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A study to investigate the safety, tolerability and concentration in the blood of nicotine compared between different types of nicotine replacement therapies (NRTs)

Submission date
29/07/2022

Recruitment status
No longer recruiting

Registration date
05/08/2022

Overall study status
Completed

Last Edited
18/12/2023

Condition category
Other

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
The purpose of this study is to investigate nicotine administered in the form of three different nicotine replacement therapies (NRTs); a test product (ENHALE Inhaler with cartridge) versus Nicorette® Inhalator & Nicorette® QuickMist.

The main objectives of this study are as follows:
1. To determine the maximum concentration of nicotine in the blood following the use of three different NRTs for a period of four hours each and to evaluate whether there are differences in the maximum concentration of nicotine in the blood between the three different NRTs.
2. To investigate the concentration of nicotine in the blood, how this changes over a period of time and to evaluate whether there are differences in the concentration in the blood between the three different NRTs.
3. To evaluate and compare the bioavailability (the degree and rate at which a substance (such as a drug) is absorbed into the body or is made available at the site of its' desired effect) of nicotine administered via a test product (ENHALE Electronic Inhaler with nicotine cartridge) and two commercially available NRTs (Nicorette® Inhalator & Nicorette® QuickMist).
4. To determine the safety and tolerability (the degree to which side effects of a drug can be tolerated) of nicotine when it is administered in single doses via three different NRTs.
5. To determine the effect of nicotine on the body by measuring the relief from nicotine cravings following the use of the three different NRTs.

Who can participate?
healthy adult males aged between 21 and 65 years old who are current users/smokers of conventional cigarettes and have smoked approximately 10-20 cigarettes per day for at least two consecutive years

What does the study involve?
In this study, participants will be required to use three different types of NRTs; a test product

(ENHALE Electronic Inhaler containing 0.5 milligram (mg) nicotine per cartridge), two commercially available NRTs (Nicorette® Inhalator (15 mg nicotine per cartridge) & Nicorette® QuickMist (1 mg nicotine per spray)). Participants will be required to use each of the products; one product per study day and during each study day, participants will be given the products to use once per hour for four hours (a total of five administrations per study day).

During each study day and each product use, blood samples will be taken at set time points (specifically after the first and final use) in order to measure the concentration of nicotine in the blood. The results will then be compared to determine if there are any significant differences in the safety profile of nicotine, and the concentration of nicotine in the blood and to determine whether there are any differences between the two commercially available NRTs versus the proposed test NRT (ENHALE Electronic Inhaler with nicotine cartridge).

What are the possible benefits and risks of participating?
Taking part in this study is not expected to provide participants with any direct medical benefit. However, the information from this study may help improve the available treatments for smoking cessation.

Blood Sampling: The procedure for blood collection either by direct venepuncture or indwelling cannula may cause mild pain and bruise at the collection site. The placement of an indwelling catheter is proposed in order to minimise these effects for rapid PK sampling. Very rarely, a blockage of a vein or a small nerve injury can occur, resulting in numbness and pain. If this occurs, it will resolve with time.

Blood pressure and pulse rate: The participant's blood pressure and pulse will be measured using an inflatable cuff which will be placed on the arm. They may experience mild discomfort in the arm whilst the cuff is inflated.

ECG: Small sticky pads will be placed on the participants' upper bodies before the ECG and an ECG machine will measure the electrical activity of the participant's heart. Before the pads are applied, the skin needs to be cleaned. Trained staff may need to shave/clip small patches of the participant's hair in these areas. Like Elastoplast® these sticky pads may be uncomfortable to remove.

Smokerlyser Assessments
Performing these tests may cause some coughing, shortness of breath and lightheadedness.

COVID-19 Risks: Participants should also be aware of the risks of exposure to COVID-19. When participants attend the clinical unit at each visit, they may be asked to complete a self-declaration form and temperature check to confirm that they are not showing any early signs of COVID-19 infection and that they have not had any contact with individuals who are currently self-isolating or have tested positive (dependent on risk mitigation measures employed at the clinical unit at the time of clinical conduct).

