An Open-Label, Randomized, Crossover Study to Assess Nicotine Uptake, Tobacco-Related Biomarkers of Exposure, Biomarkers of Potential Harm, and Puff Topography with Use of *my*bluTM Electronic Cigarettes in Adult Smokers

NCT# NCT04429932

Study Protocol - 04-Dec-2019

[redacted]

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Sponsor Project No.: NER 01/003

[redacted] Project No.: CA22736

Final Protocol: 04-Nov-2019
Amendment 1: 04-Dec-2019

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
04Dec2019 [redacted]	Final Protocol, Amendment 1 This protocol is amended to rearrange product designations for Products B, D, F, and G to allow better product comparisons. The following changes were made throughout the protocol (new text indicated in **bold** font and deleted text indicated in ~~strikethrough~~ font): Product Designation — Study Product Name B — *my*blu™ (freebase), Polar Mint flavor, ~~1.2~~ **2.4**% D — *my*blu™ (freebase), ~~Menthol~~ **Vanilla** flavor, 2.4% F — *my*blu™ (freebase), Polar Mint flavor, ~~2.4~~ **1.2**% G — *my*blu™ (freebase), ~~Vanilla~~ **Menthol** flavor, 2.4% In addition, changes listed in the protocol clarification letter (dated 26Nov2019) were incorporated into this amendment, as follows: 1) In Section 6.4.6.5 Clinical Laboratory, the first sentence was edited to allow for the use of an appropirate kit/method (i.e., not a CLIA-waived kit or procedure) for the urine cotinine test at screening. As the CLIA-waived cotinine kit currently available at the study site does not consistently report positive and negative results at 200 ng/mL, other appropriate kits/methods such as the Instant Drug Test Card (IDTC)-Nicotine may be used for screening purposes. 2) The Institutional Review Board (IRB) was changed to IntegReview IRB. Thus, Section 8.1.1 Institutional Review Board was updated with the new contact information.
04Nov2019 [redacted]	Final Protocol

SPONSOR SIGNATURE PAGE

An Open-Label, Randomized, Crossover Study to Assess Nicotine Uptake, Tobacco-Related Biomarkers of Exposure, Biomarkers of Potential Harm, and Puff Topography with Use of *my*blu™ Electronic Cigarettes in Adult Smokers

Sponsor Representative: [redacted] Clinical Research Manager

[redacted]

[redacted]

Signature

04 DEC 2019

Date

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

An Open-Label, Randomized, Crossover Study to Assess Nicotine Uptake, Tobacco-Related Biomarkers of Exposure, Biomarkers of Potential Harm, and Puff Topography with Use of *my*blu™ Electronic Cigarettes in Adult Smokers

Clinical Site and Principal Investigator:

Site Name:

Address:

Phone:
Fax:

_____ _____
Signature Date

_____
Printed Name

An additional signature page as a standalone document may be used for the signature of any additional clinical sites.

STUDY CONTACTS

Medical Monitor	To be provided separately
Clinical Laboratory	To be provided separately
Bioanalytical Laboratory	[redacted]

SYNOPSIS

Study Objectives	Primary: 1. To characterize nicotine uptake following controlled use of *my*blu™ electronic cigarettes (e-cigarettes). 2. To assess the change-from-baseline differences in the primary tobacco-related biomarkers of exposure (BoE) following a 9-day use period of *my*blu™ e-cigarettes. Secondary 1. To assess the change-from-baseline differences in the primary tobacco-related BoE following a 14-day use period of *my*blu™ e-cigarettes. 2. To assess the change-from-baseline differences in the secondary tobacco-related BoE following 9-day and 14-day use periods of *my*blu™ e-cigarettes. 3. To characterize the change in the primary and secondary tobacco-related BoE and biomarkers of potential harm (BoPH) during a 14-day period of use of *my*blu™ e-cigarettes and compare between exclusive e-cigarette use, exclusive combustible cigarette use and dual (combustible cigarette and e-cigarette) use. 4. To assess the change-from-baseline differences in the primary and secondary tobacco-related BoE between Day 9 and Day 14 in subjects using *my*blu™ e-cigarettes, both exclusively and alongside use of combustible cigarettes. 5. To assess change-from-baseline differences in BoPH following 9-day and 14-day use periods of *my*blu™ e-cigarettes. 6. To assess measures of subjective effects associated with use of *my*blu™ e-cigarettes. 7. To determine puffing topography parameters (puff count, puff duration, puff volume, peak puff flow rate, average puff flow rate, inter puff interval) following an 8-day use period of *my*blu™ e-cigarettes and assess change-from-baseline differences (if applicable). 8. To assess change-from-baseline differences in physiologic endpoints (i.e., blood pressure [BP], heart rate [HR], and spirometry) following 9-day and 14-day use periods of *my*blu™ e-cigarettes. 9. To characterize product use of *my*blu™ e-cigarettes under short-term controlled and *ad libitum* use conditions. 10. To assess the safety and tolerability of *my*blu™ e-cigarettes following short-term use.

Study Design	This will be an open-label, randomized, 2-part study in adult smokers. All subjects will participate in both study parts. Part 2 will begin immediately after Part 1. Screening procedures will be performed within 28 days prior to study procedures on Day -2. Subjects who successfully complete the screening procedures and meet the eligibility criteria will be eligible to check in to the clinical research unit (CRU) on Day -2 and will complete all subjective effects questionnaires for the purpose of familiarization with the questions, scales, and computerized tablet. Subjects will also participate in a brief trial on Day -2 (approximately 30 minutes) using the *my*blu™ device with a 0% nicotine e-liquid, to familiarize with the use of the device. Baseline study assessments, including BoE, BoPH, spirometry (Day -1 only), BP, HR, and puff topography (in a subset of 16 subjects [2 subjects from each sequence in Part 1] on Day -1 only) will be performed on Days -2 through -1, as appropriate. Subjects will continue to smoke their usual brand combustible cigarette from check-in through Day -1, but will abstain from use of any tobacco- or nicotine-containing products for at least 12 hours prior to the start of product use on Day 1. Subjects will be randomized to 1 of 8 sequences (Part 1) on Day -1. <u>Part 1 (Days 1 to 9)</u> On Days 1, 3, 5, and 7, subjects will use the study product they are assigned to use the following day according to the randomization scheme. Subjects will use the assigned study product *ad libitum* until the start of the abstinence period (i.e., at least 12 hours prior to the start of the first product use session on the next day). A fully charged battery and a fresh pod will be provided on each day. Additional pods will be provided as needed. Pods will be weighed within 24 hours before the start and after completion of product use on each day. On Day 1, puff topography measurements will be performed in the same subset of 16 subjects (2 subjects from each sequence in Part 1) for 1 hour during *ab libitum* product use. Puff topography should be performed within ± 2 hours of the time of the baseline assessment on Day -1. On Days 2, 4, 6, and 8, subjects will participate in two product use sessions on each day, using the assigned study product according to the randomization scheme. In the first (controlled) product use session, subjects will use the assigned study product under controlled conditions (i.e., 10 puffs taken at 30-second intervals, with puffs 3 seconds in duration). Blood samples for nicotine pharmacokinetic (PK) assessment will be collected prior to and for 3 hours following the start of the first product use session. Subjects will complete the Urge to Smoke questionnaire during and following the first product

	use session and the Product Liking, Product Evaluation Scale (PES), and Future Intent to Use questionnaires following the first product use session. Following collection of the last PK blood sample (180-minute time point) and completion of the subjective effects questionnaires, subjects will start the second (*ad libitum*) product use session, during which they will use the same assigned study product *ad libitum* (with no limits on puff duration or inter-puff interval) until approximately 23:00. Subjects will complete the Urge to Smoke, Product Liking, PES, and Future Intent to Use questionnaires at least 6 hours after the start of the second product use session. A fresh pod and fully charged device will be provided for each product use session. Pod weights will be measured before and after each product use session. On Day 8, puff topography measurements will be performed in the same subset of 16 subjects (2 subjects from each sequence in Part 1) for 1 hour during the second (*ab libitum*) product use session. Puff topography will be performed at least 4 hours after the start of the second (*ab libitum*) product use session and should be within ± 2 hours of the time of the baseline assessment on Day -1. On Day 9, subjects may use all or any of the 4 study products (used previously on Days 1 to 8) *ad libitum* until approximately 23:00. For BoE and BoPH assessments, blood samples will be collected on Day 9 and urine samples will be collected over 24 hours (starting on Day 8 after completion of the second [*ab libitum*] product use session). BP and HR measurements will be taken throughout the period of *ad libitum* product use. Subjects will complete the Questionnaire on Smoking Urges-Brief (QSU-Brief), the Minnesota Tobacco Withdrawal Scale-Revised (MTWS-R), and the Penn State [Electronic] Cigarette Dependence Index (PSCDI/PSECDI) questionnaires at least 6 hours after the start of the *ad libitum* product use session on Day 9. Spirometry measurements will be conducted following completion of all subjective effects questionnaires on Day 9. Fresh pods and a fully charged device will be provided on Day 9 and pod weights will be measured. Depending on the availability of topography equipment, puff topography may not be performed at all scheduled time points and may not be performed for some or all assigned subjects. <u>Part 2 (Days 10 to 14)</u> Subjects will be randomized to 1 of 3 study arms (Part 2) on Day 10. Subjects will use any or all of the 8 study products and/or smoke their usual brand combustible cigarettes *ad libitum* for 5 days (until approximately 23:00 on each day) according to the randomization scheme. For BoE and BoPH assessments, blood samples will be collected on Day 14 and urine samples will be collected over 24 hours (starting on Day 13 after the end of product use for that day). On Day 14, BP and HR measurements will be taken throughout the period

	of *ad libitum* product use/smoking. The QSU-Brief, MTWS-R, and PSCDI/PSECDI questionnaires will be completed at least 6 hours after the start of the *ad libitum* product use session on Day 14. Spirometry measurements will be conducted following completion of all subjective effects questionnaires on Day 14. Product use behavior will be assessed by documenting the number of cigarettes smoked, the flavor and strength of the *my*blu™ products, and pod weights, per day, as appropriate. On each study day, fresh pods and a fully charged device will be provided, as appropriate. The CRU will attempt to contact all subjects who used at least one study product (including subjects who terminate the study early) using their standard procedures approximately 14 days after the last study product use to determine if any adverse event (AE) has occurred since the last study visit.
Study Population	The study population will be comprised of healthy, adult male and female smokers, who are between 21 and 65 years of age (inclusive). Each subject must self-report smoking an average of 10 or more manufactured combustible cigarettes per day (CPD) for at least 12 months prior to Screening. Forty (40) subjects will be expected to complete the study and will participate in both study parts. Every attempt will be made to enroll no more than 60% of either sex.
Duration of Study Conduct	The duration of the study from Screening to Day 15 is approximately 6 weeks.
Study Products and Administration:	Details of the study products are presented as follows: In Part 1, 20 subjects will be randomized to use Products A to D and 20 subjects will be randomized to use Products E to H. **Product Designation** — **Study Product Name** A — *my*blu™ (freebase), Gold Leaf flavor, 2.4% B — *my*blu™ (freebase), Polar Mint flavor, 2.4% C — *my*blu™ (freebase), Cherry flavor, 2.4% D — *my*blu™ (freebase), Vanilla flavor, 2.4% E — *my*blu™ (freebase), Gold Leaf flavor, 1.2% F — *my*blu™ (freebase), Polar Mint flavor, 1.2% G — *my*blu™ (freebase), Menthol flavor, 2.4% H — *my*blu™ Intense (nicotine salts), Fresh Mint flavor, 2.4%

<table>
<tr><td></td><td>
In Part 2, subjects will be randomized to one of the following arms:
<table>
<tr><th>Arm</th><th>Product Use Description</th></tr>
<tr><td>I (myblu™)</td><td>Exclusive use of myblu™ products ad libitum</td></tr>
<tr><td>J (Combustible)</td><td>Exclusive smoking of usual brand combustible cigarettes ad libitum</td></tr>
<tr><td>K (Dual Use)</td><td>Smoking of usual brand combustible cigarettes (up to 50% of the subject's self-reported CPD) and use of myblu™ products ad libitum</td></tr>
</table>
Subjects randomized to Arms I and K may choose to use all or any of Products A to H.
</td></tr>
<tr><td>Endpoints, Key Assessments, and Summarization</td><td>
<u>Pharmacokinetics</u>:
For each first (controlled) product use session on Days 2, 4, 6, and 8, plasma nicotine PK parameters (AUC0-180, Cmax, and Tmax) will be computed from the individual plasma concentrations for each study product. Baseline adjustments will be performed.
Nicotine concentrations and PK parameters will be listed by subject and summarized using descriptive statistics.
<u>Biomarkers</u>:
For each of Days -1, 9, and 14, biomarker concentrations will be listed by subject and summarized using descriptive statistics. Absolute and percent change-from-baseline will be determined for the mass excreted and creatinine-adjusted values.
Primary Biomarkers of Exposure:
<table>
<tr><th>Biomarker</th><th>Matrix</th><th>Chemical Constituent</th></tr>
<tr><td>Carboxyhemoglobin (COHb)</td><td>Blood</td><td>Carbon monoxide (CO)</td></tr>
<tr><td>4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL)</td><td>Urine</td><td>4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)</td></tr>
<tr><td>3-hydroxypropylmercapturic acid (3-HPMA)</td><td>Urine</td><td>Acrolein</td></tr>
<tr><td>S-phenyl mercapturic acid (S-PMA)</td><td>Urine</td><td>Benzene</td></tr>
</table>
</td></tr>
</table>

Secondary 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

(8-epi-PGF2α)		
11-dehydrothromboxane B_2 (11-DHTXB2)	Urine	Platelet activation

Subjective Effects:

Urge to Smoke (Days 2, 4, 6, and 8)

Responses and derived parameters (Emax, TEmax, and AUEC0-120) will be listed by subject and summarized using descriptive statistics.

Product Liking (Days 2, 4, 6, and 8)

Responses will be listed by subject and summarized using descriptive statistics.

Product Evaluation (Days 2, 4, 6, and 8)

Responses will be considered as a 7-point scale, and will be presented as factors outlined in Section 7.3.3.3.

Descriptive statistics of the subscales will be provided by study product and product use session. Individual responses will be listed.

Future Intent to Use (Days 2, 4, 6, and 8)

Responses recorded as visual analog scale (VAS) scores will be treated as bipolar categorical variables (-50 to <0, 0, >0 to 50) and summarized by study product using frequency count tables. The bipolar score for the Future Intent to Use questionnaire is calculated by subtracting 50 from the original VAS score. The bipolar scores will also be treated as continuous variables and summarized using descriptive statistics.

QSU-Brief (Days 9 and 14)

Responses to the QSU-brief will be considered as a 7-point scale and treated as a continuous variable and will be presented as two factors as outlined in Section 7.3.3.5.

Descriptive statistics of the subscales will be provided by study day and study arm (Part 2 only). Individual responses will be listed.

MTWS-R (Days 9 and 14)

The total score to the MTWS-R will be summarized by study day and study arm (Part 2 only).

PSCDI/PSECDI (Days 9 and 14)

The total score to the PSCDI/PSECDI will be summarized by study day and study arm (Part 2 only).

Puff Topography:

Topography parameters (puff count, puff duration, puff volume, peak

	puff flow rate, average flow rate, inter-puff interval) will be listed by subject and summarized using descriptive statistics. Physiological Endpoints: *Blood Pressure and Heart Rate* Unadjusted and change from baseline BP and HR parameters (e.g., AUEC0-t, Emax, and TEmax) will be listed by subject and summarized using descriptive statistics. *Spirometry* Pre- and post-bronchodilator lung function variables (measured and percent of predicted forced expiratory volume in 1 second [FEV1], measured and percent of predicted forced vital capacity [FVC], measured and percent of predicted FEV1:FVC ratio, and measured and percent of predicted forced expiratory flow [FEF]25-75%) will be listed by subject and summarized using descriptive statistics. Product Use Behavior: All product use data, including the number of combustible cigarettes smoked and the difference in pod weights, will be summarized using descriptive statistics. Incidence of device malfunction(s) will also be tabulated. Safety: Screening evaluations will include a full physical examination, vital signs measurements, 12-lead electrocardiogram (ECG), clinical laboratory tests (serum chemistry, hematology, urinalysis, and serology), exhaled CO measurement, urine drug screen, urine/breath alcohol screen, and a serum/urine pregnancy test (females only). Safety will be monitored on-study through physical examination (symptom-driven), vital signs measurements, ECGs, and clinical laboratory tests (serum chemistry, hematology, and urinalysis). AEs spontaneously reported by the subjects or observed by the Investigator or other study personnel will be monitored from the time subjects first use a study product until the follow-up. AEs will be tabulated and summary statistics for vital signs and clinical laboratory tests may be computed and provided, as deemed clinically appropriate.

STUDY EVENTS FLOW CHART

Table 1. Study Events

EVENTS/ASSESSMENTS		PART 1																
Days →	Scr [a]	-2	-1	1, 3, 5, 7	2, 4, 6													
Hours →		C-I [b]			0									1	2	3	9+ [c]	EAS
Minutes →					0	3	5	7	10	12	15	20	30	60	120	180		
Administrative Procedures																		
Informed Consent	X [d]																	
Review of I/E Criteria	X [d]	X																
Medical History and Demographics	X [d]	X [e]																
Tobacco/Nicotine Product Use History	X																	
Usual Brand Documentation	X	X [e]																
Safety Evaluations																		
Full Physical Examination [f]	X [d]																	
Body Weight, Height, and BMI	X [d]																	
Chem [g], Hematology, Urinalysis	X [d]	X																
HIV, HBsAg, and HCV Serology	X																	
Serum/Urine Pregnancy Test (Females)	X [d]	X																
Serum FSH (Postmenopausal Females Only)	X																	
Urine Drug and Urine/Breath Alcohol Screen	X [d]	X																
12-lead ECG	X [d]	X																
Vital Signs (RR and T)	X [d]	X			X [h]													
Vital Signs (BP and HR)	X [d]	X	X [i]		X [h]													
Exhaled CO	X [d]																	
Urine Cotinine Screen	X [d]																	
Review of Concomitant Medications	X [d]	X																
Review of AEs		X																
Product Use/Study Assessments																		
Randomization			X [j]															
Controlled Product Use						X [k]												
Ad Libitum Product Use		X [l]		X [n]													X [m]	
Product Use Behavior		X [o]		X [p]		X [q]											X [o]	

EVENTS/ASSESSMENTS	Scr [a]	PART 1																
Days →		-2	-1	1, 3, 5, 7	2, 4, 6													
Hours →		C-I [b]			0									1	2	3	9+ [c]	EAS
Minutes →					0	3	5	7	10	12	15	20	30	60	120	180		
24-Hour Urine Collection for BoE and BoPH [dd]		X																
Blood Collection for BoE and BoPH [r]			X															
Blood Collection for Nicotine PK					X [s]	X	X	X	X	X	X	X	X	X	X	X		
Urge to Smoke Questionnaire					X [u]		X [t]		X [t]		X [t]		X [t]	X [t]	X [t]		X	
Product Liking Questionnaire																X	X	
PES Questionnaire																X	X	
Future Intent to Use Questionnaire																X	X	
Puff Topography [v]			X	X [w]														
Spirometry [x]	X [d]		X															
Other Procedures																		
Tobacco Cessation Information	X																	
Questionnaire Training		X																
Visit	X																	
Confinement in the CRU		X																

EVENTS/ASSESSMENTS	PART 1																		PART 2						FU [y]
Days →	8															9			10-12	13	14			15	
Hours →	0									1	2	3	7+	9+ [c]	EAS	0	6+ [c]	EAS			0	6+ [c]	EAS		
Minutes →	0	3	5	7	10	12	15	20	30	60	120	180													
Safety Evaluations																									
Full Physical Examination [f]																								X [z]	
Chem [g], Hematology, Urinalysis																								X [z]	
12-lead ECG																								X [z]	
Vital Signs (RR and T)	X [h]																		X [h]					X [z]	
Vital Signs (BP and HR)	X [h]															X [i]			X [h]		X [i, z]				
Review of Concomitant Medications	X																								
Review of AEs	X																								
Product Use/Study Assessments																									
Randomization																			X [aa]						
Controlled Product Use	X [k]																								
Ad Libitum Product Use												X [m]				X [bb]			X [cc]						
Product Use Behavior	X [q]											X [o]				X [o]			X [o]						
24-Hour Urine Collection for BoE and BoPH [dd]														X						X					
Blood Collection for BoE and BoPH [r]																X					X				
Blood Collection for Nicotine PK	X [s]	X	X	X	X	X	X	X	X	X	X	X													
Urge to Smoke Questionnaire	X [u]		X [t]		X [t]		X [t]		X [t]	X [t]	X [t]			X											
Product Liking Questionnaire												X		X											
PES Questionnaire												X		X											
Future Intent to Use Questionnaire												X		X											
QSU-Brief																	X					X			
MTWS-R																	X					X			
PSCDI/PSECDI																	X					X			
Puff Topography [v]													X												
Spirometry [x]																	X					X			
Other Procedures																									
Tobacco Cessation Information																								X [z]	
Confinement in the CRU	X																								

a: Within 28 days prior to study procedures on Day -2. All screening procedures will be completed at the same study site where on-study procedures will be performed.

b: Subjects will be admitted to the CRU on Day -2, at the time indicated by the CRU.

c: To be performed at least 6 hours after the start of the *ad libitum* product use session on that day.

d: To be performed also at the pre-screening visit, if applicable.

e: To be updated at Check-in as necessary.

f: Symptom-driven physical examinations may be performed at other times, at the Investigator or designee's discretion.

g: Samples for serum chemistry will be obtained following a fast of at least 8 hours, however, in case of dropouts or rechecks, subjects may not have fasted for 8 hours prior to the serum chemistry sample being taken.

h: To be performed prior to the start of the first product use session.

i: BP and HR will be measured within 2 hours prior to and at every hour after the start of *ad libitum* product use and throughout the period of *ad libitum* product use. Following completion of *ad libitum* product use on that day, BP and HR will be measured at 00:00, 03:00, and at least 30 minutes prior to the start of product use on the next day (for Day 14, the last measurement will be collected at approximately 06:00 on Day 15). Measurements are to be taken at least 15 minutes after the last tobacco- or nicotine-containing product used. When BP and HR measurements are scheduled at the same time or immediately after a puff topography session, subjects may not have abstained from tobacco- or nicotine-containing product use for 15 minutes prior to the BP and HR measurements.

j: On Day -1, subjects will be randomized to 1 of 8 sequences (Part 1).

k: Subjects will use the assigned study product under controlled conditions (i.e., 10 puffs taken at 30-second intervals, with puffs 3 seconds in duration).

l: Subjects will continue to exclusively smoke their UBCC from C-I through Day -1, but will abstain from use of any tobacco- or nicotine-containing products for at least 12 hours prior to product use on Day 1. On Day -2, subjects will participate in a brief trial (approximately 30 minutes) using the *my*blu™ device with a 0% nicotine e-liquid.

m: The *ad libitum* (second) product use session will begin after collection of the last PK blood sample (180-minute time point) and completion of the subjective effects questionnaires and will consist of unlimited use of the same assigned study product until approximately 23:00.

n: Subjects will use the study product they are assigned to use the following day according to the randomization scheme. Subjects will use the assigned study product *ad libitum* until the start of the abstinence period (i.e., at least 12 hours prior to the start of the first product use session on the next day).

o: The flavor and strength of the *my*blu™ products, pod weights, and the number of cigarettes smoked, as appropriate, will be documented.

p: Pods will be weighed within 24 hours before the start and after completion of product use on each day.

q: The number of inhalations, duration of each inhalation, and reasons for missed puffs will be documented. Pods will be weighed within 24 hours before and after each product use session.

r: To be performed following a fast of at least 8 hours, with the exception of blood collection for COHb which will be performed in the afternoon.

s: To be performed approximately 5 minutes prior to the start of the first product use session.

t: To be performed approximately 30 seconds prior the scheduled PK blood draws.

u: To be performed approximately 10 minutes prior to the start of the first product use session.

v: Puff topography measurements will be performed over 1 hour and will begin at least 4 hours after the start of the *ad libitum* product use. The puff topography session on Day 8 should be within ± 2 hours of the time of the Day -1 session. Puff topography measurements will be performed following a fast of at least 1 hour and will be prior to completing any subjective effects questionnaires during the *ad libitum* product use session. Depending on the availability of topography equipment, puff topography may not be performed at all scheduled time points and may not be performed for some or all assigned subjects.

w: To be perfomed on Day 1 only.

x: When scheduled during the same product use session, spirometry will be performed after completion of puff topography measurements and subjective effects questionnaires.

y: The CRU will attempt to contact all subjects who used at least one study product (including subjects who terminate the study early) using their standard procedures approximately 14 days after the last study product use to determine if any AE has occurred since the last study visit.

z: To be performed prior to discharge or prior to early termination from the study.

aa: On Day 10, subjects will be randomized to 1 of 3 study arms (Part 2).

bb: On Day 9, subjects may use all or any of the 4 study products (previously used on Days 1 to 8) *ad libitum* until approximately 23:00.

cc: Subjects will use the study product(s) and/or smoke their UBCC *ad libitum* (until approximately 23:00) for 5 days, according to the randomization scheme.

dd: Twenty-four (24)-hour urine collection will begin at the start of the overnight abstinence on each of Days -2, 8, and 13. The start time of each urine collection should be within ± 1 hour of the start time on Day -2.

Abbreviations: AE = Adverse event, BMI = Body mass index, BoE = Biomarkers of exposure, BoPH = Biomarkers of potential harm, BP = Blood pressure, C-I = Check-in, Chem = Serum chemistry, CO = Carbon monoxide, COHb = Carboxyhemoglobin, CRU = Clinical research unit, EAS = End of *ad libitum* product use session, ECG = Electrocardiogram, FSH = Follicle-stimulating hormone, FU = Follow-up, HBsAg = Hepatitis B surface antigen, HCV = Hepatitis C virus, HIV = Human immunodeficiency virus, HR = Heart rate, I/E = Inclusion/exclusion, MTWS-R = Minnesota Tobacco Withdrawal Scale-Revised, PES = Product Evaluation Scale, PK = Pharmacokinetic(s), PSCDI/PSECDI = Penn State [Electronic] Cigarette Dependence Index, QSU-Brief = Questionnaire on Smoking Urges-Brief, RR = Respiratory rate, Scr = Screening, T = Temperature, UBCC = Usual brand combustible cigarette.

ABBREVIATIONS

1-AN	1-aminonaphthalene
1-OHP	Hydroxypyrene
11-DHTXB2	11-dehydrothromboxane B_2
2-AN	2-aminonaphthalene
3-HPMA	3-hydroxypropylmercapturic acid
3-OH B[a]P	3-hydroxybenzo[a]pyrene
8-epi-PGF2α	Type III isoprostane 8-epi-prostaglandin $F_{2\alpha}$
AE	Adverse event
ANOVA	Analysis of variance
AUC	Area under the concentration-time curve
AUC0-180	Area under the nicotine concentration-time curve from time 0 to 180 minutes
AUEC0-120	Area under the change from baseline score versus time curve from time 0 to 120 minutes
AUEC0-t	Area under the change from baseline score versus time curve from time 0 to time t
BMI	Body mass index
BoE	Biomarker(s) of exposure
BoPH	Biomarker(s) of potential harm
BP	Blood pressure
bpm	Beats per minute
°C	Degree Celsius
CEMA	2-cyanoethyl-mercapturic acid
CFR	Code of Federal Regulations
CI	Confidence interval
CLIA-88	Clinical Laboratory Improvement Amendments of 1988
Cmax	Maximum measured plasma concentration
CO	Carbon monoxide
COHb	Carboxyhemoglobin
CPD	Cigarette(s) per day
CRU	Clinical research unit

CYP	Cytochrome P450
DMP	Data Management Plan
e-cigarette	Electronic cigarette
e-liquid	Electronic cigarette liquid
ECG	Electrocardiogram
eCRF	Electronic case report form
Emax	Maximum change from baseline score
°F	Degree Fahrenheit
FDA	Food and Drug Administration
FEF	Forced expiratory flow
FEV1	Forced expiratory volume in 1 second
FSH	Follicle-stimulating hormone
FVC	Forced vital capacity
g	Gram
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HDL-C	High density lipoprotein cholesterol
HEMA	Hydroxyethyl mercapturic acid
HIV	Human immunodeficiency virus
HMPMA	3-hydroxy-1-methylpropylmercapturic acid
HR	Heart rate
ICF	Informed consent form
ICH	International Council for Harmonisation
IRB	Institutional Review Board
K_2-EDTA	Dipotassium ethylenediaminetetraacetic acid
kg	Kilogram
ln	Natural logarithm
m^2	Meters squared
mAh	Milliampere hour
MCP-1	Monocyte chemoattractant protein 1
mg	Milligram

MHBMA	Monohydroxybutenylmercapturic acid
mL	Milliliter
mmHg	Millimeter of mercury
MTWS-R	Minnesota Tobacco Withdrawal Scale-Revised
ng	Nanogram
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)
ppm	Parts per million
PSCDI	Penn State Cigarette Dependence Index
PSECDI	Penn State Electronic Cigarette Dependence Index
QA	Quality Assurance
QSU-Brief	Questionnaire on Smoking Urges-Brief
RCF	Relative centrifugal force
S-PMA	S-phenyl mercapturic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
sICAM	Soluble intracellular adhesion molecule
SOP	Standard operating procedure
TEmax	Time of the Emax
Tmax	Time to reach the maximum measured plasma concentration
US or USA	United States of America
USB	Universal serial bus
V	Volt
VAS	Visual analog scale
WBC	White blood cell

DEFINITION OF TERMS

Check-in	Check-in is defined as the time when the subject arrives at the CRU
Concomitant medication	Concomitant medication refers to all medication taken during the study conduct period from 28 days prior to Screening through discharge. Medications started prior to Screening but which the subject continues to take during the study, are considered to be concomitant medications
Randomization	Assignment of subjects to a specific sequence
Screening	Screening is defined as the 28-day period prior to study procedures on Day -2, during which subjects will undergo screening assessments
Screening failure	Any subject who does not meet the entry criteria at Screening or Day -2 for study enrollment will be considered a Screening failure
Sponsor	'Sponsor' refers to Nerudia Ltd
Subject	'Subject' refers to an individual who participates in the clinical study

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1. INTRODUCTION AND BACKGROUND

1.1 Background

E-cigarettes have become a popular alternative to cigarette smoking 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 2016, Goniewicz 2017, O'Connell 2016, McRobbie 2015, Hecht 2015).

Therefore, to be of greatest benefit, e-cigarettes must provide smokers with an experience that would allow for maximal displacement of combustible cigarettes while at the same time not serve as a gateway to other more toxic products for nonsmokers. Key elements that contribute to an acceptable initiating experience include the nicotine content in the products as well as the response that consumers have in terms of satisfaction and prevention of symptoms of withdrawal.

1.2 *my*blu™ Previous Clinical Experience

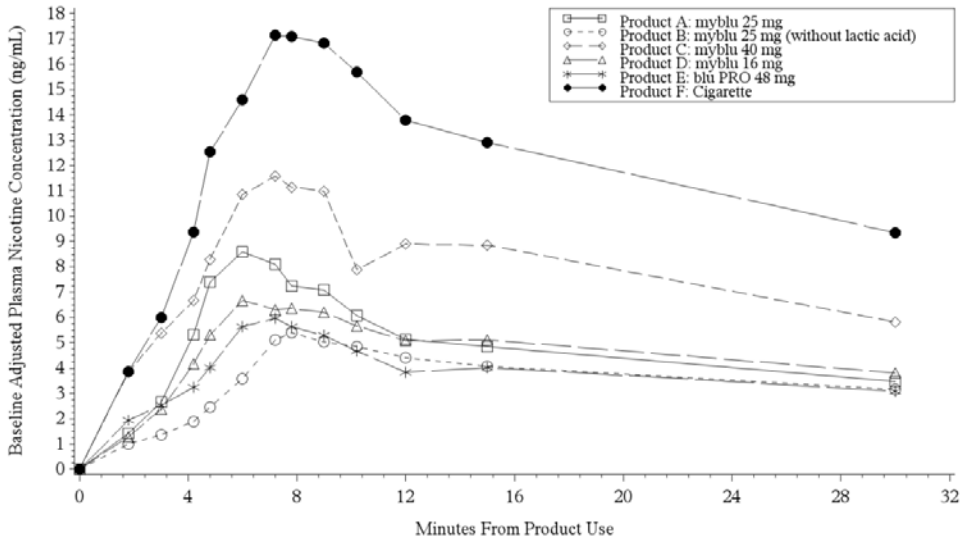
One previous clinical study has been conducted with the *my*blu™ closed system (FON-01blu-2018). Fifteen healthy adult smokers enrolled in an open-label, 6-period crossover study to characterize nicotine uptake and subjective effects during a 10-puff controlled exposure (puffs 3 seconds in duration, 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 overall exposure over 30 minutes (AUC0-30) and peak exposure (Cmax) 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 (Tmax) 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. AUC0-30 and Cmax of nicotine were lowest following use of blu PRO compared to all other products tested. AUC0-30 and Cmax of nicotine was highest following use of cigarette compared to any other product tested. Tmax 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
AUC0-30 (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]
Cmax (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]
Tmax (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 Cmax are presented as geometric mean and geometric coefficient of variability %, Tmax 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. