An Open-Label, Parallel Study to Assess Tobacco-Related Biomarkers of Exposure, Biomarkers of Potential Harm, and Nicotine Uptake During a 56-Day Switch to myblu™ e-Cigarettes in Adult Smokers

NCT# 04019626

Study Protocol – 24 March 2020

[redacted]

An Open-Label, Parallel Study to Assess Tobacco-Related Biomarkers of Exposure, Biomarkers of Potential Harm, and Nicotine Uptake During a 56-Day Switch to *my*blu™ e-Cigarettes in Adult Smokers

Sponsor Project No.: NER 01/001

[redacted] Project No.: CA22747

Final Protocol: 28JAN2019
Protocol Amendment 1: 23APR2019
Protocol Amendment 2: 17MAY2019
Protocol Amendment 3: 24MAR2020

GCP Statement

This study is to be performed in full compliance with the protocol, Good Clinical Practices (GCP), and applicable regulatory requirements. All required study documentation will be archived as required by regulatory authorities.

Confidentiality Statement

PROTOCOL REVISION HISTORY

DATE/NAME	DESCRIPTION
24MAR2020 [redacted]	Protocol Amendment 3 1) This protocol is amended to document the enrollment of additional subjects to the *my*blu™ arm (Arm A). Due to the long duration of the study, an additional 15 subjects was enrolled in Arm A (for a total of 175 subjects) to ensure at least 29 subjects complete each cohort. The following sections of the protocol were updated: • Synopsis, under Number of Subjects Planned • Section 3.1 Design and Procedures • Section 4.5 Subject Randomization and Product Assignments • Section 7.1 Sample Size Estimation 2) Flexible language was also added throughout the protocol to allow for selected procedures (e.g., 24-hour urine collection, completion of questionnaires) during Test Visit 3 (Days 28 and 29) and Test Visit 5 (Days 56 and 57) to be completed at home, as follows: • Study Events Flow Charts, footnote 14 was added to Table 2 Study Events for Baseline through Follow-up Periods – *my*blu™ and Continue-Smoking Arms • Section 6.1.2 Baseline and Product Use Period 1 • Section 6.1.3 Product Use Period 2 • Section 6.4.2 Urine • Section 6.6 Subjective Measures 3) The Sponsor project number was added to the title page of the protocol. 4) As there was a change in medical monitor as described in the protocol clarification letter dated 09Jan2020, the monitor's contact information is updated in the Study Contacts section accordingly. 5) Minor edits were made for consistency and typographical errors were corrected throughout the protocol.

DATE/NAME	DESCRIPTION
17MAY2019 [redacted]	Protocol Amendment 2 Protocol Amendment 2 is written to correct an error in one of the exclusion criteria, to note an increase in the volume of urine required for bio-banking, and to make a clarification regarding smoking history documentation as follows. • "FEV_1:FVC ratio < 0.75 and" has been removed from exclusion criterion 10 to be consistent with ATS guidelines regarding reversible airway disease (Pellegrino et al., 2005). • An edit has been made to Section 6.2.4 Smoking History and Usual Brand Combustible Cigarette Documentation to note that the average number of cigarettes smoked per day during the last year should be documented. • The volume of urine for bio-banking noted in Section 6.4.2 Urine has been increased from 4 aliquots of 5 mL each to 2 aliquots of 300 mL each, and storage of all urine aliquots will be at -20 ± 10°C until shipped for analysis.
23APR2019 Don Graff	Protocol Amendment 1 Protocol Amendment 1 is written primarily to clarify items and correct discrepancies noted in the previous version of the protocol as follows. • Trademark designations have been added to *my*blu™ and JUUL® throughout. • The selected biomarkers of exposure to be measured in the Day 3 to 4 24-hour urine collection have been specified in the Synopsis and Section 3.1 Design and Procedures (NNAL, NNN, 3-HPMA, CEMA, HMPMA, S-PMA, nicotine equivalents). In addition, Footnote 9 in Table 2 has been updated, changing "…primary BoE…" to "…selected BoE…" as NNN, CEMA, HMPMA, and nicotine equivalents are not primary biomarkers of exposure. • Footnote 12 in Table 2 has been updated to include the specific study days PK assessments will be conducted for the myblu™ and continue-smoking subjects.

DATE/NAME	DESCRIPTION
	• In Sections 4.3.1 Food, Beverage, and Activity and 6.8.1 Meals, eggplant and grilled meats have been added to the list of foods that subjects in the *my*blu™ and continue-smoking arms will be advised to avoid prior to Test Visits 1, 3, and 5, and that should not be served during confinement. • A clarifying phrase has been added to the first sentence in Section 5.6 Test Product Return/Destruction indicating that unused *my*blu™ and JUUL® products and components "remaining at the end of the study" will be returned or destroyed according to the Test Product Manual. • An omission has been corrected regarding collection of a blood samples for COHb in Table 5 (Day 4). Further, reference to this sample has been updated to "COHb" from "BoE" in Table 7 (Day 28) and Table 9 (Day 56) for clarity. • The "additional demographics documentation" event was removed from Table 7 (Day 28) to correct a discrepancy in the study day during which it is to be administered. • The requirement for high density polypropylene urine storage containers has been removed in Section 6.4.2 Urine. "HDPP" has also been removed from the abbreviations table. • The model for the device to be used for measurement of exhaled nitric oxide has been updated to the Niox Vero in Section 6.5.1 Fractional Concentration of Exhaled Nitric Oxide. • Deviation window definitions for the PK sample collections have been added to Section 6.7.2 Nicotine Pharmacokinetic Blood Sampling. • A statement has been added to section 6.7.2 Nicotine Pharmacokinetic Blood Sampling noting that additional blood may need to be collected at each sampling point for the purpose of clearing a blood collection device or line as necessary. • "o-tol" has been separated from "1-AN/2-AN" in the biomarker list in Section 6.4.2 Urine as these are measured in separate assays.

DATE/NAME	DESCRIPTION
	• The first criterion under the "*my*blu™ and continue-smoking arms" in Section 7.2.3 Per-Protocol Population has been made more specific and changed to "Have no protocol deviations significantly impacting the integrity of the analysis or interpretation of the individual endpoint under consideration (e.g., compromised urine samples, use of prohibited medications impacting the endpoint)". • Where not present previously, the specific test visits and study days during which the questionnaires are to be administered have been added to Appendices 3, 4, 5, 6, 7, 8, 9, and 10.
28JAN2019 [redacted]	Final Protocol

SPONSOR SIGNATURE PAGE

An Open-Label, Parallel Study to Assess Tobacco-Related Biomarkers of Exposure, Biomarkers of Potential Harm, and Nicotine Uptake During a 56-Day Switch to *my*blu™ e-Cigarettes in Adult Smokers

Sponsor Representative: [redacted]
Clinical Research Manager
Nerudia Ltd
[redacted]
E-mail: [redacted]

[redacted]
Signature

24 MAR 2020
Date

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

An Open-Label, Parallel Study to Assess Tobacco-Related Biomarkers of Exposure, Biomarkers of Potential Harm, and Nicotine Uptake During a 56-Day Switch to *my*blu™ e-Cigarettes in Adult Smokers

Principal Investigator:

Printed Name:

Site Name:
Address:

Tel.:
Fax:
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_____ _____
Signature Date

STUDY CONTACTS

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SYNOPSIS

Study Objectives	Primary: 1. To assess the change-from-baseline differences in the primary tobacco-related biomarkers of exposure (BoE) following a 28-day use period of *my*blu™ electronic cigarettes (e-cigarettes) relative to smoking usual brand combustible cigarettes. Secondary: 1. To assess the change-from-baseline differences in the primary tobacco-related BoE following a 56-day use period of *my*blu™ e-cigarettes relative to smoking usual brand combustible cigarettes. 2. To assess the change-from-baseline differences in the secondary tobacco-related BoE following 28-day and 56-day use periods of *my*blu™ e-cigarettes relative to smoking usual brand combustible cigarettes. 3. To characterize the change in the primary and secondary BoE and BoPH during a 56-day period of use of *my*blu™ e-cigarettes. 4. To assess the change-from-baseline differences in the primary and secondary tobacco-related BoE between Day 28 and Day 56 in subjects using *my*blu™ e-cigarettes. 5. To assess change-from-baseline differences in the biomarkers of potential harm (BoPH) following 28-day and 56-day use periods of *my*blu™ e-cigarettes relative to smoking usual brand combustible cigarettes. 6. To assess change-from-baseline differences in physiologic endpoints following 28-day and 56-day use periods of *my*blu™ e-cigarettes relative to smoking usual brand combustible cigarettes. 7. To assess elements of abuse liability, subjective effects, and perceptions associated with use of *my*blu™ e-cigarettes. 8. To characterize use of four *my*blu™ e-liquids (Tobacco Chill and Honeymoon flavor Intense e-liquids, 2.5% and 4.0% nicotine) during a 56-day use period. 9. To characterize nicotine uptake from the *my*blu™ e-cigarettes relative to an e-cigarette comparator (JUUL® Virginia Tobacco 5% nicotine) and usual brand combustible cigarettes. 10. To confirm the safety of *my*blu™ e-cigarettes during a 56-day use period.
Hypothesis	Switching from usual brand combustible cigarettes to a *my*blu™ e-cigarette will result in a significant decrease from baseline in the primary tobacco-related BoE following 28 days of use relative to the change associated with continuing to smoke combustible cigarettes. The hypothesis will be tested independently for each *my*blu™ e-liquid cohort.

Study Design	This will be an open-label, partially-randomized, parallel-arm, multi-site study in healthy adult smokers, consisting of two parts – the main study and a pharmacokinetics (PK) sub-study. The main study will assess BoE, BoPH, physiologic effects, and subjective effects with use of *my*blu™ e-cigarettes relative to continuing to smoke combustible cigarettes. Baseline study assessments will be made during use of subjects' usual brand combustible cigarettes during the initial test visit from Day -2 through the morning of Day 1 and post-baseline assessments will be made during a 56-day use of the assigned study products. Subjects randomized to the *my*blu™ arm will participate in a 3-day in-clinic product acclimation period from Day 1 through Day 3 to become familiar with the products and to choose a preferred e-liquid. The subset of subjects participating in the PK sub-study (described below) will also complete selected biomarker assessments on Days 3 and 4 (NNAL, NNN, 3-HPMA, CEMA, HMPMA, S-PMA, nicotine equivalents). All subjects in the *my*blu™ and continue-smoking arms will return to the clinic site for additional test visits scheduled to occur on Days 14, 28, 42, and 56 for study assessments, compliance checks, and product dispensing and return. The PK sub-study will characterize nicotine uptake from the *my*blu™ products relative to combustible cigarettes and an e-cigarette comparator (JUUL®). A subset of subjects assigned to each of the *my*blu™ e-liquids and the continue-smoking arm, and all subjects in the JUUL® arm, will participate in the PK sub-study. PK assessments in subjects assigned to an e-cigarette will be completed following an in-clinic period during which the subjects will become acclimated to use of the products. PK assessments will take place following a 10-hour abstention from all nicotine product use and will consist of controlled-use and *ad libitum* use sessions, with 180 minutes of blood sampling during each session. Urge to smoke will also be assessed during the *ad libitum* use sessions. Subjects in the JUUL® arm will only participate in the PK sub-study. The clinic staff will contact each subject via telephone approximately 14 days following discharge from the study (scheduled or early terminations) for reporting of adverse events (AEs) and use of concomitant medications.
Study Population	The study population will be comprised of healthy, adult male and female smokers, 21 to 65 years of age. Each subject must self-report smoking an average of 5 or more machine-manufactured combustible cigarettes per day (CPD) for at least 1 year. Smoking status will be confirmed during Screening using urine cotinine and exhaled carbon monoxide (CO) tests.
Duration of Study Conduct	Screening procedures will be performed within 28 days prior to check-in for Test Visit 1. The duration of the study from Screening through the Follow-up Period is approximately 14 weeks for subjects in the *my*blu™ and continue-smoking arms and up to 7 weeks for subjects in the JUUL® arm.
Study Products and Administration	**Test Products** *my*blu™ system with Tobacco Chill flavor Intense Liquidpod, 2.5% nicotine (Product A)

	*my*blu™ system with Tobacco Chill flavor Intense Liquidpod, 4.0% nicotine (Product B) *my*blu™ system with Honeymoon flavor Intense Liquidpod, 2.5% nicotine (Product C) *my*blu™ system with Honeymoon flavor Intense Liquidpod, 4.0% nicotine (Product D) **Control Product** Subject's usual brand combustible cigarette (Product E) **Comparator Product** JUUL® system with Virginia Tobacco JUULpod, 5.0% nicotine (Product F) All subjects in the *my*blu™ and continue-smoking arms will smoke their usual brand combustible cigarettes through the evening of Day -1. Subjects randomized to the *my*blu™ arm will participate in an in-clinic product acclimation period from Day 1 through Day 3. The acclimation period will afford the subjects the opportunity to try each of the four *my*blu™ e-liquids in order to become accustomed to their use and to determine those that they would be willing to use during the study. Initial product assignment for each subject will be based on preference to enhance compliance. To further improve compliance through Day 56, at the end of Test Visit 3, subjects using a *my*blu™ product may be allowed to choose to switch to the alternate nicotine strength of their current flavor, to switch to the alternate flavor with the same nicotine strength as their initial choice, or to continue using the same e-liquid selected initially. This method for initial flavor assignment and the opportunity to re-select after 28 days of use is based on natural experimentation that consumers experience when choosing an e-cigarette flavor and nicotine strength. Subjects randomized to the continue-smoking arm will smoke their usual brand cigarette for the duration of the study. Subjects in the JUUL® arm will begin using the assigned product after check-in for Test Visit 1 and will continue to use the product through discharge from the study on Day 1. Subjects in the JUUL® arm will not be allowed to use combustible cigarettes from the time of check-in through discharge. Product use for the PK assessments will consist of two sessions: 1) a fixed puffing session in the morning consisting of 10 puffs taken at 30-second intervals, with puffs 3 seconds in duration, and 2) an *ad libitum* use session beginning 6 hours after the start of the morning session and consisting of unlimited use of the e-cigarette product for 5 minutes or one cigarette, with no limits on puff duration or inter-puff interval. All product use during confinement will be documented by the clinic staff. Subjects in the *my*blu™ and continue-smoking arms will be required to self-report product use from Day 3 through discharge from the study on Day 57.

Number of Subjects Planned	For the main study, a sufficient number of subjects are to be screened and randomized to better ensure that at least 29 subjects assigned to each of the *my*blu™ e-liquids and to the continue-smoking arm complete the Day 28 study assessments. To account for potential attrition, up to 175 subjects are planned to be randomized into the *my*blu™ arm (with approximately 43 subjects intended to be initially assigned to each *my*blu™ e-liquid) and up to 40 subjects will be randomized into the continue-smoking arm. For the PK sub-study, up to 20 subjects assigned to each *my*blu™ e-liquid, 20 subjects randomized to the continue-smoking arm, and all 20 subjects in the JUUL® arm will be selected to participate. In total, up to 235 subjects are intended to be randomized into the study.
Subject Randomization	Each subject will be assigned to a study arm (*my*blu™, continue-smoking, or JUUL®) according to the randomization plan. The study arms will be stratified by sex (male or female) and age class (≤ 40 years of age, > 40 years of age). Each sex and age class should not account for more than 65% of the randomized population in each arm, and Caucasians should not comprise more than 80% of the randomized population in each arm. Assignment of subjects to a specific *my*blu™ product will be made based on subject product preference. As no consumer preference data is available to predict potential product selection among the sex and age categories, every effort will be made to assign subjects to a preferred product while attempting to reach the stratification limits noted above. An attempt will also be made to apply the sex and age class stratification to each product in the PK sub-study, though the same potential challenges will apply. For logistical and operational reasons, the first subject in each sex-age class stratum who successfully completes the screening procedures at each site may be assigned to the JUUL® arm.
Study Endpoints	**<u>Primary Study Endpoints</u>** **Biomarkers of Exposure** **Biomarker** / **Matrix** / **Chemical Constituent** Carboxyhemoglobin (COHb) / Blood / Carbon monoxide (CO) 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) / Urine / 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) 3-hydroxypropylmercapturic acid (3-HPMA) / Urine / Acrolein S-phenyl mercapturic acid (S-PMA) / Urine / Benzene

Secondary Study Endpoints

Biomarkers of Exposure

Biomarker	Matrix	Chemical Constituent
N-nitrosonornicotine (NNN)	Urine	NNN
2-cyanoethyl-mercapturic acid (CEMA)	Urine	Acrylonitrile
Hydroxyethyl mercapturic acid (HEMA)	Urine	Ethylene oxide
3-hydroxy-1-methylpropylmercapturic acid (HMPMA)	Urine	Crotonaldehyde
Monohydroxybutenylmercapturic acid (MHBMA)	Urine	1,3-butadiene
Hydroxypyrene (1-OHP)	Urine	Pyrene
o-toluidine (o-tol)	Urine	Toluidine
3-hydroxybenzo[a]pyrene (3-OH B[a]P)	Urine	B[a]P
1-aminonaphthalene (1-AN)	Urine	Naphthalene
2-aminonaphthalene (2-AN)	Urine	Naphthalene
Nicotine equivalents	Urine	Nicotine

Biomarkers of Potential Harm

Biomarker	Matrix	Biological Effect
Soluble intracellular adhesion molecule (sICAM)	Blood	Inflammation
White blood cells (WBCs)	Blood	Inflammation
High density lipoprotein cholesterol (HDL-C)	Blood	Inflammation
Monocyte chemoattractant protein 1 (MCP-1)	Blood	Inflammation
Type III isoprostane (8-epi-prostaglandin $F_{2\alpha}$)	Urine	Oxidative stress
11-dehydrothromboxane B_2	Urine	Platelet activation

Physiological assessments

- Fractional concentration of exhaled nitric oxide (FeNO)
- Blood pressure
- Heart rate

Subjective measures

- Penn State [Electronic] Cigarette Dependence Index (PSCDI, PSECDI)
- Cough Questionnaire
- Questionnaire of Smoking Urges-Brief (QSU-Brief)
- Minnesota Tobacco Withdrawal Scale-Revised (MTWS-R)
- Product Evaluation Scale (PES)

	• Product Liking Questionnaire • Future Intent to Use Questionnaire • Product and Health Effect Perceptions Questionnaire **Product Use** Daily in-clinic product use documented by the clinic staff: • Number of cigarettes smoked • Number of *my*blu™ and JUUL® pods started • *my*blu™ pod weight change (for pods used during the 24 hour urine collections) • Day 3 and Day 29 product preference selection Daily product use endpoints documented by subjects (Day 3 through study discharge on Day 57): • Number of cigarettes smoked • Number of *my*blu™ pods started • Number of puffs from the *my*blu™ product daily (< or ≥ 50 puffs) **Nicotine Pharmacokinetics Assessment** Product use during each product use session: • Number of puffs taken • *my*blu™ and JUUL® pod weight change PK parameters during each product use session: • C_{max} • AUC_{0-t} • T_{max} Urge to smoke parameters during the *ad libitum* product use session: • Maximum reduction from baseline score (E_{max_R}) • Time of the E_{max_R} (TE_{max}) • Area under the change from baseline "Urge to Smoke" visual analog scale (VAS) score versus time curve ($AUEC_{BL}$)
Other Compliance Assessments	Exhaled CO and urine cotinine measurements will be used to confirm smoking/nicotine use status prior to Day 1 and to assess subject compliance with product assignment requirements thereafter.
Statistical Analysis	Comparisons of the Day 28 visit primary BoE change-from-baseline values between the continue-smoking arm and each *my*blu™ e-liquid product selected at Day 2 will be made using a linear mixed model analysis of variance (ANOVA). The intent-to-treat (ITT) population will be used as the primary analysis population and an analysis using the per-protocol (PP) population will be used as a supportive analysis. An approach similar to that used for the primary endpoints will be used to make Day 28 and Day 56 change-from-baseline comparisons for the applicable secondary endpoints. For the Day 56 analysis, the initial *my*blu™ e-liquid cohort assignments for each subject will be maintained within the statistical model and a separate sensitivity analysis will be performed for subjects that do not switch flavors at Day 29.