Participants may also be required to have a negative COVID-19 test prior to admission to the clinical unit for any overnight stays as defined within the study protocol. This procedure may cause some mild discomfort in the nose or throat when the swab is being taken but this should resolve after the procedure has been completed.

Additionally, at the clinical unit, participants may be asked to wear a facemask during procedures where clinical staff cannot maintain a 2 m distance. It is noted that if participants have a medical exemption from wearing a face mask, they will not be required to do so. In any circumstance, to

prevent risk of transmission between staff and participants, all staff will be wearing appropriate personal protective equipment i.e., face masks, face shields etc during the course of the study.

Harm to the unborn child: As this study is only intending to enrol male participants and given the commercial status of the comparator products to be evaluated in the study, there are no specific contraception requirements recommended for participants in this study. However, if participants are already using contraceptive measures, they will be advised to continue to do so whilst they are participating in the study.

Throughout the study, the health of the participants will be regularly monitored and appropriate treatment for any medical condition will be provided if required. All doctors employed by Simbec-Orion are trained and certified in Advanced Life Support Procedures in order to deal with a medical emergency. Nurses and other clinical staff are also trained in emergency procedures. Simbec-Orion also has an agreement with Prince Charles Hospital for referral of participants if required following a medical emergency.

Where is the study run from?
The study will be conducted at Simbec-Orion Clinical Pharmacology Unit, an MHRA Phase 1 accredited CRO based in South Wales (United Kingdom)

When is the study starting and how long is it expected to run for?
March 2022 to October 2022

Who is funding the study?
Ventus Medical Limited (United Kingdom)

Who is the main contact?
David Lawson (Chief Regulatory Officer, Ventus Medical Limited) (United Kingdom)
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Contact information

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Additional identifiers

Clinical Trials Information System (CTIS)
2022-001982-10

Integrated Research Application System (IRAS)
1005952

Protocol serial number
CTP 001

Study information

Scientific Title
A randomised open-label, 3-way crossover, relative bioavailability study of nicotine delivered by an electronic inhaler, Nicorette® Inhalator and Nicorette® QuickMist

Study objectives
The primary objective of this study is:
To compare the nicotine Cmax and AUC between test and reference products after the first and fifth hourly administrations of each treatment

The secondary objectives of this study are:
1. To further evaluate the pharmacokinetics of nicotine after the first and fifth hourly administration of the three nicotine treatments
2. To compare the safety and tolerability of nicotine after administration of each of the three nicotine treatments

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approval pending, Wales Research Ethics Committee 2 (Castlebridge 4, 15-19 Cowbridge Road East, Cardiff, CF11 9AB, United Kingdom; +44 (0)1686 252101; Wales.REC2@wales.nhs.uk), ref: 22/WA/0188

Primary study design
Interventional

Study design
Randomized controlled open-label crossover study

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Smoking cessation and nicotine replacement therapies (NRT)

Interventions
This is a single centre, Phase I, randomised, open-label 3-way crossover study of nicotine delivery conducted in healthy male smokers. The duration of study participation is approximately 5 weeks for each individual (from the Screening visit to the post-study follow-up visit.
Screening (Days -28 to Day -2):
Screening assessments will be performed from Days -28 to Day -2, to ensure the eligibility of participants. Participants will be selected for participation based on medical history and concurrent conditions, smoking status/history, physical examination, vital signs, 12-lead ECG, routine clinical laboratory tests, urine drugs of abuse (DOA) (including alcohol and cotinine) screen and body mass index (BMI). An estimate of screening end-tidal alveolar fraction of carbon monoxide (CO) and blood concentration of carboxyhaemoglobin will be recorded by Smokerlyser analysis. The ratio of 3-hydroxycotinine/cotinine plasma concentrations will be assessed at Screening as a predictor of an individual's cigarette consumption and as a non-invasive probe for their rate of hepatic nicotine metabolism by CYP2A6. A Fagerstrom Test for Nicotine Dependence (FND) will be performed.
Treatment Period (Day -1 to Day 3):
Participants will be admitted to the Clinical Pharmacology Unit on the morning of Day -1 where testing for a negative COVID-19 and DOA result will be performed. Subjects will be trained on the use of the ENHALE Electronic Inhaler, Nicorette® Inhalator and Nicorette® QuickMist and the Smokerlyser assessment will be performed. Before dosing on Days 1 to 3, eligibility will be re-confirmed, and assessments will be carried out as per the protocol schedule of assessments. Participants will remain in the Clinical Pharmacology Unit until the final blood sample collection and post-study follow-up procedures have been performed on Day 4 (approximately 24 hours post-last nicotine administration).

