

BMJ Open Randomised, placebo-controlled, double-blind, double-dummy, multicentre trial comparing electronic cigarettes with nicotine to varenicline and to electronic cigarettes without nicotine: the ECSMOKE trial protocol

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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:* randomised, placebo and reference treatment-controlled, multicentre, double-blind, double-dummy, parallel-group trial. *Participants:* smokers smoking at least 10 cigarettes/day in the past year and motivated to quit, aged 18–70 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 EC 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 authorisation. *Treatment duration:* 1 week+3 months. *Primary outcome:* continuous smoking abstinence rate (CAR) (abstinence from conventional/combustible cigarettes) during the last 4 weeks (weeks 9–12) of the treatment period defined as self-report of no smoking during the previous 2 weeks and expired air carbon monoxide ≤ 8 at visit 4 at week 10 after target quit date (TQD), that is, 11 weeks after treatment initiation AND at visit 5, week 12 after TQD, that is, 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.

Trial registration number NCT03630614; Pre-results.

Strengths and limitations of this study

- Randomised, 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 with varenicline.
- Ad libitum electronic cigarette use mimicking conventional cigarette use.
- Only one, fixed-dose e-liquid nicotine concentration and one e-liquid flavour are used.
- A rigorous randomised controlled trial is prioritised over a pragmatic, everyday life trial, more likely to demonstrate convincingly efficacy and safety.
- However, this can reduce the generalisability of the results to everyday population use.

INTRODUCTION

Tobacco use kills >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 9–15 years.^{2–4} Implementation of tobacco control strategies, including smoking cessation behavioural and pharmacological treatments, avoided 8 million premature deaths in the USA between 1964 and 2012.⁵ Smoking cessation before the age of 40 reduces the risk of death compared with 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.

EC 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 flavourings and may or may not contain nicotine. The European Union (EU) 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 19 May 2016.⁷

As of today, ECs are consumer products and sold outside the healthcare 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-generation and second-generation EC. Venous plasma nicotine concentrations after 65 min 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.^{9–12}

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

EC reduce desire/craving to smoke and withdrawal symptoms,^{13–16} 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^{17–19} 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 randomised trials assessing the EC for smoking cessation^{20 21} and two meta-analyses of these two trials^{22 23} have been published. Caponnetto *et al*²¹ (Efficiency and Safety of an eLectronic cigAreTte [ECLAT] trial) randomised 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 (ITT) analysis of the main outcome did not show significant differences between groups. Bullen *et al*²⁰ (A Study of Cessation using Electronic Nicotine Devices [ASCEND] trial) randomised smokers wanting to quit: 289 to receive nicotine containing EC, 295 to receive 21 mg/24 hours nicotine patches and 73 to receive EC without nicotine. Cartridges of nicotine EC contained 10–16 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 carbon monoxide (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 and placebo EC groups, respectively (ITT analysis). Serious adverse event (SAE) was observed in 19.7% of the participants in the nicotine EC, 11.3% in the nicotine patch and 13.9% in the placebo EC group.

A Cochrane review of EC for smoking cessation and reduction has been published in 2014²² and updated in 2016.²³ The quality of evidence (Grading of Recommendations Assessment, Development and Evaluation [GRADE] system) rated the evidence as low or very low because of the low (n=2) number of trials. Pooling data of these two trials, the authors report a relative risk (RR) of 2.29, 95% CI 1.05 to 4.96 for abstinence rate at 6 months. Analysis of the same two trials^{20 21} did not confirm these results.¹⁷

A major randomised pragmatic but open trial has recently been published (30 January 2019).²⁴ Smokers attending UK National Service stop-smoking services (n=886) were randomised to receive NRT for 3 months or a 1 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 SAEs were observed in the EC than in the NRT group (5 vs 1). Incidence of cough and phlegm were lower in the EC than in the NRT group. However, no SAEs occurred in either arm that were considered to be related to study treatment.

There is a general consensus that high-quality, large-scale randomised 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 randomised, placebo-controlled, multi-centre, double-blind, double-dummy, parallel groups, phase III type trial.

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

- A. Control group: EC without nicotine (ECwN) plus placebo tablets of varenicline: *placebo condition*.
- B. Experimental group: EC with nicotine (ECwN) plus placebo tablets of varenicline: *ECwN condition*.
- C. Reference group: ECwN plus varenicline tablets: *varenicline condition* with a randomisation ratio of A:B:C=1:3:3.