	Comparisons of the primary and secondary BoE change-from-baseline values at each time point within and between the four *my*blu™ e-liquid flavor product cohorts will also be made using a linear mixed model ANOVA. A linear mixed model ANOVA will be performed on the log-transformed nicotine AUC and C_{max} PK parameters from each product use session. Non-parametric analysis (Wilcoxon Signed Rank test) will be performed for the comparisons of Tmax. Similar models will be used to compare the urge to smoke parameters. The comparisons of interest will include each of the *my*blu™ products compared to the usual brand cigarette and JUUL® product.
Safety Assessments	Screening safety evaluations will include a physical examination, vital signs, electrocardiogram (ECG), clinical laboratory tests (clinical chemistry, hematology, urinalysis, and serology), lung function, follicle-stimulating hormone (FSH) test (post-menopausal females), and serum and urine pregnancy tests (females only). On-study evaluations will include a symptom-driven physical examination, vital signs, ECG, clinical laboratory tests (clinical chemistry, hematology, and urinalysis), lung function, and urine pregnancy tests (females only). AEs spontaneously reported by the subjects or observed by the Investigator or other study personnel will be documented and monitored from the time of first product use after successful completion of the check-in events for Test Visit 1 through the end of the Follow-up Period. Any prior and concomitant medications taken from 30 days prior to Screening through the Follow-up Period will also be recorded.

STUDY EVENTS FLOW CHARTS

Table 1 Screening Procedures

EVENTS/ASSESSMENTS	Screening [1]
Informed Consent	X
Review of Inclusion/Exclusion Criteria	X
Medical History	X
Screening Demographics	X
Prior and Concomitant Medication Reporting	X
Smoking History and Usual Brand Combustible Cigarette Documentation	X
Tobacco/Nicotine Use History Questionnaire	X
Physical Examination	X
Body Weight, Height, and BMI	X
Clinical Chemistry, Hematology, Urinalysis	X
HIV, HBsAg, and HCV Serology Screen	X
Urine Drug Test	X
Alcohol Breath Test	X
Urine Cotinine Test	X
FSH Test (post-menopausal females)	X
Serum Pregnancy Test (females)	X
Exhaled CO	X
Vital Signs	X
12-lead ECG	X
Spirometry	X
Review of Tobacco and Nicotine Restrictions	X
Provide Smoking Cessation Information	X

[1] All subjects will complete screening procedures within 28 days of check-in for Test Visit 1.

Abbreviations: BMI = Body mass index, CO = Carbon monoxide, ECG = Electrocardiogram, FSH = follicle stimulating hormone, HBsAg = Hepatitis B surface antigen, HCV = Hepatitis C virus, HIV = Human immunodeficiency virus.

Table 2 Study Events for Baseline through Follow-up Periods – *my*blu™ and Continue-Smoking Arms

Period	Baseline		Product Use Period 1											Product Use Period 2					Follow-up
Test Visit			1							2		3			4		5		
Study Day	-2	-1	1	2	3	4	5	Test Visit 1 Discharge Events [1]	5-13	14 (± 2)	15-27	28 (± 2)	29	30-41	42 (± 2)	43-55	56 (± 2)	57	Study Discharge + 14 days (± 2)
EVENTS/ASSESSMENTS																			
Confinement	X	X	X	X	X	X	X					X [14]	X [14]				X [14]	X [14]	
Ambulatory Visit										X					X				
Review of Applicable Inclusion/Exclusion Criteria	X																		
Reminder Telephone Calls [2]	X									X		X			X		X		
Additional Demographics Documentation	X																		
Usual Brand Combustible Cigarette Documentation	X [3]									X		X			X		X		
Tobacco/Nicotine Use History Questionnaire	X [3]																		
Review of Tobacco and Nicotine Restrictions	X							X		X		X			X		X		
Provided Smoking Cessation Information																		X [4]	
Safety and Compliance Events																			
Medical History	X [3]																		
Concomitant Medication Reporting	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [4]	X
Symptom-Driven Physical Examination	X							X				X	X				X	X [4]	
Body Weight	X											X					X [4]		
Urinalysis	X											X					X [4]		
Clinical Chemistry and Hematology		X											X					X [4]	
Urine Cotinine Test	X									X		X			X		X		

Period	Baseline		Product Use Period 1											Product Use Period 2					Follow-up
Test Visit			1							2		3			4		5		
Study Day **EVENTS/ASSESSMENTS**	-2	-1	1	2	3	4	5	Test Visit 1 Discharge Events [1]	5-13	14 (± 2)	15-27	28 (± 2)	29	30-41	42 (± 2)	43-55	56 (± 2)	57	Study Discharge + 14 days (± 2)
Urine Drug Test	X																		
Alcohol Breath Test	X																		
Urine Pregnancy Test (females)	X									X		X			X		X		
Exhaled CO	X							X [5]		X		X			X		X		
Spirometry																		X	
Vital Signs	X							X				X	X				X	X [4]	
12-lead ECG																		X [4]	
AE Reporting	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [4]	X
Product Use Documentation and Assessments																			
Product Use [6]	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	
Test Product Demonstration and Training (*my*blu™ arm)			X																
Test Product Dispensing for Ambulatory Use (*my*blu™ arm)								X		X		X			X				
Test Product Collection from Ambulatory Use (*my*blu™ arm)										X			X		X		X [4]		
Test Product(s) Preference Selection (*my*blu™ arm)				X									X						
*my*blu™ Pod Weight Documentation [7]					X	X						X	X				X	X	
In-clinic Product Use Documentation	X	X	X	X	X							X	X				X	X	
Subject Product Use Reporting [8]					X	X	X		X	X	X	X	X	X	X	X	X	X	
Product Use Reporting Confirmation					X					X		X			X		X		

Period	Baseline		Product Use Period 1											Product Use Period 2					Follow-up
Test Visit	1								2		3			4			5		
Study Day **EVENTS/ASSESSMENTS**	-2	-1	1	2	3	4	5	Test Visit 1 Discharge Events [1]	5-13	14 (± 2)	15-27	28 (± 2)	29	30-41	42 (± 2)	43-55	56 (± 2)	57	Study Discharge + 14 days (± 2)
Biomarker Assessments																			
24-hour urine Collection for BoE, BoPH, and bio-banking	X	X			X [9]	X [9]						X	X				X	X	
Blood Collection for BoE	X					X [9]						X					X		
Blood Collection for BoPH and bio-banking		X											X					X	
Subjective Measures Assessments																			
PSCDI/PSECDI	X											X					X		
Cough Questionnaire	X											X					X		
QSU-Brief	X				X							X					X		
MTWS-R	X				X							X					X		
PES	X				X							X					X		
Product Liking Questionnaire	X				X							X					X		
Future Intent to Use Questionnaire	X											X					X		
Product and Health Effects Perceptions Questionnaire	X											X					X		
Physiologic Endpoint Assessments																			
FeNO		X											X					X	
Nicotine PK Assessments [10]																			
Product Use [11]			X				X												
Pod Weight Documentation [7]							X												
Blood Sampling [12]			X				X												
Urge to Smoke Assessments [13]			X				X												

[1] Discharge from Test Visit 1 will be as follows. Day -1: Subjects in the continue-smoking arm who do not participate in the PK. Day 1: Subjects in the continue-smoking arm who participate in the PK assessment. Day 3: Subjects in the *my*blu™ arm who do not participate in the PK assessment. Day 5: Subjects in the *my*blu™ arm participating in the PK assessment.

[2] The clinic staff will make a telephone call within 24 - 48 hours prior to the scheduled visits to remind subjects of the date and time of the upcoming Test Visits.

[3] Updated as necessary.

[4] Study discharge/early termination events.

[5] *my*blu™ arm only.

[6] All subjects will smoke their usual brand combustible cigarettes prior to Day 1 and will use study product according to the randomization from Day 1 through discharge from the study.

[7] Pods used during the 24-hour urine collections and PK sessions will be weighed prior to and following use.

[8] Subjects will be trained on use of the ambulatory product use reporting system.

[9] Collections for selected BoE, nicotine equivalents, and questionnaires for *my*blu™ subjects who participate in the PK sub-study.

[10] Continue-smoking arm on Day 1, *my*blu™ arm on Day 5.

[11] Two product use sessions: fixed puffing regimen in the morning and an ad libitum regimen in the afternoon.

[12] Blood samples for nicotine concentration measurement will take place approximately 5 minutes prior to and at 3, 5, 7, 10, 12, 15, 20, 30, 60, 120 and 180 minutes following the start of each product use episode (Day 1 continue-smoking, Day 5 *my*blu™).

[13] Urge to smoke assessments will take place approximately 10 minutes prior to and within approximately 30 seconds prior to the scheduled blood draws at 5, 10, 15, 30, 60, and 120 minutes following the start of the *ad libitum* product use sessions.

[14] At the discretion of the site, Test Visit 3 and Test Visit 5 may be ambulatory and subjects may complete selected procedures at home (e.g., 24-hour urine collection, completion of questionnaires). Subjects will be provided the materials required to complete the selected procedures and will be instructed on at-home procedures (e.g., urine collection method, questionnaires).

Abbreviations: AE = Adverse event, BoE = Biomarker of exposure, BoPH = Biomarker of potential harm, CO = Carbon monoxide, ECG = Electrocardiogram, FeNO = Fractional concentration of exhaled nitric oxide, MTWS-R = Minnesota Nicotine Withdrawal Scale-Revised, PES = Product Evaluation Scale, PSCDI = Penn State Cigarette Dependence Index, PSECDI = Penn State Electronic Cigarette Dependence Index, QSU-Brief = Questionnaire of Smoking Urges-Brief.

Table 3 Study Events for Baseline through Follow-up Periods – JUUL® Arm

Study Day EVENTS/ASSESSMENTS	-2 [1]	-1	1	15 (± 2)
Confinement	X	X	X	
Review of Applicable Inclusion/Exclusion Criteria	X			
Reminder Telephone Calls [2]	X			
Additional Demographics Documentation	X			
Usual Brand Combustible Cigarette Documentation	X [3]			
Tobacco/Nicotine Use History Questionnaire	X [3]			
Provide Smoking Cessation Information			X [4]	
Safety and Compliance Events				
Medical History	X [3]			
Concomitant Medication Reporting	X	X	X [4]	X
Symptom-driven Physical Examination	X		X [4]	
Body Weight	X			
Urinalysis	X			
Clinical Chemistry and Hematology	X			
Urine Cotinine Test	X			
Urine Drug Test	X			
Alcohol Breath Test	X			
Urine Pregnancy Test (females)	X			
Exhaled CO	X			
Vital Signs	X		X [4]	
12-lead ECG			X [4]	
AE Reporting	X	X	X [4]	X
Product Use Documentation and Assessments				
Review of Tobacco and Nicotine Restrictions	X			
Test Product Demonstration	X			
Product Use [5]	X	X		
Nicotine PK Assessments				
Product Use [6]			X	
Pod Weight Documentation [7]			X	
Blood Sampling [8]			X	
Urge to Smoke Assessment [9]			X	

[1] Subjects should check-in to the clinic as early as possible on Day -2.

[2] The clinic staff will make a telephone call within 24 - 48 hours prior to the scheduled visits to remind subjects of the date and time of the upcoming Test Visit.

[3] Updated as necessary.

[4] Or upon early termination.

[5] All subjects will use the assigned study product from completion of check-in events through discharge from the study.

[6] Two product use sessions: fixed puffing regimen in the morning and an ad libitum regimen in the afternoon.

[7] Pods will be weighed prior to and following use.

[8] Blood samples for nicotine concentration measurement will take place approximately 5 minutes prior to and at 3, 5, 7, 10, 12, 15, 20, 30, 60, 120 and 180 minutes following the start of each product use episode.

[9] Urge to smoke assessments will take place approximately 10 minutes prior to and within 30 seconds prior to the scheduled blood draws at 5, 10, 15, 30, 60, and 120 minutes following the start of the *ad libitum* product use sessions.

Abbreviations: AE = Adverse event, CO = Carbon monoxide, ECG = Electrocardiogram, PK = Pharmacokinetic.

ABBREVIATIONS

PK and other endpoint parameter descriptions are listed in the Sections 7.4.5 and 7.4.6.

1-AN	1-aminonaphthalene
1-OHP	1-hydroxypyrene
2-AN	2-aminonaphthalene
3-HPMA	3-hydroxypropylmercapturic acid
3-OH B[a]P	3-hydroxybenzo[a]pyrene
AE	Adverse event
ANOVA	Analysis of variance
AUC	Area under the curve
BoE	Biomarker(s) of exposure
BoPH	Biomarker(s) of potential harm
BMI	Body mass index
°C	Degree Celsius
CDMS	Clinical Data Management System
CEMA	2-cyanoethyl-mercapturic acid
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CO	Carbon monoxide
COHb	Carboxyhemoglobin
CPD	Cigarettes per day
CYP	Cytochrome P450
DMP	Data Management Plan
ECG	Electrocardiogram
eCRF	Electronic case report form
e-cigarette	Electronic cigarette
°F	Degree Fahrenheit
FDA	Food and Drug Administration
FEF	Forced expiratory flow
FeNO	Fractional concentration of exhaled nitric oxide

FEV_1	Forced expiratory volume in 1 second
FSH	Follicle stimulating hormone
FVC	Forced vital capacity
GCP	Good Clinical Practice
HbsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HEMA	Hydroxyethyl mercapturic acid
HDL-C	High density lipoprotein - cholesterol
HIV	Human immunodeficiency virus
HMPMA	3-hydroxy-1-methylpropylmercapturic acid
ICF	Informed consent form
ICH	International Council for Harmonisation
IRB	Institutional Review Board
ITT	Intent-to-treat
MCP-1	Monocyte chemoattractant protein 1
MedDRA	Medical Dictionary for Regulatory Activities
MHBMA	Monohydroxybutenylmercapturic acid
MTWS-R	Minnesota Tobacco Withdrawal Scale - Revised
n	Sample size
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
NNK	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
NNN	N-nitrosonornicotine
o-tol	o-toluidine
PES	Product Evaluation Scale
PK	Pharmacokinetic(s)
PP	Per-protocol
PSCDI	Penn State Cigarette Dependence Index
PSECDI	Penn State Electronic Cigarette Dependence Index
QTcB	QT interval corrected for heart rate using Bazett's formula
QSU-Brief	Questionnaire of Smoking Urges – Brief
SAE	Serious adverse event
SAP	Statistical analysis plan

SD	Standard deviation
SEM	Standard error of the mean
sICAM	Soluble intracellular adhesion molecule
SOP	Standard operating procedure
S-PMA	S-phenyl mercapturic acid
US	United States of America
VAS	Visual analog scale
WBC	White blood cell

DEFINITION OF TERMS

Concomitant medication	Concomitant medication refers to all medication taken during the study conduct period from Screening through the Follow-up Period. Medications started prior to Screening but which the subject continues to take during the study, are considered to be concomitant medications.
*my*blu™ Cohorts	Each of the four *my*blu™ e-liquid cohorts will be comprised of a subset of subjects randomized to the *my*blu™ arm who are assigned to receive one of the four *my*blu™ e-liquids based on subject product preference.
Product Use Period 1	The period of time from first use of study product on Day 1 through the end of Test Visit 3 (*my*blu™ and continue-smoking arms).
Product Use Period 2	The period of time from the end of Test Visit 3 through the end of Test Visit 5 (*my*blu™ and continue-smoking arms).
Randomization	Assignment of subjects to a product use arm. The randomization arms will include: *my*blu™, continue-smoking, and JUUL®.
Screening	Screening is defined as the period during which subjects must satisfy criteria for entry into the study (i.e., through completion of Test Visit 1 check-in events).
Screen failure	Any subject who initiates screening events but does not meet the study entry criteria will be considered a screening failure.
Sponsor	'Sponsor' refers to Nerudia Ltd.
Study Arms	Refers to the subjects randomized to receive a *my*blu™ product, to continue smoking their usual brand cigarette, or assigned to the JUUL® product
Subject	'Subject' refers to an individual who participates in the clinical study.

TABLE OF CONTENTS

List of Tables

1. INTRODUCTION AND BACKGROUND

1.1 Background

E-cigarettes have become a popular alternative to cigarette smoking globally and are garnering significant attention as potentially reduced exposure products and smoking cessation products. E-cigarettes consist of a battery, heating component, and a reservoir (often referred to as a pod, cartridge, or tank) containing tobacco-derived nicotine in a solution composed of glycerin and/or propylene glycol and flavorings. Upon activation, the heating element heats the solution and the consumer inhales the resulting vapor.

Because e-cigarette use does not involve the combustion of tobacco, it is expected that e-cigarette consumers will experience reduced exposure to most biomarkers of tobacco exposure compared to combustible cigarettes. Previous studies have shown that switching from combustible cigarettes to e-cigarettes with high rates of compliance results in large reductions in a number of cigarette smoke toxicants (Cravo et al. 2016, Goniewicz et al. 2017, O'Connell et al. 2016, McRobbie et al. 2015, Hecht et al. 2015). This study will evaluate a number of urine and blood biomarkers commonly associated with tobacco exposure during a 56-day period of use of the *my*blu™ e-cigarette system. Subjects randomized to the *my*blu™ study arm will be allowed to choose from one of four e-liquids (Tobacco Chill or Honeymoon flavor Intense e-liquids, containing either 2.5% or 4.0% nicotine) rather than be randomized to a particular flavor that they may not prefer to better represent the flavor selection that e-cigarette consumers experience while choosing a product in real-life situations. In addition, several BoPH, physiological assessments related to cigarette smoking health outcomes, subjective effects, and nicotine uptake will also be assessed.

1.2 *my*blu™ Previous Clinical Experience

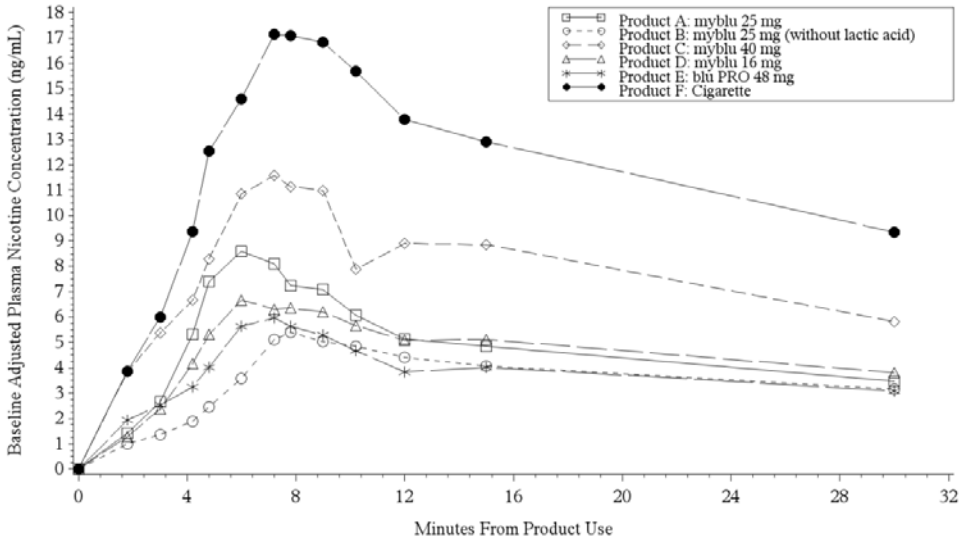
One previous clinical study has been conducted with the *my*blu™ closed system (FON-01blu-2018). Fifteen healthy adult smokers enrolled in an open-label, 6-period crossover study to characterize nicotine uptake and subjective effects during a 10-puff controlled exposure (puffs 3 seconds in duration, taken at approximately 30-second intervals) relative to usual brand combustible cigarettes and the blu PRO open system product and to determine the potential impact of a nicotine salt e-liquid (with lactic acid).