On each study day (Days 1-3), participants will receive each of the following treatments according to a randomisation code produced by Simbec-Orion using the PROC PLAN procedure of SAS (the most up-to-date version will be used).
• ENHALE Electronic Inhaler containing an ENHALE 0.5 mg Nicotine Inhalation Cartridge.
• Nicorette® Inhalator containing a 15 mg/cartridge Nicotine Concentration.
• Nicorette® QuickMist containing a 1 mg/spray Nicotine Concentration.
Participants will receive their first nicotine administration on Day 1 and subsequent administrations on Days 2 and 3. On each treatment day, participants will self-administer nicotine once hourly for 4 hours (a total of 5 administrations from 0 hours to 4 hours) – each administration for the ENHALE Electronic Inhaler and Cartridge and Nicorette® Inhalator will consist of 10 inhalations at 30-second intervals and each administration of the QuickMist spray will consist of one mouth spray, totalling 5 administrations from 0 hours to 4 hours. Single blood samples will be taken just before and after the first, second, third and fourth hourly administrations. A number of blood samples will be taken before and after the fifth administration for a detailed characterisation of the pharmacokinetic profile. The Visual Analogue Scale (VAS) of Nicotine Cravings assessment will be completed before and after each nicotine product administration.
Participants will abstain from smoking from 12 hours prior to the first nicotine product administration until the end of clinical confinement, except for smoking/product use during the nicotine administrations on Days 1 to 3. On each study day, after the five administration sessions have been completed, participants will abstain from smoking/product use until the following days dosing and PK session.
Post-Study Follow-Up (Day 4):
Post-study follow-up procedures will take place on Day 4. Participants will be provided with verbal smoking cessation advice prior to discharge from the study.
If any adverse events are recorded at this final visit, arrangements will be made with the participant, such that they are followed up appropriately and the final outcome determined. In addition, any serious adverse events occurring within 30 days of the final visit must be reported by the participant so that they can be followed up appropriately.

The study end is defined as the last subject last visit.
The study will take place in the Clinical Unit of Simbec-Orion Clinical Pharmacology (Clinical Unit) under full medical and nursing supervision. Simbec-Orion Clinical Pharmacology has on-site designated smoking rooms which are exempt from being smoke-free in accordance with Section 3 of The Smoke-free Premises (Wales) Regulations 2007.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
ENHALE inhaler with cartridge, Nicorette® Inhalator, Nicorette® QuickMist

Primary outcome(s)
The primary endpoints for this study are pharmacokinetic parameters derived from the analysis of plasma samples for the concentration of nicotine.

1. The following non-compartmental pharmacokinetic parameters will be calculated for the 1st administration of nicotine:

1.1. Cmax, 0-tau - The maximum plasma concentration of nicotine observed over the dosing interval (i.e., 60 minutes)
1.2. pAUC0-tau - The partial area under the concentration-time curve calculated using the trapezoidal rule observed over the dosing interval (i.e., 60 minutes).

2. The following non-compartmental pharmacokinetic parameters will be calculated for the fifth hourly administration of nicotine:
2.1. Cmax, lastdose-t - The maximum plasma concentration of nicotine observed from the last administration to the last measurable concentration
2.2. pAUClast dose-t - The partial area under the concentration-time curve calculated using the trapezoidal rule from the last administration to last measurable concentration.

3. Blood samples for PK analysis of nicotine will be taken at the following timepoints:
3.1. Days 1-3
3.2. First administration: pre-dose and at 2, 4, 6, 8, 10, 12, 15, 20, 30, and 60 min post-dose
3.3. Second, third and fourth hourly administrations: pre-dose and at 10 minutes post-dose
3.4. Fifth administration pre-dose and at 2, 4, 6, 8, 10, 12, 15, 20, 30, and 60 min post-dose and 2, 4, 8 and 19 hours post-dose

Key secondary outcome(s)

The secondary endpoints for this study are pharmacokinetic parameters derived from the analysis of plasma samples for the concentration of nicotine and safety endpoints.

