired air CO along with time (minutes) since last cigarette smoked
  - Craving for tobacco using the FTCQ-12 (34)
  - Withdrawal symptoms using the Minnesota Tobacco Withdrawal Scale (35)
– Substance use
  - Cannabis use in the last 30 days
  - Alcohol use

The AUDIT (Alcohol Use Disorders Identification Test) will be used to screen for alcohol problems. It has been suggested as the most effective instrument identifying individuals at-risk, hazardous or harmful drinking (37). Its sensitivity ranges from 51 % to 97 % and specificity from 78 to 96 % according to a systematic review (38). The corresponding values for the CAGE questionnaire (39) are: 43 % to 94 % and 70 % to 97 %.
The short French language form, AUDIT-C of the questionnaire will be used as recommended by recent French guidelines (40).

*At each visit will be measured:*

- Systolic and diastolic blood pressure in sitting position.
- Body weight
- Cannabis use since the last visit
- Alcohol use since the last visit (more than 1 drink per day/less than one drink per day)
- Expired air CO along with time since last cigarette
- Current self-reported number of cigarette smoked per day in the last 7 days
- Craving for tobacco using the FTCQ-12 (34)
- Withdrawal symptoms using the Minnesota Tobacco Withdrawal Scale (35)

Expired air CO will be measured with a Smokerlyzer (Bedfont Scientific Ltd, Kent, UK) a value of less than or equal to 8 ppm will be required to support the self-report of abstinence.
The FTCQ-12 and MNWS are paper and pencil self-report questionnaires.

*At each further visit adverse reactions/events* are inquired with the following question:
"Did you experience since the last visit a health symptom or event which is unusual?"
If the answer is "Yes", the adverse reaction/event will be recorded.

**Sample size**

According to the EAGLES study (30) with N=8144 smokers, the percent abstinent at the main efficacy criterion – similar to that used in the current study – was 33.5 %. Taking this percentage as reference, with an OR=1/0.60=1.664 and a power of 80 % we would need at least 272 participants in each of the varenicline (reference) and the ECwN group (41). We would randomize 1/3 of the participants to the group ECwoN, that is 91 smokers. These numbers would allow to show a significant difference between varenicline and ECwN with an alpha=0.05. The total number needed to be randomized will, thus, be of 2*272+91= 635 smokers. To take into account lost to follow up, we plan to randomize *at least* 650 smokers: 280 in each of the ECwN and varenicline arm and 90 (rounded) in the ECwoN arm.

*Justification to randomize only 90 participants in the placebo-placebo condition (ECwoN)*
The main research question is the superiority of ECwN and varenicline (reference) – justifying of testing of non-inferiority between these groups including 280 participants/group.
If the superiority testing is non-significant, we propose to switch to non-interiority testing.
We conclude on the non-inferiority if and:

- ECwN is non-inferior to varenicline
- ECwN superior to ECwoN
- Varenicline is superior to ECwoN

Thus, the comparison involving ECwoN will be run "after" the comparisons between ECwN and varenicline.

We considered the following percent of abstinence: p(varenicline)=33.5 % and p(ECwoN)=15 %. Thus with 280 participants in the varenicline and 90 participants in the ECwoN group we will have sufficient power to conclude.

**Decision rules**

We will conclude that ECwN is superior to varenicline if the two tailed superiority test at 5 % on the main outcome measure (percent abstinent (p)) will be significative such as p(ECwN) > p(varenicline).

Would this test show a p value higher than 0.05, we would switch to non-inferiority. We will conclude that ECwN is non-inferior to varenicline if:

- the two-tailed superiority test is non-significant at the 5 % level
- the test of non-inferiority at 5 % one-tailed with a delta=5% is significant
- the two-tailed superiority test of p(ECwN) versus p(ECwoN) is significative at 5%;
- the two-tailed superiority test of p(varenicline) versus p(ECwoN) is significative at 5%.

In any case we will conclude that ECwN is superior to ECwoN, if the test of superiority at 5 % (two-tailed) is significant such as p(ECwN) > p(ECwoN).

A Pearson's two-tailed Chi square test at 5 % will be used to test the superiority. A Dunnet & Gent Chi square test at 5 %, one-tailed, will be used for testing the non-inferiority (42).

