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Study in adult smokers to evaluate changes in biomarkers of tobacco exposure after switching to exclusive use of the JUUL2 system

Submission date
19/08/2022

Recruitment status
No longer recruiting

Registration date
01/09/2022

Overall study status
Completed

Last Edited
07/01/2025

Condition category
Other

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

Plain English summary of protocol

Background and study aims
Cigarette smoking is a leading cause of preventable human disease including lung cancer, obstructive lung disease, and heart disease. Risks from smoking are mainly due to breathing in a number of toxicants transferred into cigarette smoke during the combustion of tobacco. Quitting smoking reduces the disease risk, and as such, the public health priority of reducing the health burden of cigarette smoking has led to the development of a variety of initiatives to reduce smoke toxicant exposure by encouraging smoking abstinence.
While the long-term effects of electronic nicotine delivery system (ENDS) use ("vaping") are unknown, prominent public health bodies such as Public Health England have determined, following extensive reviews of scientific research, that "vaping poses only a small fraction of the risks of smoking and switching completely from smoking to vaping conveys substantial health benefits". Although ENDS products have been commercially available in the UK for over a decade, only one ENDS product has received medicinal licensing authorisation from the UK Medicines and Healthcare product Regulatory Agency for use as a smoking abstinence aid. That product has not been marketed as a licensed product.
This study will compare biomarkers of toxicants associated with tobacco use in blood and urine samples. The aim is to determine if switching from combustible cigarettes to exclusive use of JUUL2 will result in significantly decreased levels of these biomarkers, as compared to people who continue to smoke combustible cigarettes.

Who can participate?
Male or female daily cigarette smokers, 21 to 65 years of age, who currently smoke an average of 10 or more manufactured combustible cigarettes per day.

What does the study involve?
Participants will stay in a clinical facility for 9 days/8 nights and provide blood and urine samples throughout their stay, and have a follow-up phone call about 7 days after leaving the clinic. Each participant will be assigned into a group and provided either no nicotine, a JUUL2 product to use as they wish between 7 am and 11 pm, or their own cigarette brand to use as they wish between 7 am and 11 pm.

What are the possible benefits and risks of participating?
Participants are not likely to receive any direct benefit from taking part in the study. Products used in this study contain nicotine which is a highly addictive substance. There is a remote chance that the study product may cause an allergic reaction, which in some cases may be severe. Symptoms include sudden shortness of breath, decreased consciousness and rash. Some of the most likely health risks or adverse events/experiences of participation include:
1. Mouth, tongue, and gum irritation
2. Throat irritation
3. Coughing
4. Headache
5. Dizziness
6. Feeling ill (or nauseated)
7. Vomiting
8. Abdominal pain
9. Diarrhoea

In addition to the health risks listed above, there may be unknown, infrequent, and/or unforeseeable health risks associated with the use of the study product, including severe or life-threatening reactions or unexpected interactions with another medication. These symptoms may include:
1. Abdominal pain
2. Diarrhoea
3. Trouble breathing
4. Swelling of face, tongue or throat
5. Rash
6. Flushing
7. Itching
8. Sneezing or runny nose
9. Dizziness
10. Light-headedness or fainting
11. Irregular or racing heart rate
12. The JUUL2 System should be kept at least 15.3 cm away from pacemakers and other sensitive medical equipment
13. ENDS and e-cigarette product use may aggravate pre-existing lung or heart conditions
14. Nicotine over-dosage symptoms may include vomiting, diarrhoea, nausea, dizziness, increased saliva, abdominal pain, headache, weakness, or rapid heartbeat
15. Injuries, such as burns, from ENDS product malfunctions have occurred

The potential exposures from participating in this study are not anticipated to result in an overall increase in long-term health risks as compared to the health risks from your current tobacco product use, but the full extent of long-term health risks associated with the use of ENDS products are not yet known.
All combustible cigarette smokers are at increased risk for:
1. Heart disease
2. Lung cancer
3. Increased risk of other types of cancer
4. Chronic Obstructive Pulmonary Disease (COPD)
5. Premature death

