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Study on nicotine uptake in smokers using electronic nicotine delivery systems compared to combustible cigarette

Submission date
12/06/2023

Recruitment status
No longer recruiting

Registration date
13/06/2023

Overall study status
Completed

Last Edited
12/08/2026

Condition category
Other

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

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 14% in the United States (US) (Wang, et al., 2018), 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 quit attempt 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/potentially harmful constituents (HPHCs) compared to combustible cigarettes.

The purpose of this study is to characterize the PK profile of plasma nicotine for a new, third generation JUUL Electronic Nicotine Delivery System (ENDS) Device, and two new flavour pods (JUUL2 Autumn Tobacco and Summer Menthol, both containing 18 mg/mL nicotine) compared to a commercially available NJOY Ace with a commercially available pod, and the subject's commercially available usual brand (UB) of combustible cigarette. Subjective effects will also be assessed to gain an understanding of nicotine withdrawal and dependence, satisfying and reinforcing effects.

Who can participate?
Adult, male and female smokers (who smoke at least 10 manufactured combustible cigarettes per day) between the ages of 21-65. 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 complete screening procedures including laboratory tests to ensure subject safety and eligibility. After successfully completing screening procedures, subjects will be checked into a clinic for 4 days/3 nights. Subjects will be trained on how to complete the subjective assessments and questionnaires. They will be allowed to smoke their usual brand cigarettes for a 4 hour period ad libitum, ending approximately 12 hours prior to study product use on Day 1. On Study Days 1-3, subjects will be given their assigned study product for two product use sessions each day. The study days include a controlled product use session (10 puffs, 3 seconds long, taken every 30 seconds), 4 hours of abstinence from nicotine, then a 5-minute ad libitum session with the same study product.Before, during, and after both product use sessions, blood samples will be collected at predetermined time points to assess plasma nicotine PK parameters (nicotine uptake), and subjects will complete subjective effects questionnaires at predetermined time points during each product use session (after collection of any coincident blood sample for nicotine analysis).Subjects will be discharged after study procedures on Day 3.A follow-up phone call with subjects will be made approximately 7 days after the subject's last study day. Subjects will have completed the study following the 7-day FU phone call.

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?
January 2023 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

Type(s)
Public

Contact name

Ms Sandra Miller

Contact details
1000 F Street NW, Suite 800
Washington DC
United States of America
20004
+1 8043500014
sandra.miller@juul.com

Additional identifiers

Protocol serial number
JLI-22-03

Study information

Scientific Title
A two-part, open label, randomized, controlled, crossover study to characterize nicotine pharmacokinetics of a new generation of JUUL Electronic Nicotine Delivery System (ENDS) device compared to a commercially available ENDS device and the subjects' usual brand of combustible cigarette

Acronym
JUUL2PK

Study objectives
The purpose of this study is to characterize the PK profile of plasma nicotine for a new, third generation JUUL Electronic Nicotine Delivery System (ENDS) Device, and two new flavour pods (JUUL2 Autumn Tobacco and Summer Menthol, both containing 18 mg/mL nicotine) compared to a commercially available NJOY Ace with a commercially available pod, and the subject's commercially available usual brand (UB) of combustible cigarette. Subjective effects will also be assessed to gain an understanding of nicotine withdrawal and dependence, satisfying and reinforcing effects.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 11/05/2023, Komisja Bioetyczna Okregowej Izby Lekarskief w Warszawie (Bioethical Commission of the District Medical Chamber in Warsaw) (Pulawska 18, Warszawa, 02-512, Poland; +48 22 54 28 312; j.puchala@oilwaw.org.pl), ref: Resolution 28/23

Primary study design
Interventional

Study design
Interventional open label randomized controlled crossover single center study

Study type(s)