Some simulations

1. If p(Varenicline) = 33.5 %, p(ECwN)=33.5% and p(ECwoN)=15% then
   a. the probability that ECwN is superior to varenicline is of 2.5 %
   b. the probability that ECwN is non-inferior to varenicline is of 31.5%.
   c. the probability that ECwN is superior to varenicline is of 2.5%+31.5%=34%.
   d. the probability that ECwN is superior to ECwoN is of 95%.

2. If p(Varenicline)=33.5%, p(ECwN)=40% and p(ECwoN)=15% then
   a. the probability that ECwN is superior to varenicline is of 33.6 %
   b. the probability that ECwN is non-inferior to varenicline is of 52.7 %.
   c. the probability that ECwN is superior to varenicline is of 33.6%+52.7%=86.3 %.
   d. the probability that ECwN is superior to ECwoN is of 99.8 %.

3. If p(Varenicline)=33.5 %, p(ECwN)=45 % and p(ECwoN)=15 % then
   a. the probability that ECwN is superior to varenicline is of 80.1 %
   b. the probability that ECwN is non-inferior to varenicline is of 19 %.
   c. the probability that ECwN is superior to varenicline is of 80.1%+19.0%=99.1 %.
   d. the probability that ECwN is superior to ECwoN is of 99.9 %.

The estimate of an abstinence rate of around 40 % with the two active treatments and a 15 % abstinence rate in the placebo condition seems reasonable and clinically significant.

There is no justification to run first a global comparison. Either the ECwN arm is better than the varenicline arm and we have answered the main research question or the ECwN is non-inferior to the varenicline arm and there will be a necessity to run two separate comparisons against ECwoN (i.e.ECwN against ECwoN; varenicline against ECwoN).

**Recruitment**

Recruitment is either local (a) directly by the centres or centralized (b) using a web page and a centralised study specific phone number and email address.

a) Smokers intending to quit smoking are recruited by advertisement in pharmacies, physicians' offices situated in the catchment area of each investigator's centre, by local newspapers and in public places of the centres' health care facilities.

b) Candidates to participate can register by the study's website, unique email address and phone number. Registration is followed by a phone screening before dispatching to the study centres. Only one person by household will be recruited.

## Assignment of interventions and blinding

To assure allocation concealment, computer generated randomization list (allocation ratio: 1:3:3) involving blocks, stratified by age (<45 versus ≥ 45 years) and centre, will be prepared and is kept blinded to all participants to the trial. The randomization list is incorporated into the eCRF, and a treatment number is attributed automatically upon completion of the randomization visit. The random, computer generated allocation sequence is prepared by a statistician of the Clinical Reseach Unit of Pitié Salpêtrière Charles Foix.

The randomization list is being kept in a secured place by the sponsor and a copy of the randomization code is being kept separately in the Poison Centre of Fernand Widal Hospital, Paris, in case of a serious adverse event necessitating the opening of the participant's group assignment (see below). Investigators, members of the coordination centre, hospital pharmacists, and the sponsor's clinical research assistants in charge of monitoring will be kept blinded.

*Blinding methods and measures to protect the blinding*

Varenicline and its placebo are administered as non-identifiable tablets.
Because nicotine solutions tend to become yellow with time, the following provisions have been taken to make EC liquids non-identifiable:
Liquids of EC will be delivered to the participants in white, non-transparent vials of 10 mL specifically manufactured for the study. Both nicotine and no nicotine containing liquids will have a tobacco flavour and smell (blond tobacco). The EC's clearomiser' Pyrex walls will be transparent but of grey colour allowing the user to see the level of the liquid but not its colour.

*Unblinding procedures*

Unblinding is the sponsor's decision. However, the investigating physician may request unblinding if he/she considers essential in the participant's interest/care.

## Data collection and management

Data will be collected through the study's eCRF. Data entry is carried out on electronic media via a web browser by co-investigators. The source documents are any original document or item that proves the existence or accuracy of a data-point or fact recorded during the trial. Source documents are kept by the investigator, or by the hospital in the case of hospital medical records, for the statutory period. During and after the clinical study, all data collected about the study participants and sent to the sponsor by the investigators (or any other specialised collaborators) will be anonymised. CNIL, the French Data Protection Authority implemented the "Méthodologie de référence" (MR-001) according to the provisions of Article 54, paragraph 5 of modified Law No. 78-17 of 6 January 1978. The sponsor, Assitance publique-Hôpitaux de Paris has signed a commitment to comply with it.

