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A clinical study to evaluate the contents of exhaled breath after use of the JUUL2 electronic nicotine delivery system and conventional cigarettes

Submission date
18/06/2024

Recruitment status
No longer recruiting

Registration date
20/06/2024

Overall study status
Completed

Last Edited
20/06/2024

Condition category
Other

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims

While recent surveys have shown that the prevalence of cigarette smoking has reached a historic low of 11.5% in the United States (US) (Cornelius, et al., 2023), millions of Americans continue to smoke despite overwhelming scientific evidence demonstrating negative health consequences. Additionally, cigarette smoking continues to be a leading cause of preventable death in the US (USDHH, 2014). However, in 2015, nearly 70% of American adult smokers reported wanting to quit smoking, and though 55% had attempted a to quit within the previous year, only 7.4% reported to have recently stopped smoking (Babb, et al., 2017). These data exemplify the difficulty that smokers face when trying to quit. The US Food and Drug Administration (FDA) proposed to implement a comprehensive approach to nicotine product regulation with the intention to reduce the impact of the harms associated with cigarette smoking (Gottlieb, et al., 2017). Within such a harm reduction framework, alternate forms of nicotine delivery that do not subject consumers to the toxic chemicals found in combustible cigarette smoke may play a critical role. To this end, the JUUL® ENDS has been developed as an alternative to combustible cigarettes for adult smokers.

The JUUL2 Device and pods comprise an ENDS product that is currently being marketed in the United Kingdom to adult smokers as an alternative to combustible cigarettes. The JUUL ENDS design is that of a typical ENDS product described above. However, JUUL ENDS products do not contain tobacco leaf, and product data to date indicate JUUL ENDS use has demonstrated production of significantly lower levels of chemicals identified by the FDA as harmful and potentially harmful constituents (HPHCs) compared to combustible cigarettes.

Potential health effects of product use on non-product users depends on their exposure. With closed system ENDS products, the key potential source of exposure of non-product users is the exhaled breath of product users. This study is designed to collect and measure chemical constituents in the exhaled breath of JUUL product users.

Who can participate?

Adult, male and female smokers of conventional menthol cigarettes (who smoke at least 10

manufactured combustible cigarettes per day) between the ages of 22-65. Subjects must also be experienced using e-cigarettes and meet all inclusion and none of the exclusion criteria.

What does the study involve?
Subjects will be screened for participation in the trial up to 28 days before Day 1. Along with screening procedures, all subjects will receive training on exhaled breath sample collection procedures and the controlled puffing sequence using a training video and site instructions. Trained subjects will have the opportunity to try the JUUL2 study products.
Eligible subjects will be scheduled for a Day 1 clinic visit. In this 2-part, 2-way cross-over study, subjects will be randomized first to either Part A (tobacco flavor product) or Part B (menthol flavor product) of the study then randomized again to one of two product use sequences within the assigned study Part. Following completion of the check-in events, subjects will participate in the exhaled breath collection test sessions for the first product in their randomization sequence. The subjects will have a 3-hour break and then participate in the exhaled breath collection test sessions for the second product in their randomization sequence.
In parts A and B, subjects will complete two periods of baseline (sham) and test sample collections with a 45-minute break in between each collection for each product in their randomization sequence. Exhaled carbon monoxide will be measured before and after the baseline and test sample collections; the analysis lab will provide personnel to assist with sample collection. Pods used during the test sessions will be weighed before and after use.
A follow-up phone call with subjects will be made 7 days, +2, after Check-out (or early withdrawal). Provided there are no adverse events which require further attention, the subject's participation in the trial will be complete.
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. Diarrhea

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. Trouble breathing
2. Swelling of face, tongue or throat
3. Rash
4. Flushing
5. Itching
6. Sneezing or runny nose
7. Light-headedness or fainting
8. Irregular or racing heart rate
9. The JUUL2 System should be kept at least 15.3 cm away from pacemakers and other sensitive medical equipment

10. ENDS and e-cigarette product use may aggravate pre-existing lung or heart conditions
11. Nicotine over-dosage symptoms may include vomiting, diarrhea, nausea, dizziness, increased saliva, abdominal pain, headache, weakness, or rapid heartbeat
12. 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 (venipuncture) 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?
May 2024 to November 2024