1. Secondary (pharmacokinetic) variables for assessment endpoints are defined as follows. The following non-compartmental pharmacokinetic parameters will be calculated for the fifth hourly administration of nicotine:
1.1. AUC0-∞ - The area under the concentration-time curve extrapolated to infinity from dosing time, based on the last measurable concentration
1.2. AUC0-8 - The area under the concentration-time curve calculated using the trapezoidal rule from the time of dosing to 8 hours post-dose
1.3. AUC% extrapolated - Percentage of AUC0-inf due to extrapolation from last observed concentration to infinity
1.4. Tmax - The time to maximum observed plasma nicotine concentration (also calculated for the 1st administration of nicotine
1.5. t½ - The terminal half-life calculated from the terminal slope of the log concentration-time curve as log(2)/slope
1.6. λz - Elimination rate constant

2. The following pharmacokinetic parameters will be calculated for each hourly nicotine administration 1 to 5:
2.2. Ctrough - The plasma concentration of nicotine immediately prior to each administration
2.3. Cn - The plasma concentration of nicotine at each planned nominal timepoint post each nicotine administration

3. Secondary (safety) variables for assessment are adverse events, vital signs (as measured by systolic blood pressure, diastolic blood pressure and heart rate, respiration rate and oral temperature), ECG test results and laboratory test results. The safety endpoints:
3.1. Adverse events (AEs)
3.2. Laboratory safety (biochemistry, haematology and urinalysis)
3.3. Vital signs (systolic/diastolic blood pressure, heart rate, respiration rate, oral body temperature)
3.4. 12 lead ECG (heart rate, PR interval, QRS duration, QT interval and QTcF interval)

4. Exploratory (pharmacodynamic) variables for assessment:
4.1. Visual Analogue Scale of Nicotine Craving

5. Blood samples for PK analysis of nicotine will be taken at the following timepoints:
5.1. Days 1-3
5.2. First administration: pre-dose and at 2, 4, 6, 8, 10, 12, 15, 20, 30, and 60 min post-dose
5.3. Second, third and fourth hourly administrations: pre-dose and at 10 minutes post-dose.
5.4. Fifth administration pre-dose and at 2, 4, 6, 8, 10, 12, 15, 20, 30, and 60 min post-dose and 2, 4, 8 and 19 hours post-dose.

AEs - recorded from consent through to post-study (Day 4)

Laboratory Safety - Screening only

Vital Signs - Screening, Day -1, Days 1-3 (pre-first dose) & Day 4

ECG - Screening & Day 4

VAS for Nicotine Craving
Days 1-3: pre-dose & 10 mins post-dose for each administration on each day
Administration 5: pre-dose, 10 mins & 30 mins post-dose on each day

Completion date
28/10/2022

Eligibility

Key inclusion criteria
1. Healthy male participants, aged between 21 and 65 years old, inclusive
2. Participant with a body mass index (BMI) of 18-32 kg/m2. BMI = body weight (kg) / [height (m)] 2
3. Participants must be current conventional, factory-made cigarette smokers (approximately 10 to 20 cigarettes per day for at least two consecutive years, defined by a positive urine cotinine result of ≥ 200 ng/ml and ≥ 7 ppm exhaled CO breath test (Smokerlyser) at Screening) or participants who have been consistent dual users of conventional cigarettes and e-cigarettes /vape for 12 months, who are not intending to make a quit attempt during the study
4. Participants will be willing to use the study products ENHALE Electronic Inhaler with ENHALE 0.5 mg Nicotine Inhalation Cartridge, Nicorette® Inhalator and Nicorette® QuickMist and use only the products provided to them and abstain from regular cigarette use during clinical confinement (participants are allowed to smoke ad libitum on Day -1 until 12 hours prior to planned first nicotine administration on Day 1)
5. No clinically significant history of previous allergy/sensitivity to nicotine, ENHALE Electronic Inhaler with ENHALE 0.5 mg Nicotine Inhalation Cartridges, Nicorette® Inhalator and Nicorette® QuickMist or any of the excipients contained within the investigational products
6. No clinically significant abnormal test results for serum biochemistry, haematology and/or urine analyses within 28 days before the first dose administration of the IMP
7. Negative urinary drugs of abuse (DOA) screen (including alcohol) test results, determined within 28 days before the first dose administration of the IMP (N.B.: A positive test result may be repeated at the Investigator’s discretion)
8. Participant with negative human immunodeficiency virus (HIV), hepatitis B surface antigen