Other

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

Interventions
Randomisation:
Forty-four participants, twenty-two in each Study Part (Part A is tobacco flavored products and Part B is menthol flavored products), 7 participants
in each of the 3 randomization sequences (ABC, CAB, or BCA) in each Study Part.
Subjects will be screened for participation up to 28 days before pre-randomization assessments on Check-in (Day -1). On Screening Day 2, following successful completion of all non-clinical laboratory testing screening procedures, subjects will be trained on the correct use of the JUUL2 devices and pods by way of a training video and be instructed on the use of NJOY Ace products per the manufacturer's directions. Trained subjects will have the opportunity to try a JUUL2 Device and Pod with 18 mg/mL nicotine and NJOY Ace product with 5% nicotine; subjects will be provided Tobacco or Menthol flavours depending upon the Study Part in which they potentially will be randomized. Subjects will be assessed on their ability to properly complete the controlled puffing sequence.
Once a subject fulfils the enrolment criteria including specific requirements on Day -1, they are eligible to be randomized into the study.
On study Days 1 through 3, subjects will first perform a controlled use session, followed by a 5-minute ad libitum use session, separated by at least 4 hours of nicotine product abstention. Blood will be drawn at set times to assess plasma nicotine levels and PK, and subjects will also complete subjective measures questionnaires during the controlled as well as the ad libitum sessions.

Part A
A. JUUL2 Device with Autumn Tobacco flavoured e-liquid at 18 mg/mL nicotine concentration JUUL2 pod
B. NJOY Ace Device with Classic Tobacco flavoured e-liquid at 5.0% nicotine concentration Ace pod
C. Subject's usual brand (UB) combustible cigarette

Part B
A. JUUL2 Device with Summer Menthol flavoured e-liquid at 18 mg/mL nicotine concentration JUUL2 pod
B. NJOY Ace Device with Menthol flavoured e-liquid at 5.0% nicotine concentration Ace pod
C. Subject's usual brand (UB) combustible cigarette

Methodology:
Subjects will be assigned to either Part A (tobacco flavor) or Part B (menthol flavor) and only participate in one Part of the study. Each day the subject will be provided with the assigned product for that day for their controlled and ad lib product use sessions. Blood samples will be taken throughout the product use sessions and subjective assessment questionairres will be taken throughout each day.

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 NJOY ACE product has 5.0% nicotine. Changes in JUUL2 Product pod weight will recorded, as well as the number of cigarettes smoked and the amount of JUUL2 and NJOY product is used (number of pods).

Frequency:
During the study product use sessions on each of the three study days, subjects will use a single study product according to the randomized product use sequence. No other use of tobacco or nicotine-containing products will be allowed before or during the testing sessions. The start and stop time of each
product use session will be documented. On each study day, subjects will complete the controlled use session, followed by at least a 4-hour nicotine abstention period, and then the 5-minute ad libitum use session using the same assigned study product.
For controlled puff sessions, blood samples for nicotine analysis will be collected approximately 5 minutes prior to initiation of the first product use (i.e., -5 minutes ± 2, the baseline sample) and approximately 1.5, 3, 5, 6, 7, 8, 10, 15, 30, 60, and 120 minutes after initiation of study product use.
For ad libitum sessions, blood samples for nicotine analysis will be collected approximately 5 minutes prior to initiation of the ad libitum session (i.e., -5 minutes ± 2, the baseline sample) and approximately 1.5, 3, 5, 6, 7, 8, 10, 15, 30, 60, and 120 minutes after initiation of the ad libitum session.
The mPES, Product-Liking, and Future Intent to Use the Product Questionnaires will be completed at approximately 30 minutes post start of each product use session (controlled and ad libitum use session, after collecting the 30-minute blood sample during both the controlled and ad libitum product use sessions).
The Urge to Smoke a Cigarette Questionnaire will be administered at 10 minutes prior to first puff, and at 5, 10, 15, 30, and 45 minutes relative to the first puff during each puffing session (controlled and ad libitum use session, after collecting any coincident blood sample during both the controlled and ad libitum product use sessions).
All pods (without cap) will be weighed before and after both the controlled and ad libitum sessions for each subject. The change in weight between these two measurements will be recorded.