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

Who is the main contact?
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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
JLI-24-02

Study information

Scientific Title
An open-label, single-center clinical study to evaluate selected chemical constituents in the exhaled breath with the use of the JUUL2 Electronic Nicotine Delivery System (ENDS) and conventional cigarettes

Acronym
JUUL2EBS

Study objectives
The purpose of this study is to investigate potential health effects of product use on non-product users. Potential health effects of product use on non-product users depends on their

exposure. With closed system ENDS products, the key potential source of exposure of non-product users is the exhaled breath of product users. This study is designed to collect and measure chemical constituents in the exhaled breath of JUUL product users.

Ethics approval required
Ethics approval required

Ethics approval(s)
Not yet submitted 17/06/2024, Advarra (6100 Merriweather Dr., Suite 600, Columbia, 21044, United States of America; +1 410.884.2900; Email not provided), ref: Reference number not provided

Study design
2-part open-label single-center 2-way cross-over study

Primary study design
Interventional

Secondary study design
Randomised cross over trial

Study setting(s)
Other

Study type(s)
Other

Participant information sheet
No participant information sheet available

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

Interventions
Randomisation:
Approximately 20 subjects will be screened for participation in the trial up to 28 days before Day 1. Along with screening procedures, all subjects will receive training on exhaled breath sample collection procedures and the controlled puffing sequence using a training video and site instructions. Trained subjects will have the opportunity to try the JUUL2 study products.
Eligible subjects will be scheduled for a Day 1 clinic visit. In this 2-part, 2-way cross-over study, subjects will be randomized first to either Part A (tobacco flavor product) or Part B (menthol flavor product) of the study then randomized again to one of two product use sequences within the assigned study Part. Following completion of the check-in events, subjects will participate in the exhaled breath collection test sessions for the first product in their randomization sequence. The subjects will have a 3-hour break and then participate in the exhaled breath collection test sessions for the second product in their randomization sequence.
In parts A and B, subjects will complete two periods of baseline (sham) and test sample collections with a 45-minute break in between each collection for each product in their randomization sequence. Exhaled carbon monoxide will be measured before and after the baseline and test sample collections; the analysis lab will provide personnel to assist with sample collection. Pods used during the test sessions will be weighed before and after use.

Subjects will be assigned to one of the following 2 study parts:
Part A (n = 10)
Healthy conventional menthol cigarette smokers who will smoke their UB cigarette (product C) as well as use the JUUL2 Device with Virginia Tobacco flavored e-liquid at 18mg/mL nicotine concentration JUUL2 pod (Product A) under prescribed use conditions1. See study design figure.
Part B (n = 10)
Healthy conventional menthol cigarette smokers who will smoke their UB cigarette (product C) as well as use the JUUL2 Device with Polar Menthol flavored e-liquid at 18mg/mL nicotine concentration JUUL2 pod (Product B) under prescribed use conditions1. See study design figure.
1Prescribed use: 10 puffs, one 3-second puff every 30 seconds.

A follow-up phone call with subjects will be made 7 days, +2, after Check-out (or early withdrawal). Provided there are no adverse events which require further attention, the subject's participation in the trial will be complete.

Products:
Product A: JUUL2 Device with Virginia Tobacco flavored e-liquid at 18mg/mL nicotine concentration JUUL2 pod.
Product B: JUUL2 Device with Polar Menthol flavored e-liquid at 18mg/mL nicotine concentration JUUL2 pod.
Product C: Subject's usual brand (UB) of conventional combustible menthol cigarettes.

Methodology:
The following sequence will be performed in one day: 2 baseline collections 15 minutes apart, a 45 minute break, 2 product 1collections 15 minutes apart, 3 hour interval with no nicotine, 2 baseline collections 15 minutes apart, a 45 minute break, 2 product 2 collections 15 minutes apart.