## Data analysis

### Populations submitted to the analyses

1. The *intent-to-treat* (ITT) efficacy analysis will include all participants who were randomized and having received at least one dose of any study treatment.
2. *Safety population*: All participants who were randomized and having received at least one dose of any study treatment.
3. *Full analysis set* (FAS) population: All participants who were randomized and having received at least one dose of study treatment except those who had no data at all post-randomisation.
4. *Per-protocol* population: All participants who are followed up to Week 12 and for whom the main efficacy criterion (CAR week 9 to 12) is available and who received at least one dose of treatment.

*Handling of missing data*
Participants who miss a visit will receive at least 2 phone calls as a reminder.
Missed visits are not a criterion for discontinuation. All participants will be strongly encouraged to stay in the trial up to the end of the research that is up to week 25.
Smoking (lapse: some puffs or relapse: relapse to regular conventional cigarette consumption) will not be a reason for discontinuation.

**Primary analysis**

We want to demonstrate the effectiveness of ECwN over varenicline. For that we will compare the percentage of success (CAR) between the two arms with a two-tailed Chi square test. If this test is not significant (i.e. p>5%), we will perform a non-inferiority test (switch) for ECwN over varenicline with a unilateral Dunnet and Gent test at 5% and a non-inferiority bound of $\Delta_L$ = 5%.
In parallel with the non-inferiority test, we will perform two tests of superiority, one comparing the ECwN to ECwoN on the one hand, and one comparing varenicline to ECwoN on the other hand to ensure that the non-inferiority is not obtained by lack of efficacy in both ECwN and varenicline arms. Thus, non-inferiority will be achieved if the non-inferiority test is significant as well as the two superiority tests described above.
For the superiority tests, the analysis will focus on the ITT population and will be confirmed on the per protocol population. The non-inferiority test will be done on the per protocol population and will be confirmed on the ITT population. (See details in Decision rules)

**Secondary analyses**

Comparisons will be made between ECwN and varenicline arms but may be done between the 3 treatment arms. Qualitative variables will be analyzed with a Chi2 test. Quantitative variables will be compared with Student's t test (or non-parametric tests as appropriate). Censored variables, such as the time to relapse will be analyzed by the log rank test.
These three tests will be generalized with a logistic model, ANOVA or a Cox model if adequate. Variables collected at different visits will be analysed in longitudinal, linear or logistic random effect models. In the same way the absolute variation or the relative variation can be studied there also with linear models with random effect.

Missing secondary endpoints will be imputed in both ITT and per protocol populations. The primary endpoint will be imputed by a multiple imputation method. The other criteria will not be imputed, since most of these criteria will be analyzed in longitudinal analysis.We will

perform a sensitivity analysis by rerunning the population analysis of subjects whose primary endpoint is non-missing.

**Monitoring**

Clinical Research Associates (CRAs) appointed by the sponsor are responsible for the proper running of the study, for collecting, documenting, recording and reporting all handwritten data, in accordance with the Standard Operating Procedures applied within the DRCI and in accordance with Good Clinical Practice as well as with the statutory and regulatory requirements.
The investigator and the members of the investigator's team agree to make themselves available during regular Quality Control visits by the Clinical Research Associate. During these visits, the following elements will be reviewed:

- written consent
- compliance with the study protocol and its procedures
- quality of the data collected in the case report forms: accuracy, missing data, consistency of the data with the "source" documents (medical files, appointment books, original copies of laboratory results, etc.)
- management of the treatments used.

**Safety assessment**

Safety will be assessed at each visit during the treatment period. However, the safety assessment will also be conducted at Visit 6 (end of research) even if no adverse event/reaction has previously been reported. Rational: one cannot exclude occurrence of adverse events/reactions even 3 months after stopping study medications.

*Safety endpoints*

- AE diagnosis/description
- The date when the AE started and stopped
- CTCAE grade maximum intensity (Comon Terminology Criteria for Advesre Events (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf)
- Whether the AE is serious or not
- Reason why the SAE was serious (e.g. hospitalisation)
- Investigator causality rating against the investigational product (yes or no)
- Action taken with regard to investigational product
- Outcome

*Anticipated methods and timetable for measuring, collecting and analysing the safety endpoints*

Safety and tolerance are recorded as follows:
- adverse events will be recorded in the "adverse event" section of the case report form;
- adverse effects' declaration by the participant will be collected at each visit or anytime when the participant establishes a contact with his/her investigator. Investigators reports to the Sponsor the participants' declaration and/or examinations' results linked to any adverse reaction/event along with its estimated severity and imputability. The Data Safety Monitoring Board (DSMB) will monitor safety data to avoid continuing the trial if it estimates that the risk prevails the benefit.