Follow up:
Study site personnel will perform a followup telephone call at 7±2 days post study Day 3 (or early termination). During this call, the Principal Investigator (PI) or designee, will obtain information on any new or changes to Adverse Events (AEs) and new or changes to concomitant medications associated with an AE since the last site visit. If there are no AEs that require further attention, the subject's participation in the study will be complete.

Intervention Type
Other

Primary outcome(s)
Cmax-BL and AUC0-120-BL under controlled puffing conditions (i.e., 10 puffs of 3 seconds each, spaced 30 seconds apart) using blood samples for nicotine analysis collected approximately 5 minutes prior to initiation of the first product use (i.e., -5 minutes ± 2, the baseline sample) and approximately 1.5, 3, 5, 6, 7, 8, 10, 15, 30, 60, and 120 minutes after initiation of study product use

Key secondary outcome(s)

1. Nicotine pharmacokinetics (PK) during controlled and 5-minute ad libitum puffing conditions using blood samples for nicotine analysis collected approximately 5 minutes prior to initiation of the first product use (i.e., -5 minutes ± 2, the baseline sample) and approximately 1.5, 3, 5, 6, 7, 8, 10, 15, 30, 60, and 120 minutes after initiation of study product use
2. Subjective assessments:
2.1. Modified Product Evaluation Scale (mPES) completed at approximately 30 minutes post start of each product use session (controlled and ad libitum use session, after collecting the 30-minute blood sample during both the controlled and ad libitum product use sessions).
2.2. Product-Liking Questionnaire completed at approximately 30 minutes post start of each product use session (controlled and ad libitum use session, after collecting the 30-minute blood sample during both the controlled and ad libitum product use sessions).
2.3. Urge to Smoke a Cigarette Questionnaire administered at 10 minutes prior to first puff, and at 5, 10, 15, 30, and 45 minutes relative to the first puff during each puffing session (controlled and ad libitum use session, after collecting any coincident blood sample during both the controlled and ad libitum product use sessions).
2.4. Future Intent to Use the Product Questionnaire completed at approximately 30 minutes post start of each product use session (controlled and ad libitum use session, after collecting the 30-minute blood sample during both the controlled and ad libitum product use sessions).
3. Products use: changes in pod weights while using ENDS study products. All pods (without cap) will be weighed before and after both the controlled and ad libitum sessions for each subject. The change in weight between these two measurements will be recorded.
4. Puffing topography while using JUUL2 test products (collected by device).

Completion date
20/11/2023

Eligibility

Key inclusion criteria
1. Provides voluntary consent to participate in this study documented on the signed ICF(s).
2. Adult, male or female smoker, 21 to 65 years of age, inclusive, at the Screening visit.
3. Has been a smoker ≥ 12 months prior to Screening.
4. Currently smokes an average of ≥10 manufactured combustible CPD, as self-reported at Screening.
5. Has past 30-day history of some day or every day ENDS use.
6. Has a positive urine cotinine (≥200 ng/mL) at the Screening visit and Check-in.
7. Has an eCO ≥10 ppm at the Screening visit and Check-in.
8. Completes the screening process within 28 days prior to study Day -1.
9. Is willing 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.
10. A 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:
10.1. hormonal (e.g., oral, vaginal ring, transdermal patch, implant, or injection) consistently for at least 3 months prior to study Day 1;
10.2. double-barrier method (e.g., condom with spermicide, diaphragm with spermicide) from Day 1;
10.3. intrauterine device for at least 3 months prior to study Day 1;
10.4. abstinence beginning at least 6 months prior to Day 1;
10.5. a partner who has been vasectomized for at least 6 months prior to Day 1.