Exhaled Breath Sample 1 collection- analysis of nicotine, menthol, propylene glycol and glycerin
Exhaled Breath Sample 2 collection- analysis of acetaldehyde, acrolein, and formaldehyde

1. Research staff will instruct subjects to wear dedicated nose clips and await further instruction in the allocated study rooms.
2. Baseline CO will be measured using sham inhalation/puff and exhaled breath into the CO analyzer.
3. Research staff will instruct subjects to respective seating arrangement and provide the CPS regimen instructions.
4. Subjects will perform exhaled breath sampling in accordance with controlled puffing sequence (CPS) regimen.
5. Subjects will remove nose clips and wait until next collection and research staff will instruct subjects on next steps.

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.

Intervention Type
Other

Primary outcome measure

The absolute change from baseline (sham) level of specific constituents (nicotine, propylene glycol, vegetable glycerin, acetaldehyde, acrolein, formaldehyde, menthol, and CO) for each subject.

All data will be summarized descriptively by study part and product. Continuous variables will be summarized using the mean, standard deviation, median, and range (minimum to maximum). For select variables, two-sided 90% CIs for the mean may also be provided to quantify the uncertainty associated with the estimated sample statistic.
A linear mixed model will be used for the analysis of the primary endpoints. In the model, the response variable is the absolute change from baseline in the EBS level of a constituent and the fixed effect factor are the product group, sequence and period and the random effect is participant nested within sequence. For each EBS constituent, the least squared mean difference between UB cigarette (reference) and the JUUL2 product and 90% confidence interval will be provided.

Secondary outcome measures
There are no secondary outcome measures

Overall study start date
01/05/2024

Completion date
01/11/2024

Eligibility

Key inclusion criteria
Subjects must meet all of the following inclusion criteria to be eligible for participation in the study:
1. Is able to read and understand the ICF and provides voluntary consent to participate in this study documented on the signed ICF(s).
2. Adult, male or female smoker, 22 to 65 years of age, inclusive, at the Screening visit.
3. Has been a smoker ≥12 months prior to Screening.
4. Individuals who self-report smoking a minimum of 10 manufactured combustible menthol CPD for a minimum of 3 months prior to Screening.
5. Has past 30-day history of some day ENDS use.
6. Has a positive urine cotinine (≥200 ng/mL) at the Screening visit and Day 1.
7. Has an eCO ≥10 ppm at the Screening visit.
8. Has an eCO <10 ppm at Day 1.
9. Completes the screening process within 28 days prior to study Day 1.
10. Is willing and able to comply with the requirements of the study, including a willingness to use the study products during the study and to stop smoking during the required abstention periods in the study.
11. A heterosexually active female subject of childbearing potential must have been using one of the following forms of contraception, and agree to continue using it through completion of the study:
11.1. hormonal (e.g., oral, vaginal ring, transdermal patch, implant, or injection) consistently for at least 3 months prior to study Day 1;
11.2. double-barrier method (e.g., condom with spermicide, diaphragm with spermicide) from Day 1;
11.3. intrauterine device for at least 3 months prior to study Day 1;

11.4. abstinence beginning at least 6 months prior to Day 1;
11.5. a partner who has been vasectomized for at least 6 months prior to Day 1.
12. A female subject of non-childbearing potential must be postmenopausal with amenorrhea for at least 1 year prior to study Day 1 or have undergone one of the following sterilization procedures at least 6 months prior to study Day 1:
12.1. hysteroscopic sterilization;
12.2. bilateral tubal ligation, occlusion, or bilateral salpingectomy;
12.3. hysterectomy;
12.4. bilateral oophorectomy