*Recording and reporting adverse events*

*Definitions*

**Adverse event**

Any untoward medical occurrence in a trial subject, which does not necessarily have a causal relationship with the clinical trial or with the investigational product (43).

- **Adverse reaction to an investigational medicinal product**

Any adverse event occurred in a trial subject, which has a causal relationship with the clinical trial or with the investigational medicinal product.

- **Serious adverse event or reaction**

Any adverse event or reaction that at any dose of medication, results in death, threatens the life of the research subject, requires hospitalisation or prolongs hospitalisation, causes a severe or long-term disability or handicap, or results in a congenital abnormality or deformity.

- **Unexpected adverse reaction to an investigational medicinal product**

Any adverse reaction to the product, whose nature, severity, frequency or outcome is inconsistent with the safety information described in the Reference Safety Information (summary of product characteristics, or the investigator's brochure if the product is not authorised).

- **Emerging safety issue**

Any new safety information that may lead to a reassessment of the risk/benefit ratio of the trial or the investigational medicinal product, modifications in the investigational medicinal product use, the conduct of the clinical trial, or the clinical trial documents, or a suspension, interruption or modification of the protocol of the clinical trial or other similar trials..
Examples:
a) any clinically significant increase in the frequency of an expected serious adverse reaction
b) suspected unexpected serious adverse reactions in patients who have terminated their participation in the clinical trial that are notified by the investigator to the sponsor together with follow-up reports
c) any new safety issue relating to the conduct of the clinical trial or the development of the investigational medicinal product, that may impact the safety of the trial subjects.
d) recommendations from the DSMB that may affect the safety of the trial subjects
e) any suspected unexpected serious adverse reaction (SUSAR) reported to the sponsor by another sponsor of a trial carried out in a different country but relating to the same medication.

**Data Safety Monitoring Board (DSMB)**

A Data Safety Monitoring Board has been set up for this trial. Its primary mission is to serve as a committee for monitoring safety data. The sponsor is responsible for justifying the creation the DSMB to the Competent Authority (ANSM) and to the Ethics committee (CPP).

The DSMB's preliminary meeting took place on 12 December 2017, before the protocol submission to competent health authority (ANSM) and Ethics committee (CPP). DSMB's operating methods and the meeting schedule have been defined during this first meeting. All missions as well as the precise operating methods of the DSMB are described in the DSMB's charter for the research.

The members of the DSMB are:

- Pr Eric Bellissant, President, clinical pharmacologist with expertise in public health and social medicine, Centre Hospitalier Universitaire de Rennes, Rennes, France
- Pr. Daniel Thomas, cardiologist, previous head of the Department of Cardiology, Hôpitaux Universitaires Pitié-Salpêtrière, Paris, France
- Pr Laurence Galanti, physician, smoking cessation specialist, CHU Mont-Godinne, Belgium.

General information about the DSMB

The DSMB makes recommendations to the sponsor about the continuation, modification or termination of the research. The recommendations that the DSMB can make are:

- to continue the research with no modifications
- to continue the research with a modification to the protocol and/or to the monitoring of subjects
- to temporarily halt inclusions
- to permanently terminate the research in light of safety data: serious adverse reactions.

## Ethics and dissemination

The ethics committee (Comité de protection des personnes, CPP Ouest II-Angers, France, approved this protocol on 17 April 2018.

The potential participant is granted a reflection period of one week between the time when the subject receives the information and the time when he or she signs the consent form. Informed consent is obtained before the inclusion by the investigator physician as required for this type of study by French regulations. The form is available in French on request.

The persons responsible for the quality control of clinical studies (44) take all necessary precautions to ensure the confidentiality of information relating to the investigational medicinal products, the study, the study participants and in particular the identity of the participants and the results obtained. These persons, as well as the investigators themselves, are bound by professional secrecy (45, 46).

During and after the clinical study, all data collected about the study participants and sent to the sponsor by the investigators (or any other specialised collaborators) will be anonymised.

The principal investigator, the Unité de Recherche Clinique (Clinical Research Unit) and the sponsor will have access to the final trial dataset without limitation.