Each participant will use an EC and takes two 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 postgraduate 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 18–70 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 1 month before the first research visit.
7. Individual affiliated to a health insurance system.
8. Previous failure of NRT 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 <3 months.
3. Alcohol use disorder defined as a score ≥ 10 on the Alcohol Use Disorders Identification Test (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, NRTs.
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 EU between 0 and 19.9 mg/mL. Third-generation 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 month.

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-month 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%–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 randomised, 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 2012–2014.¹²

Dawkins *et al*²⁹ assessed 6 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 (AEs). However, the blood nicotine concentration was higher at 60 min 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 grey colour not allowing to distinguish the colouration 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 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 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 three available smoking cessation medications with marketing authorisation (bupropion, NRT, varenicline)^{30 31} (but its efficacy is similar to that of combined (short-acting+long-acting) NRT³²). 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 licence 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 phial 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 labelled by a pharmaceutical subcontractor according to the Good Manufacturing Practices and under the responsibility and supervision of Agence générale des équipements et produits de santé (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 that is, 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 AEs is needed.

EC and tablets are started 1 week before the target quit date (TQD) to stop smoking and followed up for 3 months after TQD.

Behavioural 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, ie, 5 weeks after treatment initiation) and at visit 5 (week 12 after TQD, ie, 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 EC without nicotine? Yes/No
- ▶ Placebo tablets and EC with nicotine? Yes/No
- ▶ Varenicline (Champix) tablets and EC 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, methadone, 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 postquit 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 non-compliance with the study protocol.

Primary outcome

Continuous smoking abstinence rate (CAR) (abstinence from conventional/combustible cigarettes) during the last 4 weeks (weeks 9–12) of the treatment period of 3 months.

Definition: self-report of no smoking during the previous 2 weeks and expired air CO \leq 8 ppm. At visit 4 at week 10 after TQD, that is, 11 weeks after treatment initiation AND at visit 5, week 12 after TQD, that is, 13 weeks after treatment initiation.

	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	
Visit 6 Follow-up visit/end of study	Week 24/TQD	

Figure 1 The ECSMOKE trial's outline.

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 \leq 8 ppm.
- ▶ Time to relapse to smoking after TQD.
- ▶ CAR confirmed by urinary anabasine concentration \leq 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 Questionnaire³⁴ with respect of baseline.
- ▶ Change in withdrawal symptoms as assessed by the modified Minnesota Nicotine Withdrawal Scale³⁵ 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', that is, correct identification of the treatments by participants.

Participant timeline

Randomisation visit=visit 0–dispensing of the treatment.

Treatment initiation within the 7 days following randomisation.

TQD should occur between 7 and 15 days after randomization and after 7 days of treatment intake (figure 1).

The first post-TQD visit (visit 1) is at week 2 after TQD, that is, 3 weeks after treatment initiation.

Visit 2 is at week 4 after TQD, that is, 5 weeks after treatment initiation.

Visit 3 is at week 8 after TQD, that is, 9 weeks after treatment initiation.

Visit 4 is at week 10 after TQD, that is, 11 weeks after treatment initiation.

Visit 5 is at week 12 after TQD, that is, 13 weeks after treatment initiation.

Visit 6 is at week 24 after TQD, that is, 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 (€)
 - <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 <3 months.
- ▶ Alcohol use disorder defined as a score \geq 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 EC.
- ▶ 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 French tobacco craving questionnaire (FTCQ)-12.³⁴
- ▶ Withdrawal symptoms using the Minnesota Tobacco Withdrawal Scale (MNWS).³⁵

Substance use

- ▶ Cannabis use in the last 30 days.

- ▶ Alcohol use.

The AUDIT 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 questionnaire³⁹ are: 43%–94% and 70%–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 one 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 MNWS.³⁵

Expired air CO will be measured with a Smokerlyzer (Bedfont Scientific, Kent, UK), a value of ≤ 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 study³⁰ with $n=8144$ smokers, the per cent 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 randomise one-third of the participants to the group ECwN, 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 randomised will, thus, be of $2 \times 272 + 91 = 635$ smokers. To take into account lost to follow-up, we plan to randomise at least 650 smokers: 280 in each of the ECwN and varenicline arm and 90 (rounded) in the ECwN arm.

Justification to randomise only 90 participants in the placebo-placebo condition (ECwN)

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-inferiority testing.

We conclude on the non-inferiority if:

- ▶ ECwN is non-inferior to varenicline;
- ▶ ECwN is 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 per cent of abstinence: $p(\text{varenicline})=33.5\%$ and $p(\text{ECwoN})=15\%$. 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 significant such as $p(\text{ECwN}) > p(\text{varenicline})$.