(HBsAg)) and hepatitis C virus antibody (HCV Ab) test results at Screening
9. No clinically significant abnormalities in 12-lead electrocardiogram (ECG) determined within 28 days before first dose of IMP including heart rate, PR interval QRS width and QT interval corrected using Fredericia's formula (QTcF)
10. No clinically significant abnormalities in vital signs (e.g., blood pressure, heart rate, respiration rate, oral temperature) determined within 28 days before first dose of IMP
11. Participants must be available to complete the study (including all follow-up visits)
12. Participants must satisfy an Investigator about their fitness to participate in the study
13. Participants must provide written informed consent to participate in the study
14. Participants must be willing to comply with all relevant study restrictions including; avoiding strenuous exercise completely from 3 days before the first dose until the final study visit; limiting alcohol consumption to a maximum of 2 units per day from 7 days prior to the first administration of investigational medicinal product (IMP) and avoid alcohol completely for a period of not less than 2 days prior to the first administration of IMP and throughout the study period and; avoiding food or drink containing caffeine, including coffee, tea, cola, energy drinks or chocolates completely from 2 days prior to dosing and during the study

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
21 Years

Upper age limit
65 Years

Sex
Male

Total final enrolment
24

Key exclusion criteria
1. Participants who use roll-your-own cigarettes. or are sole e-cigarette/vape users
2. Participants who have had any treatment with smoking cessation medications (e.g., Bupropion, Champix or any NRTs) within 8 weeks of the planned first nicotine dosing occasion
3. Participants who, prior to enrolment, are planning to quit smoking in the next 12 months. All participants will be informed that they are free to quit smoking and withdraw from the study at any time
4. Participants who have an acute illness (e.g., respiratory tract infection) requiring treatment within 4 weeks prior to first dose
5. Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements within 28 days or 5 half-lives (whichever is longer) prior to the first dose of IMP, with the exception of paracetamol (which may be taken as an analgesic to a maximum of 2 g in 24 h) and ibuprofen (which may be taken as an analgesic to a maximum of 1.2 g in 24 h (400 mg 3

times a day))
6. Evidence of renal, hepatic, central nervous system, respiratory (including COPD), cardiovascular or metabolic dysfunction
7. A clinically significant history of drug or alcohol abuse (defined as the consumption of more than 21 units of alcohol a week) within the past two years
8. Inability to communicate well with the Investigators (i.e., language problem, poor mental development or impaired cerebral function)
9. Participation in any other clinical study of an investigational product within the previous 3 months or five half-lives, whichever is longer, or a marketed drug clinical study within the 30 days or five half-lives, whichever is longer, before the first dose of IMP. (Washout period between studies is defined as the period of time elapsed between the last dose of the previous study and the first dose of the next study).
10. Donation of 450 mL or more blood within the 3 months before the first dose of IMP
11. Vegans, vegetarians or other dietary restrictions (e.g., restrictions for medical, religious or cultural reasons, etc.)
12. Participants who have received a COVID-19 vaccine injection within 14 days prior to first dose of IMP

Date of first enrolment
30/08/2022

Date of final enrolment
24/10/2022

Locations

Countries of recruitment
United Kingdom

Wales

Study participating centre
Simbec Research Limited
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Sponsor information

Organisation
Ventus Medical Limited

Funder(s)

Funder type
Industry

Funder Name
Ventus Medical Limited

Results and Publications

Individual participant data (IPD) sharing plan
The study data will be shared with relevant research groups and external stakeholders collaborating with the study sponsor to support the future development of the IMP within the boundaries of strict confidentiality agreements

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results	version 1.0	15/12/2023	18/12/2023	No	No
HRA research summary			28/06/2023	No	No