Blood samples for plasma nicotine analysis were collected approximately 5 minutes prior to and at 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, and 30 minutes following the start of product use. The subjective effects questionnaires were completed at approximately 20 minutes following the start of each product use and included 6 questions presented on a scale of 1 (not at all) to 7 (extremely).

Nicotine AUC_{0-30} and C_{max} increased with increasing nicotine content in the *my*blu™ products (16 – 40 mg nicotine), and was higher in the 25 mg nicotine salt formulation compared to the non-salt formulation. The time to reach maximal plasma nicotine concentrations (T_{max}) ranged from approximately 6.0 – 7.9 minutes following use of *my*blu™ and blu PRO products with nicotine salts and approximately 8.0 minutes following use of *my*blu™ non-salt formulation. AUC_{0-30} and C_{max} to nicotine were lowest following use of blu

PRO compared to all other products tested. Overall exposure over 30 minutes (AUC_{0-30}) and peak exposure (C_{max}) to nicotine was highest following use of cigarette compared to any other product tested. The time to reach peak exposure (T_{max}) was shorter following use of the five e-cigarette test products compared to the cigarette.

Arithmetic Mean Baseline Adjusted Plasma Nicotine Concentration-Time Profiles Following Fixed Product Use by Product (Linear Scale)



Summary of Baseline Adjusted Plasma Nicotine Pharmacokinetics by Study Product

Parameter	Product A: *my*blu™ 25 mg	Product B: *my*blu™ 25 mg (free-base)	Product C: *my*blu™ 40 mg	Product D: *my*blu™ 16 mg	Product E: blu PRO 48 mg	Product F: Cigarette
AUC_{0-30} (ng*min/mL)	125.2 (53.4) [n=13]	98.99 (35.8) [n=14]	190.7 (71.8) [n=15]	118.5 (60.8) [n=15]	84.84 (89.8) [n=14]	324.9 (35.8) [n=15]
C_{max} (ng/mL)	7.576 (80.6) [n=13]	5.048 (49.9) [n=14]	10.27 (83.6) [n=15]	6.510 (76.5) [n=15]	4.845 (108.3) [n=14]	17.81 (49.6) [n=15]
T_{max} (min)	6.033 (4.58, 16.77) [n=13]	8.034 (2.28, 15.10) [n=14]	7.900 (1.97, 15.00) [n=15]	6.967 (3.98, 15.05) [n=15]	6.908 (2.35, 15.03) [n=14]	8.050 (5.00, 15.13) [n=15]

AUC and C_{max} are presented as geometric mean and geometric coefficient of variability %, T_{max} values are presented as median (min, max).
n: number of observations included in the summary statistics

Product A: *my*blu™ closed system with CF Cosmic Fog Chilled Tobacco flavor, nicotine salt liquid 25 mg
Product B: *my*blu™ closed system with CF Cosmic Fog Chilled Tobacco flavor, non-nicotine salt liquid 25 mg
Product C: *my*blu™ closed system with CF Cosmic Fog Chilled Tobacco flavor, nicotine salt liquid 40 mg
Product D: *my*blu™ closed system with CF Cosmic Fog Chilled Tobacco flavor, nicotine salt liquid 16 mg
Product E: blu PRO open system with Purilum Cosmic Fog Chilled Tobacco flavor, nicotine salt liquid 48 mg
Product F: Subject's usual brand combustible cigarette

Mean scores for the subjective effects assessments tended to be highest after combustible cigarette use and generally followed by *my*blu™ 40 mg. With the exception of the questions "was it enough nicotine?" and "was it too much nicotine?", the responses following use of the 25 mg salt formulation were comparable to the 25 mg non-salt formulation.

Summary of Subjective Effects Score by Study Product (Safety Population)

Questions	Study Products					
	A	B	C	D	E	F
	n =13	n =14	n =15	n =15	n =14	n =15
Did it make you dizzy?	2.1 ± 1.32	1.9 ± 1.73	2.8 ± 1.78	1.5 ± 0.74	1.7 ± 0.99	3.7 ± 1.80
Did it make you nauseous?	1.2 ± 0.44	1.3 ± 0.83	1.4 ± 0.91	1.1 ± 0.26	1.4 ± 0.84	1.9 ± 1.44
Did you enjoy it?	3.5 ± 1.98	3.5 ± 1.87	4.0 ± 1.36	3.5 ± 1.46	3.2 ± 1.81	4.9 ± 1.44
Did it relieve the urge to smoke?	3.5 ± 1.98	3.6 ± 2.10	4.1 ± 1.79	3.3 ± 1.91	3.1 ± 2.11	5.5 ± 1.60
Was it enough nicotine?	3.1 ± 1.93	4.0 ± 1.96	4.3 ± 1.79	3.3 ± 1.99	3.2 ± 2.08	5.4 ± 1.55
Was it too much nicotine?	1.5 ± 0.97	2.5 ± 2.21	2.2 ± 1.66	1.7 ± 1.11	1.4 ± 0.63	2.4 ± 1.55

Scoring: 1 – Not at all, 2 – Very little, 3 – A little, 4 – Moderately, 5 – A lot, 6 – Quite a lot, 7 – Extremely.
Scores are presented as mean ± SD.
n = Number of subjects used in the analysis

Product A: *my*blu™ closed system with CF Cosmic Fog Chilled Tobacco flavor, nicotine salt liquid 25 mg
Product B: *my*blu™ closed system with CF Cosmic Fog Chilled Tobacco flavor, non-nicotine salt liquid 25 mg
Product C: *my*blu™ closed system with CF Cosmic Fog Chilled Tobacco flavor, nicotine salt liquid 40 mg
Product D: *my*blu™ closed system with CF Cosmic Fog Chilled Tobacco flavor, nicotine salt liquid 16 mg
Product E: blu PRO open system with Purilum Cosmic Fog Chilled Tobacco flavor, nicotine salt liquid 48 mg
Product F: Subject's usual brand combustible cigarette

Overall, the study products were well-tolerated under the conditions of use in the study. There were no serious adverse events (SAEs) reported in the study, and no subjects were discontinued due to AEs. Product use emergent AEs were infrequently reported with four subjects reporting a total of 10 AEs. Vessel puncture site pain was the most frequently reported AE, experienced by two subjects. All remaining AEs were experienced by one subject each. All AEs were mild in severity, with the exception of moderate insomnia (blu PRO 48 mg). The PI considered one AE of headache (*my*blu™ 25 mg [non-salt formulation]) to be possibly related to study product and the remaining nine events unlikely or unrelated.

1.3 Rationale for the Study

This study is being conducted to provide information on the *my*blu™ e-cigarette system with Tobacco Chill and Honeymoon flavor Intense e-liquids, and two nicotine strengths (2.5% and 4.0%). Along with other pre-clinical in vitro studies, clinical, and behavioral and population studies, the results of this study are intended to contribute to a body of evidence demonstrating the reduced exposure potential of these products. The data may be included in future premarket tobacco application submissions to the United States (US) Food and Drug Administration (FDA) Center for Tobacco Products. The endpoints to be assessed are based on the FDA Electronic Nicotine Delivery Systems Draft Guidance for Industry (May 2016).

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

The primary objective of this study is:

1. To assess the change-from-baseline differences in the primary tobacco-related BoE following a 28-day use period of *my*blu™ e-cigarettes relative to smoking usual brand combustible cigarettes.

The secondary objectives of this study are:

1. To assess the change-from-baseline differences in the primary tobacco-related BoE following a 56-day use period of *my*blu™ e-cigarettes relative to smoking usual brand combustible cigarettes.
2. To assess the change-from-baseline differences in the secondary tobacco-related BoE following 28-day and 56-day use periods of *my*blu™ e-cigarettes relative to smoking usual brand combustible cigarettes.
3. To characterize the change in the primary and secondary BoE and BoPH during a 56-day period of use of *my*blu™ e-cigarettes.
4. To assess the change-from-baseline differences in the primary and secondary tobacco-related BoE between Day 28 and Day 56 in subjects using *my*blu™ e-cigarettes.
5. To assess change-from-baseline differences in the BoPH following 28-day and 56-day use periods of *my*blu™ e-cigarettes relative to smoking usual brand combustible cigarettes.
6. To assess change-from-baseline differences in physiologic endpoints following 28-day and 56-day use periods of *my*blu™ e-cigarettes relative to smoking usual brand combustible cigarettes.
7. To assess elements of abuse liability, subjective effects, and perceptions associated with use of *my*blu™ e-cigarettes.
8. To characterize use of four *my*blu™ e-liquids (Tobacco Chill and Honeymoon flavor Intense e-liquids, 2.5% and 4.0% nicotine) during a 56-day use period.
9. To characterize nicotine uptake from the *my*blu™ e-cigarettes relative to an e-cigarette comparator (JUUL® Virginia Tobacco 5% nicotine) and usual brand combustible cigarettes.
10. To confirm the safety of *my*blu™ e-cigarettes during a 56-day use period.

2.2 Study Hypothesis

The study hypothesis is that switching from usual brand combustible cigarettes to a *my*blu™ e-cigarette will result in a significantly larger decrease from baseline in the primary tobacco-related biomarkers following 28 days of use relative to the change associated with continuing to smoke combustible cigarettes. The following hypothesis will be tested independently for each *my*blu™ e-liquid.

H_0: $\Delta\mu_{test} = \Delta\mu_{cont}$

H_A: $\Delta\mu_{test} > \Delta\mu_{cont}$

Where H_0 is the null hypothesis, H_A is the alternative hypothesis, $\Delta\mu$ = the mean decrease from baseline, "test" = *my*blu™ product, and "cont" = combustible cigarette

2.3 Study Endpoints

2.3.1 Primary Study Endpoints

Biomarkers of Exposure

Biomarker	Matrix	Chemical Constituent
COHb	Blood	CO
NNAL	Urine	NNK
3-HPMA	Urine	Acrolein
S-PMA	Urine	Benzene

2.3.2 Secondary Study Endpoints

Biomarkers of Exposure

Biomarker	Matrix	Chemical Constituent
NNN	Urine	NNN
CEMA	Urine	Acrylonitrile
HEMA	Urine	Ethylene oxide
HMPMA	Urine	Crotonaldehyde
MHBMA	Urine	1,3 butadiene
1-OHP	Urine	Pyrene
o-tol	Urine	Toluidine
3-OH B[a]P	Urine	B[a]P
1-AN	Urine	Naphthalene
2-AN	Urine	Naphthalene
Nicotine equivalents	Urine	Nicotine

Biomarkers of Potential Harm

Biomarker	Matrix	Biological Effect
sICAM	Blood	Inflammation
WBCs	Blood	Inflammation
HDL-C	Blood	Inflammation
MCP-1	Blood	Inflammation
8-epi-prostaglandin $F_{2\alpha}$	Urine	Oxidative stress
11-dehydrothromboxane B_2	Urine	Platelet activation

Physiological Assessments

- FeNO
- Blood pressure
- Heart rate

Subjective Measures

- PSCDI/PSECDI
- Cough Questionnaire
- QSU-Brief
- MTWS-R
- PES
- Product Liking Questionnaire
- Future Intent to Use Questionnaire
- Product and Health Effect Perceptions Questionnaire

Product Use

Daily in-clinic product use documented by the clinic staff:

- Number of cigarettes smoked
- Number of *my*blu™ pods started
- *my*blu™ pod weight change (for pods used during the 24 hour urine collections)
- Day 3 and Day 29 product preference selection

Daily product use endpoints documented by subjects (Day 3 through study discharge on Day 57):

- Number of cigarettes smoked
- Number of *my*blu™ pods started
- Number of puffs from the *my*blu™ product daily (< or ≥ 50 puffs)

Nicotine PK Assessments

Product use during each product use session:

- Number of puffs taken
- *my*blu™ and JUUL® pod weight change

PK parameters during each product use session:

- C_{max}
- AUC_{0-t}
- T_{max}

Urge to smoke parameters during each product use session:

- Maximum reduction from baseline score (E_{max_R})
- Time of the E_{max_R} (TE_{max})
- Area under the change from baseline "Urge to Smoke" VAS score versus time curve ($AUEC_{\_BL}$)

Other Compliance Assessments

- Exhaled CO
- Urine cotinine

Safety

Safety assessments will include physical examinations, vital signs, ECGs, clinical laboratory tests, lung function, pregnancy tests, AEs, and use of concomitant medications.

3. SUMMARY OF STUDY DESIGN

3.1 Design and Procedures

This will be an open-label, partially-randomized, parallel-arm, multi-site study in healthy adult smokers, consisting of the main study and a PK sub-study.

The main study will assess BoE, BoPH, physiologic effects, and subjective effects with use of *my*blu™ e-cigarettes relative to continuing to smoke combustible cigarettes. To account for potential attrition, up to 175 subjects are planned to be randomized into the *my*blu™ arm (with approximately 43 subjects intended to be assigned to each *my*blu™ e-liquid) and up to 40 subjects will be randomized into the continue-smoking arm. Baseline study assessments will be made during use of subjects' usual brand combustible cigarettes during the initial test visit through the morning of Day 1. All subjects in the *my*blu™ and continue-smoking arms will return to the clinic site for test visits scheduled to occur on Days 14, 28, 42, and 56 for post-baseline study assessments, compliance checks, and product dispensing and return. The subset of subjects participating in the PK sub-study (described below) will also complete selected biomarker assessments (NNAL, NNN, 3-HPMA, CEMA, HMPMA, S-PMA, nicotine equivalents) on Days 3 and 4.

Subjects randomized to the *my*blu™ arm will participate in an in-clinic product acclimation period from Days 1 to 3. The acclimation period will afford the subjects the opportunity to try each of the four *my*blu™ e-liquids in order to become accustomed to their use and to determine those that they would be willing to use during the study. Initial product assignment for each subject will be based on preference as a method to enhance compliance. To further improve compliance through Day 56, at the end of Test Visit 3, subjects using a *my*blu™

product may be allowed to choose to switch to the alternate nicotine strength of their current flavor, to switch to the alternate flavor with the same nicotine strength as their initial choice, or to continue using the same e-liquid selected initially. This method for initial flavor assignment and the opportunity to re-select after 28 days of use is based on natural experimentation that consumers experience when choosing an e-cigarette flavor.

The PK sub-study will assess nicotine uptake and urge to smoke from the *my*blu™ products relative to combustible cigarettes and an e-cigarette comparator (JUUL®). A subset of up to 20 subjects assigned to each of the *my*blu™ e-liquids, 20 subjects from the continue-smoking arm, and all 20 subjects in the JUUL® arm will participate. Subjects in the JUUL® arm will begin using the product after check-in for Test Visit 1 and will continue to use the product through discharge on Day 1 from the study following the PK assessment (subjects in the JUUL® arm will only participate in the PK sub-study). PK assessments will be preceded by a minimum 10-hour abstention from product use and will take place on Day 1 for the JUUL® and continue-smoking arms, and on Day 5 for the *my*blu™ arm. Product use for the PK assessments will consist of two sessions: 1) a fixed puffing session in the morning consisting of 10 puffs taken at 30 second intervals, with puffs 3 seconds in duration, and 2) an *ad libitum* use session beginning 6 hours after the start of the morning session and consisting of unlimited use of the e-cigarette product for 5 minutes or one cigarette, with no limits on puff duration or inter-puff interval. No product use of any kind will be allowed between the sessions. E-cigarette pods used for each session will be weighed before and after use to measure the amount of e-liquid used.

All product use during confinement will be documented by the clinic staff. Subjects in the *my*blu™ and continue-smoking arms will be required to self-report product use from Day 3 through discharge from the study.

Exhaled CO and urine cotinine measurements will be used to confirm smoking/nicotine use status prior to Day 1 and to assess subject compliance with product assignment requirements thereafter.

The clinic staff will contact all subjects via a telephone call approximately 14 days after discharge from the study (either as scheduled or after early termination) for reporting of AEs and use of concomitant medications.

Screening safety evaluations will include a physical examination, vital signs, ECG, clinical laboratory tests (clinical chemistry, hematology, urinalysis, and serology), lung function, urine drug tests, urine cotinine tests, and alcohol breath tests, FSH tests (post-menopausal females) and serum and urine pregnancy tests (females only). On-study safety evaluations will include a symptom-driven physical examinations, vital signs, ECG, clinical laboratory tests (clinical chemistry, hematology, and urinalysis), lung function, and urine pregnancy tests (females only). AEs spontaneously reported by the subjects or observed by the Investigator or other study personnel will be documented and monitored from the time of first product use after successful completion of the check-in events for Test Visit 1 through the end of the Follow-up Period. Any prior and concomitant medications taken from 30 days prior to Screening through the Follow-up Period will also be recorded.

3.2 Justification for Study Design

A parallel study design was chosen due to the length of the exposure period. The continue-smoking arm is included as a control group to account for natural variations in responses associated with participation in a long-term clinical trial.

Subjects randomized to receive a *my*blu™ product will be assigned to an e-liquid flavor based upon their preference established during the acclimation period and may be allowed to switch flavors after a period of approximately 28 days. This method was chosen to emulate a natural condition whereby consumers initially experiment with e-liquid flavors in the market before selecting a product for long-term use, and then have the option to switch among other flavors and nicotine strengths in the market as their needs change.

A previous study demonstrated that switching to an early version of the blu product resulted in decreases in BoEs in as few as 5 days (O'Connell et al. 2016). The current study will be primarily conducted in a less-controlled ambulatory environment over a longer period of time to determine whether reductions can be maintained when subjects have access to combustible cigarettes. A longer assessment period also provides for a more comprehensive assessment of subjective effects and impressions of the study products.

4. STUDY POPULATION

Subjects selected for this study will be identified via standard recruitment methods.

4.1 Inclusion Criteria

Subjects must fulfill all of the following inclusion criteria to be eligible for participation in the study.

1. Healthy, adult, male or female smoker, 21 to 65 years of age, inclusive, at Screening.

2. Reports smoking an average of 5 or more machine-manufactured non-menthol or menthol combustible CPD for at least 1 year 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. Has a positive urine cotinine test (approximately 200 ng/mL using NicAlert, Accutest Urine Cotinine Test, or other test that provides a similar level of sensitivity, the same type of kit will be used at each site) at Screening and check-in for Test Visit 1.

4. Has an exhaled CO > 10 ppm at Screening and check-in for Test Visit 1.

5. A female subject of childbearing potential must have been using 1 of the following forms of contraception and agree to continue using it through completion of the study:

    - hormonal (e.g., oral, vaginal ring, transdermal patch, implant, or injection) consistently for at least 3 months prior to check-in for Test Visit 1;

- double barrier method (e.g., condom with spermicide, diaphragm with spermicide) consistently for at least 14 days prior to check-in for Test Visit 1;
- intrauterine device for at least 3 months prior to check-in for Test Visit 1;
- a partner who has been vasectomized for at least 6 months prior to check-in for Test Visit 1;
- abstinence for at least 14 days prior to check-in for Test Visit 1 through discharge from the study.

6. A female subject of non-childbearing potential must have undergone one of the following sterilization procedures at least 6 months prior to check-in for Test Visit 1:
   - hysteroscopic sterilization;
   - bilateral tubal ligation or bilateral salpingectomy;
   - hysterectomy;
   - bilateral oophorectomy;

   Or be postmenopausal with amenorrhea for at least 1 year prior to check-in for Test Visit 1 and follicle-stimulating hormone (FSH) level consistent with postmenopausal status.

7. Is willing to comply with the requirements of the study, including a willingness to use alternative tobacco products as required by the protocol.

8. Has daily access to text messaging capable cellular phone for daily product use reporting.

9. Provides voluntary consent to participate in this study documented on the signed informed consent form (ICF).

4.2 Exclusion Criteria

Subjects may be excluded from the study if there is evidence of any of the following criteria during Screening or check-in for Test Visit 1, as applicable.

1. Has a history or presence of clinically significant gastrointestinal, renal, hepatic, neurologic, hematologic, endocrine, oncologic, urologic, pulmonary (especially bronchospastic diseases and asthma), immunologic, psychiatric, or cardiovascular disease, 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, or clinical laboratory results, in the opinion of the Investigator.

3. Has a positive test for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV).

4. Has had an acute illness (e.g., upper respiratory infection, viral infection) requiring treatment within 14 days prior to Test Visit 1.

5. Has a fever (> 100.5°F) at Screening or check-in for Test Visit 1.

6. Has a body mass index (BMI) greater than 40.0 kg/m^2 or less than 18.0 kg/m^2 at Screening.

7. Has a history of drug or alcohol abuse within 24 months of Screening, as determined by the Investigator.

8. 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 at Screening.

9. Has a post-bronchodilator forced expiratory volume in 1 second to forced vital capacity (FEV_1:FVC) ratio < 0.7 and FEV_1 < 80% of predicted at Screening.

10. Has a post-bronchodilator FEV_1 increase ≥ 12% and > 200 mL from pre- to post-bronchodilator at Screening.

11. Is allergic to propylene glycol or glycerin.

12. Has an estimated creatinine clearance < 70 mL/minute (using the Cockcroft-Gault equation) at Screening.

13. Has a positive urine drug or alcohol breath test at Screening or check-in for Test Visit 1.

14. If female, the subject is pregnant, lactating, or intends to become pregnant during the time period from Screening through the duration of the study.

15. Has taken medication for depression or asthma within 12 months of check-in for Test Visit 1.

16. Has used prescription anti-diabetic medication and/or insulin therapy within 12 months of check-in for Test Visit 1.

17. Has used medications known to interact with cytochrome P450 (CYP) 2A6 (including, but not limited to, amiodarone, desipramine, isoniazid, ketoconazole, miconazole, phenobarbital, rifampin, tranylcypromine, methoxsalen) within 3 months prior to check-in for Test Visit 1.

18. Has used medications known to impact HDL-C (including, but not limited to, “statins”, ezetimibe, fenofibrate, gemfibrozil, niacin) within 3 months prior to check-in for Test Visit 1.

19. Has used inhalers to treat any chronic medical condition within 3 months prior to check-in for Test Visit 1.

20. Has used nicotine-containing products other than manufactured cigarettes (e.g., e-cigarettes, roll-your-own cigarettes, bidis, snuff, nicotine inhaler, pipe, cigar, chewing tobacco, nicotine patch, nicotine spray, nicotine lozenge, or nicotine gum)

within 14 days prior to check-in for Test Visit 1.

21. Has received any medications or substances (other than tobacco) which interfere with the cyclooxygenase pathway (e.g., anti-inflammatory drugs including aspirin and ibuprofen) within 7 days prior to check-in for Test Visit 1.

22. Has used methylene blue within 7 days prior to check-in for Test Visit 1.

23. Has used any prescription smoking cessation treatments, including, but not limited to, varenicline (Chantix®) or buproprion (Zyban®) within 3 months prior to check-in for Test Visit 1.

24. Is a self-reported puffer (i.e., adult smokers who draw smoke from the cigarette into the mouth and throat but do not inhale).

25. Is postponing a planned smoking quit attempt in order to participate in the study.

26. Has donated plasma within 7 days prior to check-in for Test Visit 1.

27. Has donated blood or blood products (with the exception of plasma as noted above), had significant blood loss, or received whole blood or a blood product transfusion within 56 days prior to check-in for Test Visit 1.

28. Has participated in a previous clinical study for an investigational drug, device, biologic, or tobacco product within 30 days prior to check-in for Test Visit 1.

29. Is or has a first-degree relative (e.g., spouse, parent, sibling, child) who is a current or former employee of the tobacco or e-cigarette industry or is a named party or class representative in litigation with the tobacco or e-cigarette industry.

30. Is or has a first-degree relative (e.g., spouse, parent, sibling, child) who is a current employee of one of the clinic sites.

31. Is or has a first-degree relative (e.g., spouse, parent, sibling, child) who is a current employee of the Sponsor.

32. Has previously taken part in (from completion of any baseline measurements), has been withdrawn from, or has completed this study.

33. 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 1.

34. In the opinion of the Investigator, the subject should not participate in this study.

4.3 Study Restrictions

4.3.1 Food, Beverages, and Activity

Subjects will be advised of the following study restrictions.

- Alcohol should be avoided for 48 hours prior to Screening and Test Visits 1, 3, and 5.
- Foods containing poppy seeds should be avoided for 48 hours prior to Screening and Test Visit 1 to avoid exclusion for a positive urine drug test.
- Subjects randomized to the *my*blu™ and continue-smoking arms will be advised to avoid eggplant, meats cooked at high temperatures (e.g., barbecued, grilled, or pan-fried), cured sandwich meats, bacon, salami, and sausages for 2 days prior to Test Visits 1, 3, and 5 and during confinement.
- Strenuous physical activity which could cause muscle aches or injury, including contact sports should be avoided for 48 hours prior to Screening and Test Visits 1, 3, and 5 and during confinement.
- Donation of blood or blood products, other than for the purpose of this study, should be avoided from Screening through Test Visit 5.

Subjects will be asked to report violations of this advice.

Exceptions of the above study restrictions may be permitted at the discretion of the Investigator and will be documented.

4.3.2 Medications

Medication use will be assessed to satisfy the inclusion and exclusion criteria. All medications (and reasons for their use) taken from 30 days prior to Screening through the Follow-up Period will be recorded. Except for those medications noted in the exclusion criteria, prescription or over-the-counter medications required to treat an Investigator-approved disease or condition are permitted at the discretion of the Investigator. Hormonal contraceptives (e.g., oral, vaginal ring, transdermal patch, implant, injection) and hormonal replacement therapy are permitted. Use of over-the-counter analgesics (e.g., acetaminophen), antihistamines, nasal decongestants, and dietary supplements are permitted.

Use of anti-inflammatory medications (e.g., ibuprofen) and methylene blue should be avoided for 7 days prior Test Visits 1, 3, and 5 as these medications may interfere with biomarkers being assessed. Decisions to use other concomitant medications (including, but not limited to, those known to impact HDL-C or to interact with CYP2A6; taken for depression, asthma, chronic obstructive pulmonary disease, or diabetes; smoking cessation and nicotine replacement therapy products; or inhalers) during the study will be made in the best interest of the health of the subject. If other drug therapy is required, a joint decision will be made by the Investigator and Sponsor to continue or discontinue the subject. Exceptions may be permitted at the discretion of the Investigator in consultation with the Sponsor (or Sponsor designee), providing the medication in question would have no impact on the study.

Any exceptions will be documented and required medications that might impact study endpoints should be considered during interpretation of the study results.

4.3.3 Tobacco Use

Except as required by the study, consumption of other tobacco- or nicotine-containing products should be avoided during the entire duration of the study from screening through discharge from the study.

Use of tobacco or nicotine-containing products other than those consistent with the randomization will not necessarily lead to discontinuation of the subject, though subjects will be encouraged to comply with the randomization requirements. During each Test Visit, the clinic staff will stress the importance of compliance with the study requirements and honestly reporting product use. Subjects will be reminded that the study procedures will provide an indication of compliance with the study requirements (for example, exhaled CO results may be provided to the subjects during the compliance discussion).

Use of any tobacco or nicotine containing products other than combustible cigarettes or the test products will be documented as protocol deviations. However, combustible cigarette use by subjects in the *my*blu™ arm during the ambulatory periods will not be documented as protocol deviations.

4.4 Subject Early Discontinuation or Withdrawal

Subjects will be advised that they are free to withdraw from the study at any time. In addition, subject participation in this study may be discontinued for any of the following reasons:

- AEs
- Lost to follow-up
- Non-compliance with study procedures
- Protocol violations
- Study terminated by Sponsor, US FDA, or other regulatory authorities
- Withdrawal of consent
- Investigator's discretion, including a severe laboratory abnormality or other medical condition that indicates to the Investigator that continued participation is not in the best interest of the subject

Protocol deviations/violations should not lead to subject withdrawal unless they indicate a significant risk to the subject's safety or jeopardize the scientific integrity of the study.

If premature withdrawal from the study occurs for any reason, the Investigator must determine the primary reason and record this information in the electronic case report form (eCRF). Additionally, subjects withdrawing after first use of study product according to the randomization requirements will undergo all discharge safety procedures as feasible and as

deemed necessary by the Investigator and will be contacted approximately 14 days after early termination to determine if any AE has occurred since the last study visit.

A subject withdrawn from the study due to any AE or clinically significant abnormal laboratory test values will be evaluated by the Investigator or other monitoring physician and will be treated and/or followed up until the symptoms or values return to normal or acceptable levels, or until lost to follow-up, as appropriate in the opinion of the Investigator.

If a subject becomes lost to follow-up, a reasonable effort will be made to contact the subject and perform the end-of-study safety procedures noted in the Study Events tables. A reasonable effort is considered, at minimum, two attempts via telephone (at least 1 day apart) followed by a certified letter to the subject's last known address requesting their return to the clinic site for a safety evaluation and return of any study products.

Subjects withdrawing or removed from this study cannot re-enter.

4.5 Subject Randomization and Product Assignments

Each subject will be assigned to a study arm (*my*blu™, continue-smoking, JUUL®) according to the randomization plan. The study arms will be stratified by sex (male or female) and age class (≤ 40 years of age, > 40 years of age). Each sex and age class should not account for more than 65% of the randomized population in each arm, and the Caucasian race should not comprise more than 80% of the randomized population in each arm. For logistical and operational reasons, the first subject in each sex-age class stratum who successfully completes the screening procedures at each site may be assigned to the JUUL® arm.

For the main study, a sufficient number of subjects are intended to be randomized to better ensure that at least 29 subjects in each of the *my*blu™ e-liquids and the continue-smoking arm complete the Day 28 study assessments. To account for potential attrition, up to 175 subjects are planned to be randomized into the *my*blu™ arm (with approximately 43 subjects intended to be assigned to each *my*blu™ e-liquid) and up to 40 subjects will be randomized into the continue-smoking arm. Assignment of subjects to a specific *my*blu™ product will be based on subject product preference. An attempt will also be made to apply the sex and age class stratification to each product in the PK sub-study, though the same potential challenges will apply.

For the PK sub-study, up to 20 subjects assigned to each *my*blu™ e-liquid, 20 subjects in the continue-smoking arm, and all 20 subjects in the JUUL® arm will be selected to participate. An attempt will also be made to apply the sex and age class stratification to each product in the PK sub-study, though the same potential challenges will apply.

Subjects randomized to the *my*blu™ or continue-smoking arms must not be informed of their arm assignment until completion of baseline assessments to avoid changes in behavior that might impact those assessments. Therefore, subjects should be prepared to stay in the clinic through Day 5 with the understanding that they may be discharged from the test visit early depending on which arm to which they are randomized. As subjects in the JUUL® arm will only participate from Days -2 through 1, these subjects may be informed once the assignment is made.

4.6 Replacement Subjects

Subjects withdrawn or removed from the study may be replaced at the discretion of the Sponsor in order to better ensure that the intended subject completion target is reached. If replacement subjects are used, the replacement should be made with subjects matching the sex, age class, and race of the subject being replaced, if possible. Replacement subjects will be assigned a randomization number 100 higher than the subject being replaced.

5. STUDY PRODUCTS

5.1 Description of Study Products

The following products will be used during this study:

Arm	Product Designation	Study Product Name
A	A	*my*blu™ system with Tobacco Chill flavor Intense Liquidpod, 2.5% nicotine
	B	*my*blu™ system with Tobacco Chill flavor Intense Liquidpod, 4.0% nicotine
	C	*my*blu™ system with Honeymoon flavor Intense Liquidpod, 2.5% nicotine
	D	*my*blu™ system with Honeymoon flavor Intense Liquidpod, 4.0% nicotine
B	E	Usual brand combustible cigarettes
C	F	JUUL® system with Virginia Tobacco Flavor JUULpod, 5.0% nicotine

5.1.1 Test Product

*my*blu™ is a two-piece closed system available in the US market. The *my*blu™ system is comprised of a rechargeable 350 mAh battery and a disposable pod. The pods connect directly and contain the mouthpiece, heating element, are pre-filled with e-liquid, and are compatible only with *my*blu™ batteries. During use, a consumer inhales through the mouthpiece and a sensor in the battery detects the change in air pressure which activates the heating element. The e-liquid heats to an aerosol which the consumer inhales.

The battery is charged with a micro-USB charger and produces a typical output of 3.7V (maximum 3.9V). The pods contain 1.5 mL of e-liquid which lasts approximately 200 puffs, depending on individual use behaviors. Each e-liquid contains a mixture of glycerin, propylene glycol, nicotine-lactic acid salt, and a proprietary blend of flavors.

The Tobacco Chill and Honeymoon Intense e-liquids are available in the US market.

5.1.2 Control Product

Usual brand combustible cigarettes will serve as the control product. Subjects will supply their own usual brand combustible cigarettes for use during the study. There will be no limitation on brand, brand style, or cigarette size; however, they must be machine-manufactured and commercially available in the US market. Each subject's usual brand combustible cigarette will be documented at Screening and will be updated at subsequent visits as necessary.

5.1.3 Comparator Product

The JUUL® Virginia Tobacco product was chosen as a similar, pod-based, closed-system in the e-cigarette category currently in the US market. According to the company website (www.juul.com), JUUL® e-liquids contain propylene glycol, glycerin, benzoic acid, nicotine, and natural and artificial flavor ingredients.

5.2 Study Product Accountability

The staff at each site will coordinate shipping of the *my*blu™ products from the Sponsor (or a distribution vendor). JUUL® products will be obtained from commercial sources. The clinic staff will document the date products were received and recorded in the inventory records, the content of all shipments received, the total number of products dispensed during the study, and the total number of products remaining at the end of clinical conduct.

Appropriate documentation of the receipt and return of products supplied by subjects must also be kept. Subjects will be required to provide enough unopened packs of their usual brand cigarettes for use during the test visits (calculated as cigarettes smoked per day times the number of days in confinement, rounded up to the next pack, plus two packs). Cigarette packages that have been opened prior to check-in for the test visit are not to be accepted for use in the clinic and subjects will be reminded of this requirement during the reminder phone call. If a subject presents to a test visit with only opened packages, presents to the clinic with an insufficient supply based on reported CPD, or if the subject runs out of cigarettes during the confinement period, the subject or site should purchase a sufficient number of packages for use and this information will be documented appropriately. Unused cigarettes will be returned to the subjects in the continue-smoking arm at discharge for each confinement test visit and to the *my*blu™ and JUUL® arms at discharge from the study.

For each subject, dispensing records for in-clinic use must include the date and time study products were dispensed and returned, or in the case of the PK sessions, the start and stop time of the session. If a subject mistakenly disposes of a product, a reasonable effort should be made to retrieve the product. If retrieval is not possible, the approximate time that use of the product was finished and a description of the occurrence should be noted in the source documents. The subject will be advised that further disposal may result in dismissal from the study. Reconciliation of the dispensed and returned products should be completed to ensure adequate accountability of the products. If a daily allotment of products is transferred to the

clinic from a central storage location (e.g., site pharmacy or product storage room), the number of products transferred from and back to the central storage location must be documented. Only one product at a time may be dispensed to a subject.

For each subject, dispensing records for at-home use of the *my*blu™ products will include the date and time of dispensing, the number of products dispensed, the number of unused products returned, and where appropriate, the number of and reason for missing or lost products. Subjects will be asked to return used pods, but the number returned will not be used for accountability purposes. Used pods may be disposed of by the site.

5.3 Study Product Storage

All products will be stored in a locked, limited-access area in the clinic site (e.g., pharmacy or other storage area) and kept at controlled room temperature (defined as 20 - 25°C [68 - 77°F], with excursions permitted to 15 - 30°C [59 - 86°F]), until dispensed to the clinic for daily subject use or to the subjects for ambulatory use. Subjects will be advised to store the products at room temperature during ambulatory periods, to avoid prolonged exposure at temperature extremes, and to keep the products out of the reach of children during the ambulatory periods.

During each day of the confinement periods, a sufficient supply for each subject may be transferred and kept in a secure area in the clinic (e.g., locked drawer or cupboard) as necessary.

5.4 Study Product Dispensing

Study products (including the *my*blu™ batteries, pods, and USB chargers, usual brand cigarettes, and JUUL® products) will be dispensed for use during the confinement and ambulatory periods by the Investigator or an appropriate designee in accordance with the protocol, the site's usual dispensing process, and any required local regulations. Individual study product dispensing records for confinement and ambulatory periods will be maintained by the clinic site for each subject as appropriate.

Care should be taken when repackaging the study products to avoid exposure to air and moisture to the extent possible. Appropriate protection (e.g., gloves) should be considered when handling the products.

Female subjects should not be provided study products at any test visit until a negative pregnancy result has been obtained.

5.4.1 Confinement Periods

Instructions on the proper use of the *my*blu™ and JUUL® products will be provided prior to use, and subjects will demonstrate an understanding of the instructions. All *my*blu™ and JUUL® products will be provided assembled, charged, and ready for use during confinement. On Days 1 through 3, *my*blu™ pods should be used until the contents are fully consumed at which time a new pod will be provided. On Days -2 and -1, JUUL® pods should be used until

the contents are fully consumed. Fresh *my*blu™ and JUUL® pods will be provided for use during each PK session. Any product failures will be reported to the clinic staff and documented, and the product will be immediately replaced.

Except for use during the PK sessions, study products will be dispensed by the clinic staff upon subject request and subjects will be instructed to return the study products (e-cigarettes or cigarette butts) when they are finished using them. Only one combustible cigarette may be dispensed at each request. Use during the PK sessions will be under a controlled regimen or *ad libitum* as described in Section 6.7.1.

5.4.2 Ambulatory Periods

Only *my*blu™ products will be dispensed by the staff for use during the ambulatory periods. All *my*blu™ products for use during ambulatory periods will be packaged and labeled with, at minimum, the product identifier, the subject number, protocol number, date of dispensing, statements of "For investigational use only" and "Keep out of reach of children", and any other information as required by local law.

Prior to discharge from Test Visit 1, subjects in the *my*blu™ arm will be dispensed two batteries (batteries used during the confinement period may be re-dispensed), an initial supply of 22 pods of the assigned e-liquid, and necessary accessories for use through Day 14. The number of pods dispensed at subsequent visits will be based on the subject's prior daily use. All used and unused pods will be returned to the clinic site at each subsequent Test Visit. Unused pods may be re-dispensed provided any applicable expiration date will not be exceeded.

Subjects will be reminded to keep the study products out of the reach of children and to not share the study products with anyone. Subjects will also be reminded at each dispensing that they are expected to exclusively use the test products without dual use of combustible cigarettes. Subjects will be instructed to contact the clinic site if they believe that they will run out of pods or if the products fail to work properly, and will make arrangements to obtain additional supplies. The clinic staff will be required to document as deviations any days during which subjects report being without sufficient working study supplies.

5.5 Test Product Failure and Misuse

Any occurrence of test product failure or misuse by subjects will be documented.

5.6 Test Product Return/Destruction

All unused *my*blu™ and JUUL® products and components remaining at the end of the study will be returned or destroyed according to the Test Product Manual. All returns or destruction of products will be documented with shipping receipts or certificates of destruction which will be included in the site study file.

Unused *my*blu™ and JUUL® products can only be destroyed after being inspected and reconciled by the study monitor or other Sponsor designee.

6. STUDY SCHEDULE AND PROCEDURES

6.1 Study Period Summaries

6.1.1 Screening Period

Potential subjects will undergo screening procedures within 28 days prior to check-in for Test Visit 1 to ensure that they meet the requirements for inclusion in the study. Pre-screening of potential subjects according to a site's usual processes may be completed to assess basic inclusion and exclusion requirements (e.g., demographics, smoking history, etc.) prior to the subject presenting to the clinic site for Screening. Screening visits will typically be scheduled in the morning, but may be scheduled according to the sites' preference as long as all pre-study visit requirements (e.g., arriving having fasted) are followed. Re-checks of applicable screening events will be at the Investigators discretion and may occur at additional visits if necessary. A subject who begins screening procedures but fails to successfully satisfy the entry requirements of the study will be considered a "screen failure". Subjects who fail screening may not re-screen. Subjects who initially pass screening procedures but who do not check-in within the allowed window may rescreen at the discretion of the Investigator and in consultation with the Sponsor.

Subjects will be instructed to maintain their usual smoking behaviors prior to Screening and through check-in for Test Visit 1.

All screening assessments must be performed after written informed consent is obtained. Unless indicated, the assessments may be performed without regard to specific timing relative to the other assessments.

Table 4 Screening Visit Schedule

Time	Procedures	Comments
	Informed consent	Must be obtained prior to completing the remaining assessments
	Screening demographics documentation/confirmation	Any information collected during pre-screening must be confirmed
	Urine collection for urinalysis, drug and cotinine tests Alcohol breath test Exhaled CO measurement	Subjects must have negative drug and alcohol tests, and have acceptable urine cotinine and exhaled CO results prior to completing the remaining assessments. Exhaled CO should be measured within 2 hours of check-in.
	Review of inclusion / exclusion criteria	
	Medical history	
	Prior and concomitant medication reporting	
	Tobacco use history/usual brand cigarette documentation	

Time	Procedures	Comments
	Physical examination	
	Body weight/height/BMI	
	12-lead ECG	Subjects must be supine for at least 5 minutes prior to measurement, must be collected at least 15 minutes after the last cigarette smoked.
	Vital signs	Subjects must be seated for at least 5 minutes prior to measurement, must be collected at least 15 minutes after the last cigarette smoked.
	Blood collection for clinical chemistry, hematology, serology, FSH (post-menopausal females) and serum pregnancy test (females)	Blood collection must be preceded by an 8-hour fast.
	Spirometry	To be performed after completion of the assessments listed above, and must be preceded by a minimum 60-minute abstention from cigarette smoking.
	Review of tobacco and nicotine restrictions	
	Smoking cessation information provided	

6.1.2 Baseline and Product Use Period 1

Upon successful completion of Screening, subjects who continue to meet study requirements will be scheduled to check in to the clinic for Test Visit 1 on Day -2 at a time designated by the clinic staff (check-in for JUUL® arm should be as early in the day as possible to maximize the time to use the product) and will remain in the clinic until completion of all study events as required by their randomization arm. Reminder telephone calls will be made to the subjects 24 to 48 hours prior to the test visit. Subjects who fail the check-in requirements will be considered a "screen failure" and will be excluded from participation. For the *my*blu™ and continue-smoking arms, the Baseline Period will consist of the time between check-in and first product use on Day 1. The following table provides the general clinic schedule for Test Visit 1. The procedures listed should be performed for subjects as appropriate for the randomization arm.

Table 5 Test Visit 1 Schedule

Time	Procedures	Comments
Day -2		
	Check-in events	
	Urine collection for urinalysis, drug, cotinine, and pregnancy (females) tests Alcohol breath test Exhaled CO measurement	Subjects must have negative drug, alcohol, and pregnancy tests, and have acceptable cotinine and exhaled CO results prior to completing the remaining assessments. Exhaled CO will be measured within 1 hour of check-in.
	Blood sample collection for clinical chemistry and hematology	JUUL® arm, following a minimum 8-hour fast.
	Vital signs	Subjects must be seated for at least 5 minutes prior to measurement, must be collected at least 15 minutes after the last study product used.
	Update medical history, and tobacco use history/usual brand cigarette documentation	
	Update medications	Throughout the day
	Symptom-driven physical examination	
	Body weight documentation	
	Additional demographics documentation	
	Review of inclusion / exclusion criteria	
	Review of in-clinic tobacco and nicotine restrictions	Any time prior to the start of product use
Immediately following check-in	Training on JUUL® product	JUUL® arm only
Through 23:00	Product use	
	Document AEs	To begin following first study product use
14:00 – 15:00	Start of 24-hour urine collection	*my*blu™ and continue-smoking arms only
17:00 – 18:00	Blood sample collection for COHb	*my*blu™ and continue-smoking arms only

Time	Procedures	Comments
20:00 – 22:00	Questionnaires administered (PSCDI, Cough, QSU-Brief, MTWS-R, PES, Product Liking, Future Intent to Use, Product and Health Effects Perceptions)	*my*blu™ and continue-smoking arms only. Subjects must be allowed a period of at least 2 hours of product use prior to questionnaire administration.
Day -1		
	Document medications	Throughout the day
	Blood sample collection for clinical chemistry, hematology, and BoPH/bio-banking	*my*blu™ and continue-smoking arms, following a minimum 8-hour fast and prior to the start of product use
07:00 – 23:00	Product use	
14:00 – 15:00	End of 24-hour urine collection	± 30 minutes from the start time on Day -2, *my*blu™ and continue-smoking arms only
After urine collection	FeNO	Must be preceded by a minimum 1 hour food and water restriction and a 30-minute abstention from study product use. *my*blu™ and continue-smoking arms only
~18:00	Discharge continue-smoking subjects not participating in PK assessments following completion of baseline assessments Symptom-driven physical Vital signs Review of tobacco and nicotine restrictions Subject cigarettes returned	Discharge events may be completed prior to 18:00
Day 1		
	Document AEs and medications	Throughout the day
	Product demonstration and training	*my*blu™ arm only
Through 23:00	*my*blu™ product use	To begin following product demonstration and training
09:00	Fixed puffing PK session	Continue-smoking and JUUL® arms, follows a 10-hour abstention from product use.
	Product use documentation	

Time	Procedures	Comments
	Blood sampling	Per sampling schedule
15:00	*Ad libitum* puffing PK session	Continue-smoking and JUUL® arms, to begin ~6 hours following the start of the fixed puffing regimen.
	Product use documentation	
	Blood sampling	Per sampling schedule
	Urge to smoke assessment	Per sampling schedule
~18:00	Discharge continue-smoking and JUUL® subjects following completion of PK assessments Symptom-driven physical Vital signs Review of tobacco and nicotine restrictions Subject cigarettes returned	Discharge events may be completed prior to 18:00
Day 2		
	Document AEs and medications	Throughout the day
07:00 – 23:00	Product use	
After 20:00	*my*blu™ test product preference selection	
Day 3		
	Document AEs and medications	Throughout the day
07:00 – 23:00	Product use	Day 3 subject self-reporting to be confirmed by clinic staff.
19:00 – 20:00	Start of 24-hour urine collection	Only *my*blu™ subjects continuing into the PK assessment
19:00 – 20:00	Questionnaires administered (QSU-Brief, MTWS-R, PES, Product Liking)	All *my*blu™ subjects
~20:00	Discharge *my*blu™ subjects not participating in PK assessments Exhaled CO Symptom-driven physical Vital signs Review of tobacco and nicotine restrictions Test product dispensing	Discharge events may be completed prior to 20:00. Subjects must be seated for at least 5 minutes prior to vital signs measurement, and must be collected at least 15 minutes after the last study product used.
Day 4		
	Document AEs and medications	Throughout the day

Time	Procedures	Comments
07:00 – 23:00	Product use	
17:00 – 18:00	Blood sample collection for COHb	
19:00 – 20:00	End of 24-hour urine collection	± 30 minutes from the start time on Day 3
Day 5		
	Document AEs and medications	Throughout the day
09:00	Fixed puffing PK session	Follows a 10-hour abstention from product use.
	Product use documentation	
	Blood sampling	Per sampling schedule
15:00	*Ad libitum* puffing PK session	To begin ~6 hours following the start of the fixed puffing regimen.
	Product use documentation	
	Blood sampling	Per sampling schedule
	Urge to smoke assessment	Per sampling schedule
~18:00	Discharge subjects Exhaled CO Symptom-driven physical Vital signs Review of tobacco and nicotine restrictions Test product dispensing	Discharge events may be completed prior to 18:00. Subjects must be seated for at least 5 minutes prior to vital signs measurement, and must be collected at least 15 minutes after the last study product used.

Following discharge from Test Visit 1, subjects in the *my*blu™ and continue-smoking arms will follow the product use requirements of their randomization arm and will report product use daily. All subjects in the *my*blu™ and continue-smoking arms will be required to present to the clinic site on Day 14 and Day 28 (each ± 2 days) for Test Visits 2 and 3, respectively. Reminder phone calls will be made to the subjects 24 to 48 hours prior to each test visit. Test Visit 2 will be ambulatory and primarily for the return and dispensing of test products for the *my*blu™ arm and for compliance and safety checks for both study arms. Test Visit 3 will be for these purposes in addition to completion of the endpoint assessments during confinement. At the discretion of the site, Test Visit 3 (i.e., Days 28 and 29) may be ambulatory and selected procedures may be performed by subjects at home (e.g., 24-hour urine collection, completion of questionnaires). Subjects will be provided the materials required to complete the selected procedures and will be instructed on at-home procedures (e.g., urine collection method, questionnaires).

Table 6 Test Visit 2 Schedule

Time	Procedures	Comments
	Document AEs and medications	
	Urine sample for cotinine and pregnancy (females) tests	Female subjects must have a negative pregnancy test prior to product dispensing
	Exhaled CO measurement	Exhaled CO should be measured within 1 hour of check-in.
	Document non-compliant tobacco product use and update usual brand cigarette documentation	
	Review of tobacco and nicotine restrictions	
	Test product collection/dispensing	
	Subject product use reporting confirmation	

Table 7 Test Visit 3 Schedule

Time*	Procedures	Comments
Day 28		
	Check-in events	
	*my*blu™ product return and combustible cigarette check-in	
	Urine collection for urinalysis, cotinine, and pregnancy (females) tests	Female subjects must have a negative pregnancy test prior to completing the remaining assessments.
	Exhaled CO measurement	Exhaled CO should be measured within 1 hour of check-in.
	Vital signs	Subjects must be seated for at least 5 minutes prior to measurement, must be collected at least 15 minutes after the last study product used.
	Document non-compliant tobacco product use and update usual brand cigarette documentation	
	Update AEs and medications	Throughout the day
	Symptom-driven physical examination	

Time*	Procedures	Comments
	Body weight documentation	
	Review of in-clinic tobacco and nicotine restrictions	Any time prior to the start of product use
	Subject product use reporting confirmation	Any time prior to discharge
Through 23:00	Product use	
14:00 – 15:00	Start of 24-hour urine collection	
17:00 – 18:00	Blood sample collection for COHb	
20:00-22:00	Questionnaires administered (PSCDI/PSECDI, Cough, QSU-Brief, MTWS-R, PES, Product Liking, Future Intent to Use, Product and Health Effects Perceptions)	Subjects must be allowed a period of at least 2 hours of product use prior to questionnaire administration.
Day 29		
	Document AEs and medications	Throughout the day
	Blood sample collection for clinical chemistry, hematology, and BoPH/bio-banking	Following a minimum 8-hour fast and prior to the start of product use
07:00 – 14:00	Product use	End of product use period will coincide with the end of the 24-hour urine collection
14:00 – 15:00	End of 24-hour urine collection	± 30 minutes from the start time on Day 28
After urine collection	FeNO	Must be preceded by a minimum 1 hour food and water restriction and a 30-minute abstention from study product use.
Prior to discharge	*my*blu™ product preference selection	May include brief trial with alternate products
~18:00	Discharge subjects Symptom-driven physical Vital signs Review of tobacco and nicotine restrictions Test product dispensing and continue-smoking subject cigarettes returned	Discharge events may be completed prior to 18:00. Subjects must be seated for at least 5 minutes prior to vital signs measurement, and must be collected at least 15 minutes after the last study product used.

* For any procedures to be performed at home, subjects will be instructed to perform these procedures as close to the scheduled times as possible. Subjects will also record the exact clock time of performing the procedures.

6.1.3 Product Use Period 2

Following discharge from Test Visit 3, subjects in the *my*blu™ and continue-smoking arms will follow the product use requirements of their randomization arm and will report product use daily. All subjects in the *my*blu™ and continue-smoking arms will be required to present to the clinic site on Day 42 and Day 56 (each ± 2 days) for Test Visits 4 and 5, respectively. Reminder phone calls will be made to the subjects 24 to 48 hours prior to each test visit. Test Visit 4 will be ambulatory and primarily for the return and dispensing of test products for the *my*blu™ arm and for compliance and safety checks for both study arms. Test Visit 5 will be for these purposes in addition to completion of the endpoint assessments during confinement. Subjects will be discharged from the clinical portion of the study at the end of Test Visit 5. At the discretion of the site, Test Visit 5 (i.e., Days 56 and 57) may be ambulatory and selected procedures may be performed by subjects at home (e.g., 24-hour urine collection, completion of questionnaires). Subjects will be provided the materials required to complete the selected procedures and will be instructed on at-home procedures (e.g., urine collection method, questionnaires).

Table 8 Test Visit 4 Schedule

Time	Procedures	Comments
	Document AEs and medications	
	Urine sample for cotinine and pregnancy (females) tests	Female subjects must have a negative pregnancy test prior to product dispensing
	Exhaled CO measurement	Exhaled CO should be measured within 1 hour of check-in.
	Document non-compliant tobacco product use and update usual brand cigarette documentation	
	Review of tobacco and nicotine restrictions	
	Test product collection/dispensing	
	Subject product use reporting confirmation	

Table 9 Test Visit 5 Schedule

Time*	Procedures	Comments
Day 56		
	Check-in events	
	*my*blu™ product return and combustible cigarette check-in	
	Urine collection for urinalysis, cotinine, and pregnancy (females) tests	Female subjects must have a negative pregnancy test prior

Time*	Procedures	Comments
		to completing the remaining assessments.
	Exhaled CO measurement	Exhaled CO should be measured within 1 hour of check-in.
	Vital signs	Subjects must be seated for at least 5 minutes prior to measurement, must be collected at least 15 minutes after the last study product used.
	Document non-compliant tobacco product use and update usual brand cigarette documentation	
	Update AEs and medications	Throughout the day
	Symptom-driven physical examination	
	Body weight documentation	
	Review of in-clinic tobacco and nicotine restrictions	Any time prior to the start of product use
	Subject product use reporting confirmation	Any time prior to discharge
Through 23:00	Product use	
14:00 – 15:00	Start of 24-hour urine collection	
17:00 – 18:00	Blood sample collection for COHb	
20:00 – 22:00	Questionnaires administered (PSCDI/PSECDI, Cough, QSU-Brief, MTWS-R, PES, Product Liking, Future Intent to Use, Product and Health Effects Perceptions)	Subjects must be allowed a period of approximately 2 hours of product use prior to questionnaire administration.
Day 57		
	Document AEs and medications	Throughout the day
	Blood sample collection for clinical chemistry, hematology, and BoPH/bio-banking	Following a minimum 8-hour fast and prior to the start of product use
07:00 – 14:00	Product use	End of product use period will coincide with the end of the 24-hour urine collection
14:00 – 15:00	End of 24-hour urine collection	± 30 minutes from the start time on Day 56

Time*	Procedures	Comments
After urine collection	FeNO	Must be preceded by a minimum 1 hour food and water restriction and a 30 minute abstention from study product use.
After FeNO	Spirometry	Must be preceded by a minimum 60 minute abstention from study product use.
~18:00	Discharge subjects Symptom-driven physical Vital signs 12-lead ECG Provide smoking cessation information Subject cigarettes returned	Discharge events may be completed prior to 18:00. Subjects must be seated for at least 5 minutes prior to vital signs measurement and supine for at least 5 minutes prior to ECG measurement, and both must be collected at least 15 minutes after the last study product used.

* For any procedures to be performed at home, subjects will be instructed to perform these procedures as close to the scheduled times as possible. Subjects will also record the exact clock time of performing the procedures.

6.1.4 Follow-up Period

All subjects will be contacted by telephone 14 days (± 2 days) following discharge from the study on Day 57 (or following early termination if deemed necessary in the opinion of the Investigator) to document the occurrence of AEs and the need for concomitant medications since the last clinic visit. The Investigator will determine whether additional follow-up will be necessary based on the outcome of this call.

6.2 Study Events

6.2.1 Medical History

Medical history is defined as any condition that started prior to Day -2. Relevant medical history, as determined by the Investigator or a qualified designee, will be documented at Screening and updated at Test Visit 1 as necessary.

6.2.2 Demographics

Basic demographic data and subject identification information, including sex, age (each subject must show proof of age with government-issued identification (ID) [e.g., driver's license]), race, and ethnicity will be recorded for each subject at Screening.

Additional demographic data, including income level, educational level, marital status, and gender choice (if self-determined to be different from sex), will be obtained during Test Visit 1.

The demographics questionnaires are located in Appendix 1.

6.2.3 Prior and Concomitant Medications

Any prior and concomitant medications (with the exception of albuterol used during spirometry measurements) taken from 30 days prior to Screening through the Follow-up Period will be recorded. Subjects will be advised to report regular use of medications to the clinic staff as the need arises during the ambulatory periods. Occasional use of medications during the ambulatory periods may be reported at the next Test Visit. Details to be recorded include the drug name (generic and trade name if applicable), route of administration, total dose/unit, indication, start date, and stop date. Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary.

6.2.4 Smoking History and Usual Brand Combustible Cigarette Documentation

Smoking history will include the number of years the subject has smoked and the average number of cigarettes (single value, not a range) smoked per day during the past year.

In addition, a color photocopy of each subject's usual brand cigarette package will be obtained initially at the Screening. An updated photocopy will be taken and product characteristics documented if the subject's usual brand changes during the study. The following characteristics of the usual brand product will be documented: brand, brand style, flavor, and cigarette length. A data collection form will be provided to the site.

6.2.5 Tobacco/Nicotine Product Use History Questionnaire

Subjects will be required to report previous tobacco-product and nicotine-product use histories during Screening and updated at Check-in for Test Visit 1 (if necessary) to satisfy the study inclusion and exclusion criteria.

The Tobacco/Nicotine Product Use History Questionnaire is provided in Appendix 12.

6.2.6 Physical Examination

A standard physical examination assessing the general physical well-being will be performed at Screening. A symptom-driven physical examination will be conducted at other times to evaluate AEs. If no symptoms are present, an examination will not be required.

6.2.7 Body Weight, Height, and BMI

Body weight will be measured in light indoor clothing during Screening and Test Visits 1, 3 and 5. Height and BMI will be documented during Screening. Measurements will be reported in metric units. BMI will be recorded as kg/m^2.

6.2.8 Clinical Laboratory Tests

All clinical laboratory tests will be conducted by a central laboratory facility accredited by the Centers for Medicare and Medicaid Services (Clinical Laboratory Improvement Amendments of 1988 [CLIA-88]) or at the clinic site. For inclusion into the study, values for the clinical laboratory parameters are to be within the laboratory normal ranges or deemed not clinically significant in the opinion of the Investigator.

Clinical Chemistry [1]
- Albumin
- Alkaline phosphatase
- Alanine aminotransferase
- Aspartate aminotransferase
- Bicarbonate
- Bilirubin
- Blood urea nitrogen
- Creatinine
- Glucose
- Potassium
- Sodium
- Total protein
- Uric acid

Urinalysis [2]
- Bilirubin
- Blood
- Glucose
- Ketones
- Leukocyte esterase
- Nitrite
- pH
- Protein
- Specific gravity
- Urobilinogen

Additional Tests
- Serology
  - HIV
  - HbsAg
  - HCV
- FSH
- Serum/urine pregnancy [3]
- Urine cotinine [4]
- Urine drug test
  - Amphetamines
  - Cannabinoids
  - Cocaine
  - Methamphetamine
  - Opiates
- Alcohol breath test

Hematology
- Hematocrit
- Hemoglobin
- Platelet count
- Red blood cell count
- White blood cell count with differential

[1] Clinical chemistry tests will be performed after a minimum 8-hour fast; however, in case of dropouts or rechecks, subjects may not have fasted for 8 hours prior to the serum chemistry sample is taken and test results will be interpreted appropriately.

[2] A microscopic examination for red blood cells, white blood cells, bacteria, and casts will be performed if an abnormality is noted in leukocyte esterase, protein, blood, or nitrite.

[3] Human chorionic gonadotropin (females only).

[4] NicAlert, Accutest Urine Cotinine Test, or other screening kit providing real-time results with a similar level of sensitivity. The same type of kit will be used at each site.

6.2.9 Exhaled Carbon Monoxide

Exhaled CO levels will be measured using a Bedfont Micro+ Smokerlyzer, or similar device, within 2 hours of presentation to the study site at the Screening Visit and within 1 hour of presentation to the site at other Test Visits where noted. Measurements will be used to confirm eligibility prior to randomization and will be used as a measure of compliance

thereafter. Subjects may be provided their results during compliance discussions to demonstrate compliance/noncompliance.

6.2.10 Vital Signs

Vital signs (respiratory rate, heart rate, blood pressure, and oral temperature) will be measured at Screening, check-in and discharge for Test Visits 1, 3, and 5. Measurements will be taken after the subject has been in a seated position for at least 5 minutes and at least 15 minutes after the last cigarette smoked or study product used.

6.2.11 Electrocardiogram

12-lead ECGs will be taken following resting in the supine position for at least 5 minutes and at least 15 minutes after the last cigarette smoked or study product used during Screening and at discharge from the study. ECGs will be interpreted, signed, and dated by the Investigator or a qualified designee. Clinic site reference ranges will be applied to all ECG parameters. The ECG machine will compute the PR and QT intervals, QT interval corrected for heart rate using Bazett's (QTcB) formula, QRS duration, and heart rate and this information will be documented in the subject file. The ECGs will be interpreted as normal, having a clinically insignificant abnormality, or having a clinically significant abnormality. The overall interpretation will be noted in the eCRF.

6.2.12 Lung Function (Spirometry)

Subjects will undergo lung function testing at Screening to affirm eligibility (FEV_1, FEV_1:FVC ratio) and as a safety endpoint (FEV_1, FVC, FEV_1:FVC ratio, and forced expiratory flow $(FEF)_{25-75\%}$).

Spirometry measurements will be conducted in accordance with the 2005 American Thoracic Society / European Respiratory Society Joint Task Force on the standardization of spirometry (Miller et al., 2005). The spirometry predicted values will be standardized by the Third National Health and Nutrition Examination Survey predicted set. Personnel performing spirometry tests must receive appropriate training and the spirometer must be kept calibrated as recommended by the manufacturer.

The spirometry tests should be performed in a sitting position following at least 15 minutes of rest and at least 1 hour from the last cigarette smoked or last *my*blu™ product use. Spirometry must be performed after exhaled CO and FeNO measurements when these events are to be performed on the same day. Multiple measurements may be attempted, but no more than 8 test maneuvers should be performed during a test session. If a subject shows signs of fatigue during repeated testing, testing will be halted and further attempts will only be allowed at the Investigator's discretion.

The subjects will be instructed on how to correctly perform spirometry tests by appropriately trained personnel prior to the measurements being recorded. Spirometry measurements will be performed before and after administration of a short-acting bronchodilator (albuterol). Following acceptable pre-bronchodilator measurements, subjects will be administered 4 puffs

from an albuterol metered-dose inhaler at approximately 30 second intervals (~360 µg total dose assuming 90 µg per puff) using a spacer and a 5-second breath hold after each puff. Post-bronchodilator measurements will be made approximately 10 - 15 minutes following the last albuterol puff.

Each clinic site will be responsible for procuring sufficient supplies to perform the spirometry measurements, including quantities of albuterol and any additional materials for its administration, and for keeping accurate documentation of accountability, dispensing/administration, and disposal of these items as appropriate.

6.3 Study Product Use and Reporting

Subjects will never be forced to smoke or use any study product.

All subjects will smoke their usual brand cigarette according to their usual smoking behaviors through check-in of Test Visit 1 and will be instructed to follow their randomization arm assignments through discharge from the study. However, subjects will be instructed to report use of any other tobacco- or nicotine-containing products.

Each day from Day 3 through discharge from the study on Day 57, subjects randomized to the *my*blu™ arm will report the number of pods started, whether they took more than 50 puffs from the *my*blu™ product, and the number of cigarettes smoked. Subjects randomized to the continue-smoking arm will report the number of cigarettes smoked each day from Day 3 through discharge from the study. Subject self-report will be via a text-message system.

Subjects will be instructed to report product failures to the clinic staff (to be documented by the clinic staff) and to temporarily stop use if they experience any signs of nicotine toxicity (such occurrences will be reported to the clinic staff and documented as AEs).

6.3.1 Confinement Periods

Areas dedicated to product use (within the clinic or outdoors) during the confinement periods must be in accordance with applicable state and local regulations governing the facility. All applicable regulations regarding indoor and outdoor smoking/study product use must be understood and followed by the Investigator.

Dedicated space for use by product type (e-cigarette or combustible cigarette) during product use will be identified to minimize the potential for cross-contamination and illicit study product use. The subjects using an e-cigarette product should not have access to areas where smoking is allowed, and should not share confined sleeping quarters. If necessary, the clinic may schedule the study arms to be confined on separate days to alleviate these concerns.

The clinic staff will provide a demonstration and training of the proper use and care of the *my*blu™ and JUUL® products before use by subjects in those respective arms, and subjects will demonstrate an understanding of the instructions. During the product training on the *my*blu™ product, subjects may sample each e-liquid if they choose to do so.

Generally, study product use will be *ad libitum* upon request to the staff following check-in through 23:00, except during certain events or as otherwise noted. All product use during the confinement periods will be documented by the clinic staff (i.e., each product check-out and return).

Use of products during the PK product use sessions are described in Section 6.7.1.

myblu™ Product Use

Subjects randomized to the *my*blu™ arm will turn over all cigarettes to the clinic staff upon check-in on Day -2 and will smoke their usual brand cigarettes through 23:00 on Day -1. On the morning of Day 1, they will begin participation in a 3-day in-clinic product acclimation period through the evening of Day 3. The acclimation period will afford the subjects the opportunity to try each of the four *my*blu™ e-liquids in order to become accustomed to their use and to determine those that they would be willing to use during the study. Following product training on Day 1, subjects will use each of the four products individually for approximately 2 hours each, with the order of use selected by the subject. However, only one e-liquid may be used during each 2-hour period to ensure that subjects have an adequate time to try each. Following the last 2-hour period, subjects may choose any of the e-liquids freely through 23:00 on Day 2.

At 20:00 on Day 2, subjects will complete the *my*blu™ Product Preference Questionnaire (Appendix 2). Subjects will rank in the order of preference those products that they would be willing to use through the end of the study. It should be emphasized that they should only rank those products that they would be willing to use. Initial product assignment for each subject will be made by the clinic staff based on preference. Beginning on the morning of Day 3, subjects will use the assigned e-liquid through Day 28.

Subjects participating in the PK sub-study will continue to use the assigned product through the evening of Day 4. New pods will be issued for use during the 24-hour urine collection from the afternoon of Day 3 to Day 4. All pods used during the 24-hour urine collections will be weighed within 24 hours before and after use, with the weights documented. A new pod will be provided after completion of the urine collection.

Upon presentation to the clinic for Test Visits 3 and 5, subjects will turn over to the clinic staff the *my*blu™ device. Prior to the start of the urine collection, subjects may use the same pod as was being used prior to presenting to the clinic and new pods will be issued for use during the 24-hour urine collection. All pods used during the 24-hour urine collections will be weighed within 24 hours before and after use, with the weights documented. A new pod may be used after completion of the urine collection if time allows for product use prior to discharge from the test visit.

To further improve compliance through Day 56, during the Day 28 visit subjects using a *my*blu™ product may be allowed to choose to switch to the alternate nicotine strength of their current flavor, to switch to the alternate flavor with the same nicotine strength as their initial choice, or to continue using the same e-liquid selected initially. Subjects will be allowed a brief trial with the alternate products if desired. The site staff will document this use, but subjects will not need to report these as a part of their product use reporting.

Usual Brand Cigarette Use

Subjects randomized to the continue-smoking arm will smoke their usual brand cigarettes throughout each confinement visit. Subjects will turn-over all cigarettes upon check-in to each test visit.

JUUL® Product Use

Subjects in the JUUL® arm will begin using the product following the demonstration and training on Day -2 and will continue to use the product through 23:00 on Day -1. Subjects in the JUUL® arm will not be allowed to smoke at any time from the time of check-in on Day -2 through discharge on Day 1.

6.3.2 Ambulatory Periods

Study product use according to the randomization will be *ad libitum* during the ambulatory periods according to the subject's usual smoking or e-cigarette use behaviors. Subjects are to follow the product use requirements of their respective randomization arm.

6.3.3 Product Use Compliance

Subject compliance with study product use and reporting is a critical component of this study, though 100% compliance from all subjects is an unrealistic expectation. Subjects in the *my*blu™ arm will be reminded at each dispensing for ambulatory use that they are expected to exclusively use the test products without dual use of combustible cigarettes, but that they should be honest about smoking combustible cigarettes as the laboratory assessments will detect use of these products.

Subject self-reported product use will be used as a measure of compliance. The clinic staff will monitor the frequency with which subjects complete the daily product use entries leading up to each Test Visits 2 through 5 and will discuss with subjects any concerns about the entries (e.g., missed reporting, significantly abnormal product use entries). Subjects who complete the daily product use entries on less than 70% of the study days prior to a test visit will be reminded of the importance of documenting product use. Subjects who continue to regularly fail to complete the daily product use entries may be identified by the Investigator as individuals whose noncompliance may jeopardize the integrity of the study data. Disqualification for noncompliance with these product use requirements may only occur in consultation with the Sponsor.

As solely relying on self-reported product use may lead to a conclusion of a higher rate of compliance than actually occurred, biochemical verification of compliance will also be used. While it is recognized that there are many other potential sources of CO and nicotine exposure, exhaled CO and urine cotinine will be used as methods of verifying compliance in real-time. Subjects with values inconsistent with their randomization arm (i.e., subjects in the *my*blu™ arm with exhaled CO values > 8 ppm or negative urine cotinine tests, subjects in the continue-smoking arm with exhaled CO values < 10 ppm or negative urine cotinine tests) will be questioned regarding their recent product use and any information provided will be documented in the subject file. Subjects will be reminded of the importance of compliance

with study instructions, including accurate reporting of other nicotine and tobacco products used.

NNAL is a tobacco-specific nitrosamine with a longer half-life than CO, thus may provide an estimate of compliance over a long period of time by comparison of the post-baseline values to the baseline values. As this will be measured in a bioanalytical assay, real-time monitoring will not be possible and the verification will be completed at the end of the study.

6.4 Biomarker Sample Collection

6.4.1 Blood

Blood samples for COHb in whole blood (2 x 4 mL), sICAM in plasma (1 x 4 mL), WBCs in whole blood (measured in hematology sample), HDL-C in serum (1 x 3.5 mL), MCP-1 in serum (1 x 3.5 mL), and serum for bio-banking (up to 17 mL) will be collected during Test Visits 1, 3, and 5. Samples for COHb will be collected in the afternoon and samples for the other biomarkers and bio-banking will be collected following an overnight fast of at least 8 hours.

Up to approximately 118 mL of blood will be required for the planned assessments during the entire study.

Detailed instructions for collection, processing, and shipping of blood samples will be provided separately.

6.4.2 Urine

24-hour urine collections for biomarker measurements will take place during Test Visits 1, 3, and 5. Each 24-hour urine collection will begin at a time following check-in and will end at the same time ± 30 minutes the following day.

Subjects will be instructed as to urine collection methods. Subjects will be instructed to attempt to void prior to the beginning and at the end of each interval. All urine must be collected during the entire 24-hour interval. The start and stop time of each 24-hour interval and the total weight of the collection will be documented. The weight of the 24-hour urine collection containers will be documented prior to the collection (tare weight) and following completion of the collection.

Urine will be refrigerated during the collection interval. Collections for each subject will be pooled periodically into one labeled container throughout the interval and the total weight (g) will be measured and recorded at the end of the 24-hour interval. Any missed voids will be documented, including the reason for missing. Aliquots will be prepared as noted in the following chart.

At the discretion of the site, 24-hour urine collection during Test Visits 3 and/or 5 may be completed by subjects at home. Subjects will be provided the materials required and will be instructed on the at-home urine collection method.

Biomarker	Number of Aliquots/ Volume Required	Container Type
Nicotine equivalents 1-OHP 8-epi- PGF2α 11-DHTXB2 Creatinine (for adjustment)	2 aliquots of 5 mL each	polypropylene
NNAL / NNN MHBMA 3-HPMA / CEMA / HMPMA S-PMA HEMA 1-AN / 2-AN o-tol 3-OH-B[a]P	2 aliquots of 10 mL each	UV shielded polypropylene
Bio-banking	2 aliquots of 300 mL each	polypropylene

All aliquots will be prepared within 120 minutes from end of the collection and will be stored at -20 ± 10°C until shipped for analysis.

Detailed instructions for collection, processing, and shipping of urine samples will be provided separately.

6.5 Physiologic Assessments

6.5.1 Fractional Concentration of Exhaled Nitric Oxide

FeNO will be measured using a Niox Vero (or similar device) during Test Visits 1, 3, and 5.

FeNO measurements will be preceded by a 30-minute (minimum) abstention from study product use. Water and food intake should be restricted for 1 hour prior to measurement. Subjects will be requested to rinse their mouths with water prior to the procedure.

6.5.2 Blood Pressure and Heart Rate

Blood pressure (systolic and diastolic) and heart rate measurements for physiologic assessment purposes will be taken from the Test Visit 1, 3, and 5 check-in vital signs measurements.

6.6 Subjective Measures

The PSCDI/PSECDI, Cough Questionnaire, QSU-Brief, MTWS-R, PES, Product Liking Questionnaire, Future Intent to Use Questionnaire, and Product and Health Effect Perceptions Questionnaire will be completed during Test Visits 1, 3, and 5, as applicable, using an electronic device.

All relevant software and staff training specific to the electronic questionnaires will be provided.

All subjective measures questionnaires are provided in the Appendices 3 - 10.

At the discretion of the site, some or all questionnaires during Test Visits 3 and/or 5 may be completed by subjects at home. Subjects will be provided the materials required and will be instructed on the at-home questionnaire completion.

6.7 Nicotine Pharmacokinetics Assessments

6.7.1 Product Use

Product use for the PK assessments will consist of two sessions of use of the assigned study product (Day 1 for the continue-smoking and JUUL® arms, Day 5 for the *my*blu™ arm). The first session will be performed in the morning following an abstention from product use of at least 10 hours and will consist of a fixed puffing regimen of 10 puffs taken at 30-second intervals. Puff duration will be 3 seconds for the e-cigarette products and as desired for the combustible cigarette. The clinic staff will indicate to the subjects when to start and stop each puff. The second session will begin 6 hours following the start of the first session and will consist of *ad libitum* use of the e-cigarette product for 5 minutes or use of one cigarette, with no limits on the duration or inter-puff interval for any product. No product use of any kind will be allowed between the sessions.

The clinic staff will document the start and stop time of each session, the number of puffs taken, and reasons for missed puffs during the fixed puffing session. Subjects assigned to an e-cigarette arm will be provided a fully charged battery with a fresh pod for each product use. Pods will be weighed within 24 hours before and after use with the weights documented in grams to 4 decimal places. Products that stop functioning should be replaced as soon as possible, with the failure documented.

6.7.2 Nicotine Pharmacokinetic Blood Sampling

A 4 mL blood sample for plasma nicotine analysis will be drawn into a plastic K_2-EDTA (lavender top) vacutainer tube approximately 5 minutes prior to and at 3, 5, 7, 10, 12, 15, 20, 30, 60, 120 and 180 minutes following the start of each product use episode, with allowable deviation windows of ± 30 seconds for the samples collected from 3 to 15 minutes, ± 1 minute for the samples collected from 20 to 60 minutes, and ± 3 minutes for all other samples.

Approximately 96 mL of blood will be required for the planned PK assessments. Additional blood (typically up to approximately 1 mL) may need to be collected during each time point for the purpose of clearing a blood collection device or line as necessary.

The samples may be kept at room temperature prior to centrifugation, and within 60 minutes from collection will be centrifuged at approximately 1000 to 1300 RCF at ~5°C for approximately 10 minutes. After centrifugation, the plasma will be transferred to two 3.5 mL methanol prewashed polypropylene screw cap tubes, properly labeled, and then stored at -20°C (± 10°C) or below (within 120 minutes from collection) until shipped for analysis.

6.7.3 Urge to Smoke Assessment

Urge to smoke will be assessed using a 100 mm VAS (Appendix 11) approximately 10 minutes prior to and within approximately 30 seconds prior to the scheduled blood draws at 5, 10, 15, 30, 60, and 120 minutes following the start of the *ad libitum* product use sessions.

6.8 Other Clinical Considerations

6.8.1 Meals

Meals and snacks will be served at appropriate times during confinement as determined by the clinic, taking into account fasting requirements for endpoint assessments. In addition, subjects will fast for at least 1 hour prior to and 1 hour after the start of each PK product use session. Low-mutagen meals (e.g., no meats cooked at high temperatures [barbecued, grilled, or pan-fried], cured sandwich meats, smoked meats, bacon, salami, and sausages) should be served on days with urine collections for biomarkers. Eggplant is also not to be served during the confinement periods. Subjects will not be allowed to use study products during meals.

Water will be provided as desired during the study, and subjects will be encouraged to maintain their usual hydration habits. Up to one caffeinated beverage per meal may be served.

6.8.2 Reminder Phone Calls

Reminder telephone calls should be made within 24 to 48 hours prior to each test visit to remind them of the date and time of the visits. Subjects should be reminded to maintain their usual smoking/vaping behavior prior to arrival at the clinic. Subjects required to bring their cigarettes to the clinic will also be reminded to bring only unopened packs to check-in for Test Visits 1, 3, and 5.

6.9 Adverse Events

An AE is any untoward medical occurrence associated with the use of a study product, whether or not considered study product-related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study product, whether or not related to the study product.

Details of the monitoring and reporting of AEs will be provided in the Safety Management Plan.

6.9.1 Monitoring

The subjects will be instructed to inform the study physician or staff of any AEs and intercurrent illnesses experienced during the trial. Additionally, a specific inquiry regarding AEs will be conducted at each scheduled clinic visit and during follow-up telephone calls.

The inquiry will be posed in a non-specific manner using open-ended questions so as not to bias the response (e.g., How are you feeling today?).

A subject who has any clinically significant AE or clinically significant abnormal laboratory test value will be evaluated by the Investigator or other monitoring physician and will be treated and/or followed up until the symptoms or values return to normal or acceptable levels (as appropriate in the opinion of the Investigator), or until the subject is lost to follow-up. Where appropriate, medical tests and examinations will be performed to document resolution of the event(s).

6.9.2 Reporting

Events reported prior to use of study products on Day -2 will be documented as baseline signs and symptoms in the medical history. All events occurring after use of study products on Day -2 must be recorded on the eCRF as AEs. Documentation will include the date and time of onset, action taken, outcome (resolved, improved, unchanged, worse, fatal, or unknown/lost to follow-up), duration, relationship to product administration, and severity for each event. AEs will be coded using most current version of the Medical Dictionary for Regulatory Activities (MedDRA)® available at [redacted]

The Investigator will review each event and assess its relationship to product administration as unrelated, unlikely, possibly, probably, or likely.

In addition, each sign or symptom reported will be graded on a 3-point severity scale using mild, moderate, or severe.

6.9.3 Serious Adverse Events

A SAE is any AE that in the view of either the Investigator (or designee) or Sponsor, results in any of the following outcomes: death, a life threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition.

Life threatening is defined as an AE that in the view of the Investigator (or designee) or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

Unexpected is defined as an AE that is not consistent with the known risk information associated with the study product.

All SAEs, whether or not considered study-related, must be reported by telephone and by fax or e-mail to the Sponsor within 24 hours of the site's learning of the SAE or, at the latest, on the following workday. The Sponsor's representative to contact about this study is provided

in the list of study contacts. The Investigator must also inform the IRB, in compliance with GCP reporting guidelines, and the site monitor of any SAE.

6.10 Pregnancy

A positive pregnancy test prior to use of study products on Day -2 will result in the subject failing screening. A positive pregnancy test thereafter will be documented by the Investigator on the pregnancy form and will be documented as a protocol deviation. The Investigator or designee will discontinue the pregnant subject from the study and will advise her to seek prenatal care and counseling from her primary care provider. Pregnancy itself is not an AE.

The clinic staff will request the pregnant subject to notify the site of the outcome of the pregnancy (i.e., birth, loss, or termination). To help ensure this, the clinic staff will follow up with the subject until the end of pregnancy, if in compliance with the site's standard operating procedures (SOPs) and with the subject's consent. This request and the subject's response will be documented in the subject's source document.

6.11 Smoking Cessation Information

At screening and prior to discharge from the study (or upon early termination) all subjects will be advised that to reduce the health effects of smoking, the best thing to do is to quit. Subjects will be referred to the Center for Disease Control and Prevention website for quit strategies (https://www.cdc.gov/tobacco/campaign/tips/quit-smoking) and will be encouraged to contact a qualified medical professional for additional advice on smoking cessation.

7. DATA ANALYSIS

Data will be handled and processed according to [redacted] SOPs, which are written based on the principles of GCP. A brief description of the statistical analysis is included below, detailed methodology for all summary and statistical analyses of the data collected in this trial will be documented in a statistical analysis plan (SAP) prepared by [redacted] and agreed upon by the Sponsor. The SAP may modify the plans outlined in the protocol; however, any major modifications of the primary endpoints and/or their analysis will also be reflected in a protocol amendment. If deemed appropriate, additional statistical analyses other than those described in this section may be performed and included in the plan.

7.1 Sample Size Estimation

This study is prospectively powered to find significant decreases in the primary BoE in subjects who switch to *my*blu™ e-cigarettes for 28 days.

Exclusive use of blu products during a 5-day in-clinic period was previously shown to reduce the primary BoE to be assessed in this study by ~60% to ~95% (O'Connell et al., 2016). In the same study, reducing cigarette consumption by ~30% of that during the baseline period resulted in ~13% to ~27% reductions. However, no published data are available for the current test products, or similar e-cigarette products, over a longer use period from which a sample size may be estimated for this study. Therefore, the sample size estimation was made

using Day 30 data from FDA Center of Tobacco Products Docket # FDA-2017-D-3001 (study ZRHM-REXA-08-US) where the applicant assessed similar BoE in subjects who switched to a tobacco heating product or continued to smoke combustible cigarettes during an out-of-clinic product use period.

Based on this previous data, a minimum of 29 subjects per cohort is estimated to be needed to find differences in the Day 28 S-PMA change-from-baseline value equivalent to a 50% reduction in biomarker value compared to the continue-smoking arm using one-sided significance level of 0.0125 (alpha of 0.05 adjusted for multiple comparisons using the Bonferroni method) with a power of at least 80%. Approximately 43 subjects are planned to be randomized into each *my*blu™ e-liquid cohort and 40 subjects into the continue-smoking arm to better ensure that the minimum number complete the Day 28 assessments. The following table provides the power estimate for each of the primary endpoint biomarkers assuming 29 subjects in the ITT population complete the study.

Biomarker	Test group baseline value	Test group change-from-baseline SD	Control group change-from-baseline SD	Power
COHb (% sat)	6.95	2.28	1.73	>0.9999
NNAL (ng)	340	178	133	0.9623
3-HPMA (µg)	1325	494	500	0.9968
S-PMA (ng)	3348	2370	1512	0.8106

The baseline and change-from-baseline SD values in this table were derived from study ZRHM-REXA-08-US in US FDA Center of Tobacco Products Docket # FDA-2017-D-3001 who had reported Baseline and Day 30 measurements for the listed biomarkers.

Abbreviations: 3-HPMA = 3-hydroxypropylmercapturic acid, COHb = carboxyhemoglobin, NNAL = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, SD = standard deviation, S-PMA = S-phenyl mercapturic acid.

7.2 Analysis Populations

7.2.1 Safety Population

The safety population will include all subjects with at least one reported product use from Day -1.

7.2.2 Intent-to-Treat Population

The ITT population will consist of randomized subjects with at least one documented product-use experience from Day 1, irrespective of their compliance of the product-use to which they were randomized.

7.2.3 Per-Protocol Population

The PP population is a subset of the ITT population who meet the requirements below. Separate populations for Product Use Periods 1 and 2 will be established based on data collected during each of those periods.

***my*blu™ and continue-smoking arms**

- Have no protocol deviations significantly impacting the integrity of the analysis or interpretation of the individual endpoint under consideration (e.g., compromised urine samples, use of prohibited medications impacting the endpoint)
- Have a daily product use response rate of at least 70% during the product use period
- Have a positive urine cotinine test at each scheduled assessment

***my*blu™ arm**

- Self-report reducing cigarette consumption by at least 90% of that reported at baseline
- Have exhaled CO values ≤ 8 ppm at each scheduled post-baseline assessment
- Have post-baseline urine NNAL values reduced by ≥ 75% from baseline

7.2.4 Pharmacokinetics Population

The PK population for each product use session will include subjects who used a product and have evaluable PK profiles.

7.3 Calculations

7.3.1 Urine Nicotine Equivalents

Nicotine equivalents will be calculated as the molar sum of nicotine and 5 major nicotine metabolites. Values of individual components reported as below the limit of quantitation (BLQ) will be set to one-half of the limit of quantitation prior use in the calculation below. Missing urine data will not be imputed.

Nicotine equivalents (µg/mL) = (nicotine [ng/mL]/162.23 [mg/mmol] + nicotine-gluc (ng/mL)/338.36 [mg/mmol] + cotinine [ng/mL]/176.22 [mg/mmol] + cotinine-gluc [ng/mL]/352.34 [mg/mmol] + trans-3'-hydroxycotinine [ng/mL]/192.22 [mg/mmol] + trans-3'-hydroxycotinine-gluc [ng/mL]/368.34 [mg/mmol]) x 162.23 (mg/mmol) x 1 µg/1000 ng

7.3.2 Calculation of Total Mass Excreted

Urine biomarker concentrations will be converted into biomarker quantities excreted in 24 hours by multiplying the measured concentration by the total weight (i.e., 1 kilogram = 1 liter) of urine produced by the subject during the 24-hour period.

7.3.3 Creatinine Adjustments

Urine creatinine will be measured and used to adjust the values of the primary and secondary urine BoPH and BoE as follows.

$$\text{Biomarker (unit/g creatinine)} = \frac{\text{Biomarker (units)} \times 100}{\text{creatinine (mg/dL)}}$$

7.4 Data Summarization

Data summarizations and statistical analyses will be performed using SAS procedures. In general, all data will be listed by subject, product, and period (and time point as necessary) and summarized by product and period (and time point as necessary). Absolute and percent change-from-baseline values, and absolute and percent differences between Test Visits 3 and 5, will also be listed and summarized where indicated. Descriptive statistics (number of observations, mean, median, standard deviation, minimum, and maximum) will be used for continuous data variables and frequency counts (number of observations and percentage) for categorical data variables. Figures will be used to display the data graphically. All data summarizations and figures will be generated using the ITT and PP populations.

Additional information specific to certain study endpoints are discussed in the sections that follow.

7.4.1 Product Use and Compliance

Product use (including the PK product use sessions) and compliance variables will be summarized descriptively by time point, period, and product use session as appropriate. No inferential statistical analysis will be performed.

7.4.2 Biomarkers of Exposure and Potential Harm

Biomarker concentrations reported as below the limit of quantitation will be reported as "BLQ" in the listings and set to one-half of the limit of quantitation for summarization and statistical analysis.

The following variables will be determined and summarized for each urine biomarker.

- Measured concentration
- Total biomarker mass excreted per 24 hours
- Creatinine-adjusted excretion level

Absolute and percent change-from-baseline will be determined for the mass excreted and creatinine-adjusted values. The total urine biomarker mass excreted per 24 hours change-from-baseline value will be used as the primary variable in the statistical analysis.

7.4.3 Physiologic Assessments

Test Visit 1, 3, and 5 check-in blood pressure (systolic and diastolic) and heart rate measurements will be assessed for physiologic assessment purposes.

7.4.4 Subjective Measures

Each item on each of the subjective measures questionnaires will be summarized. In addition, the following total scores, factor scores, and subscales will also be calculated and summarized.

- PSCDI/PSECDI total score
- MTWS-R total score
- QSU-brief factor scores:
    - Factor 1 (anticipation of pleasure from smoking) - average of items 1, 3, 6, 7, and 10
    - Factor 2 (relief of nicotine withdrawal) - average of items 2, 4, 5, 8, and 9
- PES subscales:
    - Satisfaction - average of items 1, 2, 3, and 12
    - Psychological reward - average of items 4 through 8
    - Aversion - average of items 9, 10, 16, and 18
    - Relief - average of items 11, 13, 14, 15, and reversed for item 20
    - Items 17, 19, 21 will be summarized as individual item scores

7.4.5 Nicotine Pharmacokinetic Analysis

Nicotine PK parameters will be determined from the individual plasma concentrations applying a noncompartmental approach using appropriate validated PK software (e.g., Phoenix® WinNonlin® version 7.0 or higher).

For each study product and product use session, the following PK parameters will be calculated from the nicotine concentration-time data:

AUC_{0-t} Area under the nicotine concentration-time curve from time zero (defined as the start of product use) to the last quantifiable concentration during the interval as calculated by the linear trapezoidal with linear interpolation method.

C_{max} Maximum measured plasma concentration over the duration of the measurement interval.

T_{max} Time to reach the maximum measured plasma concentration over the duration of the measurement interval. If the maximum value occurs at more than one time point, Tmax is defined as the first time point with this value.

For the calculation of the PK parameters, plasma concentrations below the limit of quantitation (BLQ) will be set to one-half of the LLOQ for the calculation of descriptive statistics of unadjusted plasma nicotine concentrations.

Adjustments for existing pre-product use nicotine concentrations will be performed for calculation of PK parameters. The values used for all pre-product use adjustments is the plasma nicotine concentration value obtained before the first product use of each session and the adjustment will be subject-specific.

*Baseline-adjustment method: For each PK profile, the pre-product administration nicotine concentration value for each subject will be subtracted from each nicotine concentration obtained after test product administration in that period/day using the following equation:

$$C_t = C_{t\ uncorrected} - [C_0 \cdot e^{-Kel \cdot t1}]$$

Where:

C_t = Corrected concentration.

$C_{t\ uncorrected}$ = the uncorrected concentration.

C_0 = the pre-product administration concentration.

$Kel^{£} = \frac{\ln(2)}{t1/2}$

t1/2 is 2.0 hours for all subjects (estimated nicotine half-life)

t = actual sampling time since product administration.

t1 = actual sampling time since pre-product administration sampling.

After correction for pre-product administration values, some concentrations may be below the lower limit of quantitation and some may be negative values. Negative values will be assigned a value of zero in the analyses and all other values obtained will be reported as is even if these values are BLQ.

7.4.6 Urge to Smoke Parameters

The following parameters will be calculated for the urge to smoke assessments performed during the PK assessments.

E_{max_R} The maximum reduction from baseline VAS score (VASpre-use – VASpost-use). If there is no reduction, a value of zero will be reported.

TE_{max} Time of the E_{max_R}. If the maximum value occurred at more than one time point, TE_{max} will be defined as the first time point with this value.

$AUEC_{0\text{-}120}$ The area under the change from baseline "Urge to Smoke" VAS score versus time curve from 0 to 120 minutes, calculated using the linear trapezoidal method with linear interpolation using actual sample times.

7.5 Statistical Analysis

7.5.1 Primary Endpoints

Comparisons of the Day 28 visit primary BoE change-from-baseline values between the continue-smoking arm and each *my*blu™ e-liquid product selected at Day 1 will be made using a linear mixed model ANOVA. The ITT population will be used as the primary analysis population and an analysis using the PP population will be used as a supportive analysis.

7.5.2 Secondary Endpoints

An approach similar to that used for the primary endpoints will be used to make Day 28 and Day 56 change-from-baseline comparisons between the *my*blu™ products and the continue-smoking arm for the applicable secondary BoE, BoPH, physiologic endpoints, and subjective measure endpoints as described in the SAP. For the Day 56 analysis, the initial *my*blu™ flavor cohort assignments for each subject will be maintained within the statistical model and a separate sensitivity analysis will be performed for subjects that do not switch flavors at Day 29.

Comparisons of the primary and secondary BoE change-from-baseline values at each time point within and between the *my*blu™ product cohorts will also be made using a linear mixed model ANOVA.

A linear mixed model ANOVA will be performed on the log-transformed nicotine PK parameters AUC and C_{max} from each product use session. Non-parametric analysis (Wilcoxon Signed Rank test) will be performed for the comparisons of Tmax. Similar methods will be used to compare the urge to smoke parameters. The comparisons of interest will include each of the *my*blu™ products compared to the usual brand cigarette and JUUL® product.

7.6 Safety

All clinical safety data will be listed by subject and time point and summarized as described in the SAP.

All reported events captured in the database will be listed in by-subject data listings. However, only study product use-emergent AEs. A study product use-emergent AE is defined as an AE that is starting or worsening at the time of or after the first study product use on Day -2.

Frequencies of subjects with study product use-emergent AEs, regardless of relationship to study product will be summarized and sorted by system organ class. Frequencies of subjects

with study product use-emergent SAEs will be likewise summarized. Frequencies of study product use-emergent AEs will be summarized by severity and relationship to study product.

Changes in physical examinations (if any) will be described in the text of the final report.

All prior and concomitant medications recorded during the study will be listed by subject.

The following pre- and post-bronchodilator lung function variables will be summarized.

- Measured and percent of predicted FEV_1
- Measured and percent of predicted FVC
- Measured and percent of predicted FEV_1:FVC ratio
- Measured and percent of predicted $FEF_{25-75\%}$

8. STUDY ADMINISTRATION

8.1 Ethics

8.1.1 Institutional Review Board

This protocol will be reviewed by an institutional review board (IRB) and the study will not start until the IRB has approved the protocol or a modification thereof. The IRB is constituted and operates in accordance with the principles and requirements described in the US Code of Federal Regulations (21 CFR Part 56). The IRB is compliant with the International Council for Harmonisation (ICH).

8.1.2 Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, US Code of Federal Regulations, 21 CFR Parts 50, 56, and 312, the ethical principles set forth in the Declaration of Helsinki, GCP, and the ICH harmonized tripartite guideline regarding GCP (E6 R2 Consolidated Guidance, November 2006).

8.1.3 Subject Informed Consent

All prospective subjects will have the study explained by the Investigator or his/her designee in non-technical terms and will be required to read, sign, and date an IRB-approved ICF prior to completion of screening or other study procedures.

The consent form will provide the subjects with the purpose of the study, procedures to be carried out, and potential hazards, and subjects will be allowed sufficient time to review and ask questions about the study. The subjects will be assured that they may withdraw from the study at any time without jeopardizing medical care related to or required as a result of study participation. The subject will be informed that any samples collected prior to withdrawal and awaiting analysis will be analyzed unless he/she provides written instruction to have such samples destroyed.

The ICF will be signed and dated by the subject and by a member of the clinical staff qualified to conduct the informed consent discussion. The fully signed ICF will be filed in the source documents and a copy will be given to the subject.

8.2 Termination of the Study

The Sponsor reserves the right to discontinue this study and the Investigator reserves the right to terminate the study for safety reasons at any time.

8.3 Data Management

Data management activities will be detailed in the Data Management Plan (DMP). Each vendor involved with this study will adhere to Good Documentation Practices and their standard operating procedures covering their respective activities relevant to participation in this study. The Investigator will ensure that all data related to the conduct of this study at his/her site is attributable, legible, contemporaneous, original, accurate, enduring, and readily accessible.

8.3.1 Database Design and Creation

An appropriate database will be designed and created within a validated Clinical Data Management System (CDMS). Electronic data capture will be used for this study and eCRFs will be developed according to the study protocol specifications. Certain clinical and analytical laboratory data will be collected external to CDMS as external data files.

8.3.2 Data Coding

AEs and medical history coding will be undertaken using most current version of MedDRA. Concomitant medications will be coded using the WHO Drug Dictionary. Each dictionary version will remain the same throughout the trial. Coding will be completed by qualified members of the [redacted] staff.

8.3.3 Data Entry and Verification

Data will be transcribed from original sources by the Investigator or Investigator's staff into the eCRF. Data received from external sources (e.g., questionnaire or clinical laboratory results) will be integrated into the Clinical Data Interchange Standards Consortium study data tabulation model datasets.

8.3.4 Study Results Data Transfer

Study data transfers will be sent to the Sponsor or their designee, electronically on a schedule and in a format mutually agreed upon by the Sponsor or their designee, and [redacted] for the analysis of these study data. No personally identifiable information will be transferred to the Sponsor at any point in the study.

8.3.5 Data Validation

After the data have been entered and source data verified by the monitor, various edit checks (including manual review of listings) will be performed to ensure the accuracy, integrity and validation of the database against the eCRF as described in the DMP.

Inconsistencies that arise from these edit checks will be resolved with the Investigator or designee.

8.3.6 Database Lock

On study completion, after data entry is complete, the data has been pronounced clean, and the Investigators have reviewed and provided approval via signature, the database will be locked and final write access will be removed.

The Sponsor will be required to provide database lock approval.

Any changes to the data following database lock will be documented and approved by the Sponsor prior to unlocking the database to make changes to the data.

The final transfer of all study data (without subject personally identifying information) to the Sponsor will be in SAS format with supporting SAS documentation according to the specifications of the Sponsor. Subject initials, date of birth (except year), and other personal identifiers will be removed from this data transfer file; any such information removed will be documented at the time of transfer.

8.4 Monitoring the Study

The responsible study monitor will contact and visit the Investigator as necessary, and he/she will be allowed, upon request, to inspect and verify all records of the study (e.g., source document, ICFs, eCRFs, regulatory documents) in a manner consistent with GCP and all other applicable state and federal law.

It will be the study monitor's responsibility to inspect the source documents to verify the adherence to the protocol and the completeness, consistency, and accuracy of the data being entered in the eCRF. The monitor will verify that each subject has consented in writing prior to any study procedures being performed. Where the terms of the informed consent, GCP, and all other applicable state and federal law permit, the monitor should have access to laboratory test reports and other subject records needed to verify the entries on the eCRF. The Investigator (or his/her designee) agrees to cooperate with the monitor to ensure that any issues detected in the course of these monitoring visits are resolved.

In addition, the Sponsor's internal auditors (or designee) and government inspectors may evaluate the study and must be allowed access to eCRFs, source documents, and other study files.

The Investigator must notify the Sponsor (or designee) promptly of any inspections of the study or activities related to the study scheduled by regulatory authorities, allow the Sponsor

(or designee) to be present, and promptly forward copies of inspection reports to the Sponsor (or designee).

8.5 Reporting for the Study

8.5.1 Case Report Forms

Electronic CRFs will be completed for each screened subject whether or not he/she has completed the study. The Investigator will assure complete and accurate entries on the forms. All eCRFs will be reviewed and signed by the Investigator.

8.5.2 Study Report

Two study reports are intended to be produced for this study: one describing the main study results and a one describing the PK sub-study. The reports will include appropriate descriptions of the clinical conduct of the study, safety evaluation, analytical methods and results, and the statistical analysis described in the statistical methodology section of the protocol and the SAP.

At the time the draft study reports are completed, [redacted] Quality Assurance (QA) unit will audit the reports against the SAS data and the raw data. At the completion of the audit, a QA report will be issued internally allowing any findings to be addressed before report finalization.

8.6 Confidentiality

All clinic sites and vendors will have signed confidentiality agreements with [redacted] will regard all information provided to the Investigator dealing with the study and information obtained during the course of the study as confidential.

Neither the clinic site nor [redacted] will supply to the Sponsor any subject names, initials, date of birth (except year), or other personal identifiers (HIPAA 2007). All such information appearing on any study document must be redacted before a copy of the document is supplied to the Sponsor. The photocopied government-issued ID to verify subject age will be kept separate from other source documentation and not provided to the Sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed during the consenting process that representatives of the Sponsor, IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in the strictest confidence and in accordance with local data protection laws.

8.7 Publication Policy

All unpublished information given to [redacted] 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.

9. REFERENCES

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10. APPENDICES

Appendix 1: Demographics Questionnaires

Screening Demographics Questionnaire

1. What is your date of birth?

   _____

2. What is your sex?

   ☐ Male
   ☐ Female

3. Which one of these groups would you say best describes your race?

   ☐ White/Caucasian
   ☐ Black/African American
   ☐ Asian
   ☐ Native Hawaiian or other Pacific Islander
   ☐ American Indian or Alaska Native
   ☐ Other (SPECIFY): _____

4. Are you Hispanic or Latino?

   ☐ Yes
   ☐ No

Additional Demographics Questionnaire

1. What was your annual household income from all sources over the past year?

   ☐ Under $20,000
   ☐ $20,000 - $29,999
   ☐ $30,000 - $39,999
   ☐ $40,000 - $49,999
   ☐ $50,000 - $59,999
   ☐ $60,000 - $74,999
   ☐ $75,000 - $99,999
   ☐ $100,000 - $149,999
   ☐ $150,000 and over
   ☐ I do not wish to answer

2. What was the highest grade or year of school you completed?

   ☐ Never attended school or only attended kindergarten
   ☐ Grades 1 through 8 (elementary)
   ☐ Grades 9 through 11 (some high school)
   ☐ Grade 12 or GED (high school graduate)
   ☐ College 1 year to 3 years (some college or technical school)
   ☐ College 4 years or more (college graduate)
   ☐ Postgraduate/masters/doctorate/law/MD
   ☐ Other
   ☐ I do not wish to answer

3. What is your marital status?

   ☐ Single
   ☐ Married/living with significant other
   ☐ Separated/divorced/widowed
   ☐ I do not wish to answer

4. Which of the following options do you identify with?

   ☐ Heterosexual or straight
   ☐ Lesbian or gay
   ☐ Bisexual
   ☐ Transgender
   ☐ Something else
   ☐ Don’t know/not sure
   ☐ I do not wish to answer

Appendix 2: *my*blu™ Product Preference Questionnaire

For the rest of the study you will be expected to replace **all** of your usual brand cigarettes with the e-cigarette product.

Please rank each product that you will be willing to use to replace **all** of your cigarettes for the rest of the study, with 1 being the most preferred. Do not use a number more than once (there are no "ties").

You will be assigned one of the products that you rank.

Do not rank a flavor that you will not be willing to use instead of your cigarettes.

____ Tobacco Chill - low nicotine

____ Tobacco Chill - high nicotine

____ Honeymoon - low nicotine

____ Honeymoon - high nicotine

Appendix 3: Penn State [Electronic] Cigarette Dependence Index (PSCDI/PSECDI) (Foulds et al., 2015)

The following questionnaire will be administered to subjects in the myblu™ and continue-smoking arms at Test Visits 1 (Day -2), 3, and 5.

Note: For the Electronic Cigarette Dependence Index, substitute the underlined word with the words in square brackets.

1. How many cigarettes *[times]* per day do you usually smoke *[use your electronic cigarette]*? *([assume that one "time" consists of around 15 puffs or lasts around 10 minutes])*
   (Scoring: 0–4 times/day = 0, 5–9 = 1, 10–14 = 2, 15–19 = 3, 20–29 = 4, 30+ = 5)

2. On days that you can smoke *[use your electronic cigarette]* freely, how soon after you wake up do you smoke your first cigarette of the day *[first use your electronic cigarette]*?
   (Scoring: 0–5 mins = 5, 6–15 = 4, 16–30 = 3, 31–60 = 2, 61–120 = 1, 121+ = 0)

3. Do you sometimes awaken at night to have a cigarette *[use your electronic cigarette]*?
   (Scoring: Yes = 1, No = 0)

4. If yes, how many nights per week do you typically awaken to smoke *[use your electronic cigarette]*?
   (Scoring: 0–1 nights = 0, 2–3 nights = 1, 4+ nights = 2)

5. Do you smoke *[use an electronic cigarette]* now because it is really hard to quit?
   (Scoring: Yes = 1, No = 0)

6. Do you ever have strong cravings to smoke *[use an electronic cigarette]*?
   (Scoring: Yes = 1, No = 0)

7. Over the past week, how strong have the urges to smoke *[use an electronic cigarette]* been?
   (Scoring: None/Slight = 0, Moderate/Strong= 1, Very Strong/Extremely Strong = 2)

8. Is it hard to keep from smoking *[using an electronic cigarette]* in places where you are not supposed to?
   (Scoring: Yes = 1, No = 0)

When you haven't used tobacco *[an electronic cigarette]* for a while or when you tried to stop smoking *[using]*…

9. Did you feel more irritable because you couldn't smoke *[use an electronic cigarette]*?
   (Scoring: Yes = 1, No = 0)

10. Did you feel nervous, restless, or anxious because you couldn't smoke *[use an electronic cigarette]*?
    (Scoring: Yes = 1, No = 0)

Total scoring: 0 - 3 = not dependent, 4 - 8 = low dependence, 9 - 12 = medium dependence, 13+ = high dependence.

Appendix 4: Cough Questionnaire

The following questionnaire will be administered to subjects in the myblu™ and continue-smoking arms at Test Visits 1 (Day -2), 3, and 5.

1. Did you have a cough during the last 5 days?
    1. Yes – PROCEED TO QUESTIONS 2 TO 5.
    2. No – STOP. DO NOT ANSWER THE REST OF THE QUESTIONS.

2. How would you rate the intensity of your cough during the last 5 days?
    1. Very mild
    2. Somewhat mild
    3. Mild
    4. Somewhat moderate
    5. Moderate
    6. Severe
    7. Very severe

3. How often did you cough up phlegm during the last 5 days?
    1. Every time
    2. Most times
    3. Several times
    4. Some times
    5. Occasionally
    6. Rarely
    7. Never

4. How often did your cough disturb your sleep during the last 5 days?
    1. All of the time
    2. Most of the time
    3. A good bit of the time
    4. Some of the time
    5. A little bit of the time
    6. Hardly any of the time
    7. None of the time

5. How often did you have coughing bouts during the day, during the last 5 days?
    1. All of the time (continuously)
    2. Most of the time
    3. A good bit of the time
    4. Some of the time
    5. A little bit of the time
    6. Hardly any of the time
    7. None of the time

Appendix 5: Questionnaire of Smoking Urges-Brief (QSU-Brief) (Cox et al., 2001)

*The following questionnaire will be administered to subjects in the myblu™ and continue-smoking arms at Test Visits 1 (Day -2), 3, and 5, and also to the subjects in the my*blu™ *arm on Test Visit 1, Day 3.*

Please check the box that best describes your urge to smoke right now.

	Strongly Disagree						Strongly Agree
I have a desire for a cigarette right now.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
Nothing would be better than smoking a cigarette right now.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
If it were possible, I would probably smoke right now.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
I could control things better right now if I could smoke.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
All I want right now is a cigarette.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
I have an urge for a cigarette.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
A cigarette would taste good right now.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
I would do almost anything for a cigarette right now.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
Smoking would make me less depressed.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7
I am going to smoke as soon as possible.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Factor 1 (anticipation of pleasure from smoking): average of items 1, 3, 6, 7, and 10.
Factor 2 (relief of nicotine withdrawal): average of items 2, 4, 5, 8, and 9.

Appendix 6: Minnesota Tobacco Withdrawal Scale-Revised (MTWS-R)

*The following questionnaire will be administered to subjects in the myblu™ and continue-smoking arms at Test Visits 1 (Day -2), 3, and 5, and also to the subjects in the my*blu™ *arm on Test Visit 1, Day 3.*

Note: The DSM-5 and craving items from the MTWS have been included here. Please see http://www.med.uvm.edu/behaviorandhealth/research/minnesota-tobacco-withdrawal-scale.

Please rate yourself for the period of the last 24 hours.

1. Angry, irritable, frustrated	0 1 2 3 4
2. Anxious, nervous	0 1 2 3 4
3. Depressed mood, sad	0 1 2 3 4
4. Difficulty concentrating	0 1 2 3 4
5. Increased appetite, hungry, weight gain	0 1 2 3 4
6. Insomnia, sleep problems, awakening at night	0 1 2 3 4
7. Restless	0 1 2 3 4
8. Desire or craving to smoke	0 1 2 3 4

Scale: 0 = none, 1 = slight, 2 = mild, 3 = moderate, 4 = severe

Appendix 7: Product Liking Questionnaire

Note: Each of these questions will be paired with a VAS. The VAS will be anchored with "Not at All" on the left and "Extremely" on the right.

The following question will be administered to subjects in the myblu™ and continue-smoking arms at Test Visit 1 (Day -2), and to the subjects in the continue-smoking arm at Test Visits 3 and 5.

Please respond to each phrase with how you feel about the study product you are using by drawing a vertical mark anywhere along the horizontal line.

How much do you like your usual brand cigarette?

The following question will be administered to the myblu™ subjects at Test Visits 1 (Day 3), 3 and 5.

Please respond to each phrase with how you feel about the study product you are using by drawing a vertical mark anywhere along the horizontal line.

How much do you like the test e-cigarette you are using?

Appendix 8: Product Evaluation Scale (PES) (Hatsukami et al., 2013)

*The following questionnaire will be administered to subjects in the myblu™ and continue-smoking arms at Test Visits 1 (Day -2), 3, and 5, and also to the subjects in the my*blu™ *arm on Test Visit 1, Day 3.*

Please mark the number that best represents how using the product made you feel.

1. Was it satisfying?
2. Did it taste good?
3. Did you enjoy the sensations in your mouth?
4. Did it calm you down?
5. Did it make you feel more awake?
6. Did it make you feel less irritable?
7. Did it help you concentrate?
8. Did it reduce your hunger for food?
9. Did it make you dizzy?
10. Did it make you nauseous?
11. Did it immediately relieve your craving for a cigarette?
12. Did you enjoy it?
13. Did it relieve withdrawal symptoms?
14. Did it relieve the urge to smoke?
15. Was it enough nicotine?
16. Was it too much nicotine?
17. Was it easy to use?
18. Were there bothersome side effects?
19. Were you comfortable using the product in public?
20. Did you still have a craving for a cigarette after using the product?
21. Are you concerned that you would become dependent on this product?

Scale: 1 = not at all, 2 = very little, 3 = a little, 4 = moderately, 5 = a lot, 6 = quite a lot, 7 = extremely

Four multi-item subscales will be derived from "Satisfaction" (items 1, 2, 3, and 12); "Psychological Reward" (items 4 through 8); "Aversion" (items 9, 10, 16, and 18); and "Relief" (items 11, 13, 14, 15, and reversed for item 20) and single items 17, 19, and 21 will be summarized.

Appendix 9: Future Intent to Use Questionnaire

Note: Each of these questions will be paired with a VAS. The VAS will be anchored with "Not at All" on the left and "Extremely" on the right.

The following question will be administered to subjects in the myblu™ and continue-smoking arms at Test Visit 1 (Day -2), and to the subjects in the continue-smoking arm during Test Visits 3 and 5.

Please respond to each phrase by drawing a vertical mark anywhere along the horizontal line.

1. How likely are you to continue to smoke after you complete this study?
2. Except as required for this study, how likely are you to use an e-cigarette product in the future?

The following questions will be administered to the myblu™ arm at Test Visits 3 and 5.

Please respond to each phrase by drawing a vertical mark anywhere along the horizontal line.

1. How likely are you to continue to smoke after you complete this study?
2. If available, how likely are you to buy your assigned study product in the future?
3. How likely are you to buy an e-cigarette other than your assigned product in the future?

Appendix 10: Product and Health Effect Perceptions Questionnaire

Note: Each of these questions will be paired with a VAS. The VAS will be anchored with "Definitely Would Not" on the left and "Definitely Would" on the right, and "Don't Know" in the center.

The following items will be administered to subjects in the myblu™ and continue-smoking arms at Test Visit 1 and to the subjects in the continue-smoking arm during Test Visits 3 and 5.

Please respond to each phrase by drawing a vertical mark anywhere along the horizontal line.

1. E-cigarettes would help me to reduce the number of cigarettes that I smoke each day.
2. E-cigarettes would help me to completely quit smoking cigarettes.
3. Using e-cigarettes instead of some of my cigarettes would be healthier for me.
4. Using e-cigarettes instead of all of my cigarettes would be healthier for me.

The following items will be administered to the myblu™ arm at Test Visits 3 and 5.

Please respond to each phrase by drawing a vertical mark anywhere along the horizontal line.

1. The study product would help me to reduce the number of cigarettes that I smoke each day.
2. The study product would help me to completely quit smoking cigarettes.
3. Using the study product instead of some of my cigarettes would be healthier for me.
4. Using the study product instead of all of my cigarettes would be healthier for me.

Appendix 11: Urge to Smoke Questionnaire

Note: The following question will be paired with a VAS. The VAS will be anchored with "Not at All" on the left and "Extreme" on the right.

Please respond to the question by drawing a vertical mark anywhere along the horizontal line.

How strong is your urge to smoke right now?

Appendix 12: Tobacco/Nicotine Product Use History Questionnaire

Please read each product description and then indicate the tobacco products that (1) you have ever used the product (even once) and (2) used in the past 14 days. If you have used in the past 14 days, indicate the approximate number of days.

Tobacco Product or Nicotine Containing Product	Have you ever used this product, even once?	Have you used the product in the past 14 days?	If "yes" indicate the number of days
ELECTRONIC CIGARETTES or E-VAPOR products: An e-cigarette is a battery-powered device that is puffed like a cigarette	☐ Yes ☐No	☐ Yes ☐No	_____ days
BIDIS OR KRETEKS: Popular in other parts of the world. Bidis are small hand-rolled cigarettes. Kreteks are clove- flavored cigarettes. An example of a kretek brand is DJARUM BLACK	☐ Yes ☐No	☐ Yes ☐No	_____ days
PREMIUM CIGARS: Come in different sizes and shapes. Some examples of premium cigar brands are MACANUDO, ARTURO FUENTE AND ROMEO Y JULIETA.	☐ Yes ☐No	☐ Yes ☐No	_____ days
LARGE CIGARS: Not premium cigars; generally wider and longer than cigarillos. PHILLIES BLUNT cigars is an example of a large cigar brand	☐ Yes ☐No	☐ Yes ☐No	_____ days

Tobacco Product or Nicotine Containing Product	Have you ever used this product, even once?	Have you used the product in the past 14 days?	If "yes" indicate the number of days
CIGARILLOS: Generally narrower and shorter than premium cigars; they may come with plastic or wooden tips. BLACK & MILD is an example of a cigarillo brand. Other examples include SWISHER SWEETS and DUTCH MASTERS	☐ Yes ☐No	☐ Yes ☐No	_____ days
LITTLE CIGARS: Look similar to cigarettes, except they are brown and have a filter like a cigarette. Some examples of little filtered cigar brands are WINCHESTER, CAPTAIN BLACK and WRANGLER	☐ Yes ☐No	☐ Yes ☐No	_____ days
CHEWING TOBACCO: Coarsely shredded and sold in pocket-sized packs of loose tobacco leaves or in a "plug" or "twist" form. Brands include RED MAN, LEVI GARRETT and BEECH-NUT	☐ Yes ☐No	☐ Yes ☐No	_____ days
SNUFF (DIP): Finely ground form of tobacco that is usually sold in a tin. It can be fine cut, long cut, pouched or pre-portioned. Brands include GRIZZLY, COPENHAGEN and SKOAL	☐ Yes ☐No	☐ Yes ☐No	_____ days
SNUS: Spitless tobacco product that comes in small pouches and is usually sold in a tin. CAMEL SNUS is an example of a snus brand	☐ Yes ☐No	☐ Yes ☐No	_____ days

Tobacco Product or Nicotine Containing Product	Have you ever used this product, even once?	Have you used the product in the past 14 days?	If "yes" indicate the number of days
OTHER NEW ORAL TOBACCO OR TOBACCO- DERIVED NICOTINE PRODUCTS: Meant to be chewed or dissolved in the mouth. Examples include CAMEL ORBS, STRIPS, or STICKS; ARIVA or STONEWALL and VERVE DISCS	☐ Yes ☐No	☐ Yes ☐No	_____ days
HOOKAH: Or "narghile" pipe, is a type of water pipe used to smoke tobacco	☐ Yes ☐No	☐ Yes ☐No	_____ days
PIPE: A regular smoking pipe has a bowl for tobacco, stem and mouthpiece	☐ Yes ☐No	☐ Yes ☐No	_____ days
NICOTINE REPLACEMENT THERAPY: Patch, gum, inhaler, nasal spray or lozenge	☐ Yes ☐No	☐ Yes ☐No	_____ days