Female smokers are also at increased risk for:
1. Cancer of the cervix
2. Problems with periods (menstrual problems)
3. Problems getting pregnant (fertility problems)
4. Premature delivery

5. Having a low-birth-weight baby
Male smokers are also at increased risk for:
1. Problems with erections (impotence/erectile dysfunction)
Risks associated with study procedures:
1. Blood drawing (venepuncture) risks: drawing blood may cause temporary discomfort from the needle stick, bleeding, bruising, infection, and fainting
2. Electrocardiogram (ECG) risks: the ECG involves placing electrodes on the skin. You may experience an allergic reaction to the adhesive used to attach the electrodes to the skin. These symptoms are generally mild and clear up on their own.
3. HIV and hepatitis testing risks: being tested for HIV and hepatitis may cause anxiety regardless of the test results.

Where is the study run from?
Juul Labs Inc. (USA)

When is the study starting and how long is it expected to run for?
August 2022 to November 2023

Who is funding the study?
Juul Labs Inc. (USA)

Who is the main contact?
Sandra Miller, sandra.miller@juul.com

Contact information

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Public

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
JLI-22-01

Study information

Scientific Title
A randomised, open-label, parallel-group study in adult smokers to evaluate changes in biomarkers of tobacco exposure after switching to exclusive use of the JUUL2 system

Acronym
JUUL2BOE

Study objectives
Switching from the use of combustible cigarettes to exclusive use of the JUUL2 System for 6 days will result in significantly decreased levels of urine and blood Biomarkers of Exposure (assessed by change from baseline to Day 6 as compared to smokers who continue to smoke their UB combustible cigarettes exclusively).

Ethics approval required
Old ethics approval format

Ethics approval(s)

Approval pending, North East York Committee (HRA Jarrow, Jarrow Business Centre, Rolling Mill Road, Jarrow, NE32 3DT, UK; +44 (0)2071048057, +44 (0)2071048079; york.rec@hra.nhs.uk)

Study design
Interventional randomized open-label parallel-group study multi-center study

Primary study design
Interventional

Study type(s)
Other

Health condition(s) or problem(s) studied
Tobacco exposure

Interventions
Randomisation:
Each subject will be assigned a unique identification number upon screening. Subjects who complete the study screening assessments and meet all the eligibility (inclusion/exclusion) criteria will be assigned a unique randomisation identification number at the start of study product use or tobacco/nicotine abstinence on Day 1 and will receive the corresponding product or stop smoking according to a randomisation scheme.
Each subject will participate in one study group only.
Separate randomisations for each site will be produced and stratified by sex (males and females) and age (21 to 44 years old and 45 to 65 years old).
Additional details will be included in the randomisation schedule request and specification form for each site based on enrollment predictions.
Additional details on study populations will be included in the statistical analysis plan (SAP).

In a randomly-allocated sequence, adult smokers will be assigned into one of four groups. Each study site will aim to stratify participants by age and gender. Study products for the four groups:
1. JUUL2 System with Tobacco flavour, OR
2. JUUL2 System with Menthol flavour, OR
3. Participant's usual brand of conventional cigarettes, OR
4. Not having any tobacco/nicotine for 6 consecutive days

Methodology:
Subjects will either exclusively use the assigned JUUL2 System ad libitum, exclusively smoke their usual brand cigarettes ad libitum, or undergo tobacco/nicotine abstinence for 6 consecutive days beginning on Day 1. Each subject will participate in one study group only. The abstinence group is a comparator group, though not a control group.

Dosage:
Dosage is not a term used for tobacco studies, as this is not a medicinal trial. However, the JUUL2 Product has 18 mg/ml nicotine, and the nicotine in the subjects' usual brand cigarettes will vary based on the brand, the abstinence arm will not have any intake of nicotine.

For subjects in the JUUL2 arms, the JUUL2pods will be weighed before and after dispensing to determine the amount of nicotine delivered to each subject each day and over all 6 days. For subjects in the cigarette smoking arm, the number of cigarettes smoked each day will be recorded for the cigarette smoking arm.