11. A female subject of non-childbearing potential must be postmenopausal with amenorrhea for at least 1 year prior to study Day 1 and FSH levels consistent with postmenopausal status or have undergone one of the following sterilization procedures at least 6 months prior to study Day 1:
11.1. hysteroscopic sterilization;
11.2. bilateral tubal ligation, occlusion, or bilateral salpingectomy;
11.3. hysterectomy;
11.4. bilateral oophorectomy.

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
21 Years

Upper age limit
65 Years

Sex
All

Total final enrolment
44

Key exclusion criteria
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. Has a clinically significant abnormal finding on the physical examination, medical history, vital signs, ECG, in the opinion of an Investigator and any abnormal findings in clinical laboratory results at the Screening visit.
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 positive test result for COVID-19.
5. Has a positive test result to HIV Ag/Ab combo, HBsAg or HCVAb.
6. Has a fever (>100.4°F [38oC]) at Screening visit or at Check-in.
7. Has a positive urine test result for alcohol or drugs of abuse, or positive alcohol breath test at the Screening visit or at Check-in. 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;
a. confirms the subject’s use of the prescribed medication, and b. the prescribed medication will cause a false positive drug test.
8. 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.
9. Has experienced an allergic reaction following previous e-cigarette use or with exposure to any primary components of the e-liquids (nicotine, flavour, benzoic acid, propylene glycol and glycerol).
10. Has participated in a previous clinical study for an investigational drug, device, biologic, or tobacco product within 30 days prior to Screening.
11. Has donated blood or blood products >500 mL, had significant blood loss, or received whole blood or a blood product transfusion within 3 months prior to Screening.
12. If female, the subject is pregnant, has a positive pregnancy test at the Screening visit or at Check-in, is lactating, breast feeding, or intends to become pregnant during the time period from Screening through EOS.
13. Has used medications known to interact with cytochrome P450 (CYP) 2A6 (including, but not limited to, amiodarone, amlodipine, amobarbital, buprenorphine, clofibrate, clotrimazole, desipramine, disulfiram, entacapone, fenofibrate, isoniazid, ketoconazole, letrozole, methimazole, methoxsalen, metyrapone, miconazole, modafinil, orphenadrine, pentobarbital, phenobarbital, pilocarpine, primidone, propoxyphene, quinidine,
rifampicin, rifampin, secobarbital, selegiline, sulconazole, tioconazole, tranylcypromine) within 14 days or 5 half-lives of the drug, whichever is longer, prior to study Day 1.
14. 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.
15. 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.
16. Requires concomitant treatment with prescription or non-prescription products that contain pseudoephedrine (e.g., nasal/sinus decongestants).
17. 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.
18. 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).
19. Is planning to quit smoking during the study or postponing a quit attempt in order to participate in the study.
20. Unable to perform CPS and draw down the JUUL2 pod weight by 20-60 mg after 3 attempts at the Screening visit.
21. Unwilling or unable to comply with study related procedures including but not limited to; schedule of assessment, PK draws and placement of indwelling catheter.
22. Is or has a first-degree relative (i.e., parent, sibling, child) who is a current employee of the study site or shareholder, or is a member of the board of directors of Juul Labs, Inc.
23. Is or has a first-degree relative (i.e., parent, sibling, child) who is a litigant in a lawsuit against an ENDS manufacturer.
24. Has previously taken part in, has been excluded or withdrawn from, or has completed this study.
25. 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.
26. In the opinion of an Investigator, the subject should not participate in this study.

Date of first enrolment
20/06/2023

Date of final enrolment
20/07/2023

Locations

Countries of recruitment
Poland

Study participating centre
BioResearch Group
Mokra 7 St
Kajetany
Nadarzyn
Poland
05-830

Sponsor information

Organisation
Juul Labs Inc.

Funder(s)

Funder type
Industry

Funder Name
Juul Labs Inc.

Results and Publications

Individual participant data (IPD) sharing plan

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		10/08/2026	12/08/2026	Yes	No