Investigators will communicate trial results to participants, health authorities, healthcare professionals, the public, and other relevant groups without any publication restrictions. The Service Presse of Assistance publique-Hôpitaux de Paris will help prepare a dissemination plan to ensure results are accessible to the public.

Main authorship eligibility for publication in medical journals will follow International Committee of Medical Journal Editors ICMJE criteria (47).

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**Author Contributions**

Concept and design: I. Berlin, B. Dautzenberg

Drafting of the manuscript: I. Berlin

Critical revision of the manuscript for important intellectual content: B. Dautzenberg, B. Lehmann, Y. de Rycke, F. Tubach, J. Palmyre, E. Liégey

Administrative, technical, material support: B. Lehmann, J. Palmyre, E. Liégey

Conflict of Interest Disclosure: I. Berlin reports occasional honoraria from Pfizer in the last 3 years for counseling and presentations at meetings

F. Tubach is head of the clinical research unit of Pitié-Salpêtrière and Charles Foix hospitals and the pharmacoepidemiology center of Assistance Publique Hôpitaux de Paris, that have received research funding, grants and fees for consultant activities from a large number of pharmaceutical companies, that have contributed indiscriminately to the salaries of its employees. She didn't receive any personal remuneration from these companies.

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**Legend for Figure 1:**

The ECSMOKE trial's outline.

| | Phone screening | |
|---|---|---|
| Visit 0 | Inclusion/<br>Randomisation to Placebo<br>Condition or Nicotine Condition or<br>Varenicline Condition | |
| | Treatment initiation<br>Day -7 | Electronic cigarette +<br>Tablets |
| | Target quit day (TQD)<br>Day 0 | x |
| Visit 1 | Week 2/TQD | x |
| Visit 2 | Week 4/TQD | x |
| Visit 3 | Week 8/TQD | x |
| Visit 4 | Week 10/TQD | x |
| Visit 5 | Week 12/TQD | |
| Visit 6<br>Follow up visit/end of<br>study | Week 24/TQD | |

254x190mm (96 x 96 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description |
|---|---|---|
| **Administrative information** | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym: *page 1* |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry: *page 2* |
| | 2b | All items from the World Health Organization Trial Registration Data Set. *Registered at ClinicalTrials.gov* |
| Protocol version | 3 | Date and version identifier: *page 2* |
| Funding | 4 | Sources and types of financial, material, and other support: *page 2* |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors: *pages 2-3* |
| | 5b | Name and contact information for the trial sponsor: *page 2* |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities: *pages 2-3* |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee): *pages 2-3* |
| **Introduction** | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention: *pages 6-7* |
| | 6b | Explanation for choice of comparators: *pages 9-11* |
| Objectives | 7 | Specific objectives or hypotheses: *pages 7-8 and 16-17* |

| | | |
|---|---|---|
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory): *pages 7-8 and 16-18* |
| **Methods: Participants, interventions, and outcomes** | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained: *page 8 and 17* |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists): *pages 8-9* |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered: *pages 9-11* |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease): *page 12* |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests): *page 12 and 19* |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial: *page 13* |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended: *pages 13-16* |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure): *page 14* |
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations: *pages 16-17* |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size: *page 17* |
| **Methods: Assignment of interventions (for controlled trials)** | | |
| Allocation: | | |

| | | |
|---|---|---|
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions: *pages 17-18* |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned: *page 18* |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions: *page 18* |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how: *page 18* |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial: *page 18* |
| **Methods: Data collection, management, and analysis** | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol: page 15-16, page 18 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols: *pages 19-20* |
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol: *page 18* |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol: *pages 19-20* |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses): *pages 19-20* |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation): *page 19* |

**Methods: Monitoring**

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|---|---|---|
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed: *page 20* |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial: *pages 16-17 and pages 21-22* |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct: *pages 20-22* |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor: NA |

**Ethics and dissemination**

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|---|---|---|
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval: *page 2, page 22* |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators): *page 22* |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32): *page 8, page 22* |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable: NA |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial: *page 18* |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site: *page 23* |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators: *page 3* |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation: *page 3* |

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|---|---|---|
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions: *pages 22-23* |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers: *page 23* |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code: NA |
| **Appendices** | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates: *page 22: available on request. The sponsor's rules exclude publication of consent form.* |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable: *page 13* |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.