Would this test show a p value > 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 $p(\text{ECwN})$ versus $p(\text{ECwoN})$ is significant at 5%;
- ▶ the two-tailed superiority test of $p(\text{varenicline})$ versus $p(\text{ECwoN})$ is significant 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 $p(\text{ECwN}) > p(\text{ECwoN})$.

A Pearson's two-tailed X^2 test at 5% will be used to test the superiority. A Dunnett and Gent X^2 test at 5%, one-tailed, will be used for testing the non-inferiority.⁴²

Some simulations

If $p(\text{varenicline})=33.5\%$, $p(\text{ECwN})=33.5\%$ and $p(\text{ECwoN})=15\%$ then

1. the probability that ECwN is superior to varenicline is of 2.5%;
2. the probability that ECwN is non-inferior to varenicline is of 31.5%;
3. the probability that ECwN is superior to varenicline is of $2.5\%+31.5\%=34\%$;
4. the probability that ECwN is superior to ECwoN is of 95%.

If $p(\text{varenicline})=33.5\%$, $p(\text{ECwN})=40\%$ and $p(\text{ECwoN})=15\%$ then

1. the probability that ECwN is superior to varenicline is of 33.6%;
2. the probability that ECwN is non-inferior to varenicline is of 52.7%;
3. the probability that ECwN is superior to varenicline is of $33.6\%+52.7\%=86.3\%$;
4. the probability that ECwN is superior to ECwoN is of 99.8%.

If $p(\text{varenicline})=33.5\%$, $p(\text{ECwN})=45\%$ and $p(\text{ECwoN})=15\%$ then

1. the probability that ECwN is superior to varenicline is of 80.1%;
2. the probability that ECwN is non-inferior to varenicline is of 19%;
3. the probability that ECwN is superior to varenicline is of $80.1\%+19.0\%=99.1\%$;
4. 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 (ie, ECwN against ECwoN; varenicline against ECwoN).

Recruitment

Recruitment is either local (a) directly by the centres or centralised (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' healthcare 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 randomisation list (allocation ratio: 1:3:3) involving blocks, stratified by age (<45 vs ≥ 45 years) and centre, will be prepared and is kept blinded to all participants to the trial. The randomisation list is incorporated into the electronic Case Report Form (eCRF), and a treatment number is attributed automatically on completion of the randomisation visit. The random, computer-generated allocation sequence is prepared by a statistician of the Clinical Research Unit of Pitié Salpêtrière Charles Foix.

The randomisation list is being kept in a secured place by the sponsor and a copy of the randomisation code is being kept separately in the Poison Centre of Fernand Widal Hospital, Paris, in case of an SAE 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, Assistance publique-Hôpitaux de Paris has signed a commitment to comply with it.

DATA ANALYSIS

Populations submitted to the analyses

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

Handling of missing data

Participants who miss a visit will receive at least two 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 X^2 test. If this test is not significant (ie, $p > 5\%$), we will perform a non-inferiority test (switch) for ECwN over varenicline with a unilateral Dunnett 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 with ECwoN on the one hand, and one comparing varenicline with 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' section).

SECONDARY ANALYSES

Comparisons will be made between ECwN and varenicline arms but may be done between the three treatment arms. Qualitative variables will be analysed with a X^2 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 analysed by the log rank test.

These three tests will be generalised with a logistic model, analysis of variance 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 end points will be imputed in both ITT and per-protocol populations. The primary end point will be imputed by a multiple imputation method. The other criteria will not be imputed, since most of these criteria will be analysed in longitudinal analysis. We will perform a sensitivity analysis by rerunning the population analysis of subjects whose primary end point 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 Département de Recherche Clinique et d'Innovation (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 CRA. 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 end points

- AE diagnosis/description;
- The date when the AE started and stopped;
- Common Terminology Criteria for Adverse Events grade maximum intensity (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_Quick-Reference_5x7.pdf)
- Whether the AE is serious or not;
- Reason why the SAE was serious (eg, 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 end points

Safety and tolerance are recorded as follows:

- AEs will be recorded in the 'adverse event' section of the case report form.
- AEs 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 AE occurred in a trial subject, which has a causal relationship with the clinical trial or with the investigational medicinal product.
- ▶ *SAE or reaction*
Any AE 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 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

A DSMB 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 events or reactions.

Ethics and dissemination

The potential participant is granted a reflection period of 1 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 studies⁴⁴ 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 criteria.⁴⁷

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Competing interests IB reports occasional honoraria from Pfizer in the last 3 years for counseling and presentations at meetings. FT 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 did not receive any personal remuneration from these companies.

Patient consent for publication Not required.

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

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