Participant type(s)
Healthy volunteer

Age group
Adult

Lower age limit
22 Years

Upper age limit
65 Years

Sex
Both

Target number of participants
22

Total final enrolment
20

Key exclusion criteria
Subjects who meet any of the following exclusion criteria will not be enrolled in the study:
1. Has a history or presence of clinically significant gastrointestinal, renal, hepatic, neurologic, hematologic, endocrine, laryngeal, oncologic, urologic, pulmonary (asthma, chronic obstructive pulmonary disease), immunologic, psychiatric, cardiovascular disease (hypertension, heart failure, chronic coronary syndrome, post-myocardial infarction status), diabetes mellitus, or any other condition that, in the opinion of the Investigator, would jeopardize the safety of the subject or impact the validity of the study results.
2. At Screening, has a clinically significant abnormal finding on the physical examination, medical history, review of systems, medication list, or vital signs that, in the opinion of the Investigator (or medically qualified designee) might jeopardize participants safety or affect data validity.
3. Has had an acute illness (e.g., upper respiratory infection, viral infection) requiring treatment within 28 days prior to study Day 1.
4. Has a fever (>100.4°F [38oC]) at Screening visit.
5. Has a positive urine test result for drugs of abuse, or positive alcohol breath test at the Screening visit or at Day 1. If a positive urine drug test is observed, and it is believed that the positive urine test is due to prescription drugs, the PI should obtain documentation that:
5.1. confirms the subject’s use of the prescribed medication, and
5.2. the prescribed medication will cause a false positive drug test.
6. Has an SBP <90 mmHg or >150 mmHg, DBP <40 mmHg or >95 mmHg, or HR <40 beats per

minute (bpm) or >99 bpm at Screening.
7. Has experienced an allergic reaction following previous e-cigarette use or with exposure to any primary components of the e-liquids (nicotine, flavor, benzoic acid, propylene glycol and glycerol).
8. Has participated in a previous clinical study for an investigational drug, device, biologic, or tobacco product within 30 days prior to Screening.
9. If female, the subject is pregnant, has a positive pregnancy test at the Screening visit or at Day 1, is lactating, breast feeding, or intends to become pregnant during the time period from Screening through EOS.
10. Has used medications reported to interact with nicotine, including theophylline, ropinirole, and clozapine, within 14 days or 5 half-lives of the drug, whichever is longer, prior to study Day 1.
11. Has used any prescription smoking cessation treatments, including, but not limited to, varenicline (Chantix®) or bupropion (Zyban®) within 30 days prior to study Day 1.
12. Requires concomitant treatment with prescription or non-prescription products that contain pseudoephedrine (e.g., nasal/sinus decongestants).
13. Negative response (i.e., unwilling to use or unable to tolerate [e.g., experiences AEs during the product familiarization that will prevent the subjects from continuing to use the JUUL product as judged by the PI]) to any of the JUUL products at the Screening visit.
14. Is a self-reported puffer (i.e., adult smokers who draw smoke from the cigarette and/or e-cigarette into the mouth and throat but do not inhale; will be observable during CPS training).
15. Is planning to quit smoking during the study or postponing a quit attempt in order to participate in the study.
16. Unable to perform CPS and draw down the JUUL2 pod weight by 20-60 mg after 3 attempts at the Screening visit.
17. Is or has a first-degree relative (i.e., parent, sibling, child) who is a current employee of the study site, JUUL Labs, Inc. shareholder, or is a member of the board of directors of JUUL Labs, Inc.
18. Is or has a first-degree relative (i.e., parent, sibling, child) who is a litigant in a lawsuit against an ENDS manufacturer.
19. Has previously taken part in, has been excluded or withdrawn from, or has completed this study.
20. Has previously been diagnosed with any form of cancer, except for basal cell or squamous epithelial carcinomas of the skin that have been resected at least 1 year prior to Screening.
21. In the opinion of an Investigator, the subject should not participate in this study.
22. Enrollment in the study has been fulfilled.

Date of first enrolment
01/07/2024

Date of final enrolment
01/08/2024

Locations

Countries of recruitment
United States of America

Study participating centre

Rose Research Center
7240 ACC Boulevard
Raleigh
United States of America
27617

Sponsor information

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Sponsor type
Industry

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Funder(s)

Funder type
Industry

Funder Name
JUUL Labs, Inc

Results and Publications

Publication and dissemination plan
All unpublished information provided by the Sponsor shall not be published or disclosed to a third party without the prior written consent of the Sponsor.
The data generated by this study are considered confidential information and the property of the Sponsor. This confidential information may be published only in collaboration with participating personnel from the Sponsor or upon Sponsor’s written consent to publish the information.

Data arising from the study will be considered for dissemination at scientific conferences and in the peer-reviewed literature after completion of the study. No other documents will be available.

Intention to publish date
01/08/2025

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