Frequency:
For subjects in the JUUL2 arms or the cigarette arms, they may smoke ad libitum between 7 am and 11 pm, upon request for product from clinic staff over all 6 days they stay in-clinic.

Follow-up:
Approximately 7 days after subjects check out of the clinic, they will be contacted by phone to document any adverse experiences since leaving the clinic. This includes subjects who voluntarily discontinue the trial unless they withdraw consent.

Intervention Type
Other

Primary outcome(s)
1. Total urine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (total NNAL) evaluated through 24-hour urine collections on Day -1 to Day 1 and from Day 6 to Day 7
2. 3-hydroxypropylmercapturic acid (3-HPMA) evaluated through 24-hour urine collections on Day -1 to Day 1 and from Day 6 to Day 7
3. Monohydroxybutenylmercapturic acid (MHBMA) evaluated through 24-hour urine collections on Day -1 to Day 1 and from Day 6 to Day 7
4. S-phenyl mercapturic acid (S-PMA) evaluated through 24-hour urine collections on Day -1 to Day 1 and from Day 6 to Day 7
5. Blood carboxyhemoglobin (COHb) evaluated through blood samples taken on Day -1 and Day 6

Key secondary outcome(s))
1. How the product tested "made you feel" on a scale of 1 to7 measured using the Modified Product Evaluation Scale (mPES) from baseline to Day 6
2. How much "you like the product" on a scale of "not at all" to "a great deal" measured using the Product-Liking Questionnaire from baseline to Day 6
3. Urge to smoke measured on a scale of "not at all" to "extreme" measured using the Urge to Smoke a Cigarette Questionnaire from baseline to Day 6
4. Likeliness to use the product in the future on the scale of "definitely would not" to "definitely would" measured using the Future Intent to Use the Product Questionnaire from baseline to Day 6
5. For subjects randomised to JUUL2 System groups, puffing topography assessed via device Bluetooth connection and mobile application over the 6-day use period
6. Exhaled carbon monoxide measured using breath samples on Day -1 and Day 6
7. N-nitrosonornicotine (NNN) evaluated through 24-hour urine collections on Day-1 to Day 1 and from Day 6 to Day 7
8. 3-hydroxy-1-methylpropylmercapturic acid (HMPMA) evaluated through 24-hour urine collections on Day-1 to Day 1 and from Day 6 to Day 7
9. 2-cyanoethyl-mercapturic acid (CEMA) evaluated through 24-hour urine collections on Day-1 to Day 1 and from Day 6 to Day 7
10. Total 1-hydroxypyrene (1-OHP) evaluated through 24-hour urine collections on Day-1 to Day 1 and from Day 6 to Day 7
11. O-toluidine evaluated through 24-hour urine collections on Day-1 to Day 1 and from Day 6 to Day 7
12. 2-aminonaphthalen (2-NA) evaluated through 24-hour urine collections on Day-1 to Day 1 and from Day 6 to Day 7
13. 4-aminobiphenyl (4-ABP) evaluated through 24-hour urine collections on Day-1 to Day 1 and from Day 6 to Day 7
14. Nicotine equivalents evaluated through 24-hour urine collections on Day-1 to Day 1 and from

Day 6 to Day 7
15. Product use data gathered by number of cigarettes used and pod weight change (JUUL2 Products) on Day -1 to Day 6

Completion date
20/11/2023

Eligibility

Key inclusion criteria
1. Adult male or female daily smoker, 21 to 65 years of age, inclusive, at Screening
2. Has been a smoker for at least 12 months prior to Screening. Brief periods of non-smoking (e.g., up to ~7 consecutive days due to illness, trying to quit, participation in a study where smoking was prohibited) during that time will be permitted at the discretion of the Investigator
3. Currently smokes an average of 10 or more conventional manufactured combustible cigarettes per day, as reported at Screening

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Total final enrolment
89

Key exclusion criteria
1. Has a history of everyday or some day use of vapour products or use of any vapour products within 2 weeks of Screening
2. Has a history or presence of clinically significant gastrointestinal, renal, hepatic, neurologic, haematologic, endocrine, oncologic, urologic, pulmonary, immunologic, psychiatric, or cardiovascular disease, or any other condition that, in the opinion of the Investigator, would jeopardise the safety of the subject or impact the validity of the study results
3. Has a clinically significant abnormal finding on the physical examination, medical history, vital signs, electrocardiogram (ECG), or clinical laboratory results, in the opinion of the Investigator
4. Has a positive test for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV)
5. Has had an acute illness (e.g., upper respiratory infection, viral infection) requiring treatment within 14 days prior to Check-in
6. Has a fever (>38°C) at Screening or Check-in
7. Has a body mass index (BMI) >40 kg/m² or <18 kg/m² at Screening
8. Has a history of drug or alcohol abuse within 24 months of Check-in
9. Has diabetes mellitus, asthma, or chronic obstructive pulmonary disease
10. Has a systolic blood pressure <90 mmHg or >150 mmHg, diastolic blood pressure <40 mmHg

or > 95 mmHg, or heart rate <40 bpm or >99 bpm
11. Has experienced an allergic reaction following previous e-cigarette use or with exposure to benzoic acid, propylene glycol and glycerol
12. Has an estimated creatinine clearance <80 ml/minute (using the Cockcroft-Gault equation) at Screening
13. Has a positive urine screen for drugs of abuse or positive breath screen for alcohol at Screening or Day -2 (Check-in)
14. If female, the subject is pregnant, lactating, or intends to become pregnant during the time period from Screening through the end of study
15. Has used medications known to interact with cytochrome P450 2A6 (including, but not limited to, amiodarone, amlodipine, amobarbital, buprenorphine, clofibrate, clotrimazole, clozapine, desipramine, disulfiram, entacapone, fenofibrate, isoniazid, ketoconazole, letrozole, methimazole, methoxsalen, metyrapone, miconazole, modafinil, orphenadrine, pentobarbital, phenobarbital, pilocarpine, primidone, propoxyphene, quinidine, rifampicin, rifampin, ropinirole, secobarbital, selegiline, sulconazole, theophylline, tioconazole, tranylcypromine) within 14 days or 5 half-lives of the drug, whichever is longer, prior to Check-in.
16. Has used nicotine-containing products other than manufactured cigarettes or ENDS (e.g., roll-your-own cigarettes, bidis, snuff, nicotine inhaler, pipe, cigar, chewing tobacco, nicotine patch, nicotine spray, nicotine lozenge, or nicotine gum) within 30 days prior to Check-in, except as required per protocol (e.g., the brief product trial at Screening Visit 2)
17. Has used any prescription smoking abstinence treatments, including, but not limited to, varenicline (Chantix®) or buproprion (Zyban®) within 3 months prior to Check-in
18. Is a self-reported puffer (i.e., adult smokers who draw smoke from the cigarette into the mouth and throat but do not inhale)
19. Is planning to quit smoking during the study, planning to quit within 3 months following Day 1, or postponing a quit attempt in order to participate in the study
20. Is unwilling to abstain from all nicotine use for approximately 6.5 days, if assigned to the tobacco/nicotine abstinence group
21. Has a negative response (i.e., unwilling to use or unable to tolerate [e.g., experiences AEs during the product trial that will prevent the subjects from continuing to use the study products
22. Has donated plasma within 7 days prior to Check-in

Date of first enrolment
10/11/2022

Date of final enrolment
15/02/2023

Locations

Countries of recruitment
United Kingdom

England

Wales

Poland

Study participating centre
Labcorp Clinical Research Unit Limited
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Study participating centre
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Study participating centre
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Sponsor information

Organisation
Juul (United States)

ROR
https://ror.org/05fcgnx79

Funder(s)

Funder type
Industry

Funder Name
Juul Labs Inc.

Results and Publications

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are not expected to be made available as the dataset may contain commercially-sensitive information.

IPD sharing plan summary

Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		02/01/2025	07/01/2025	Yes	No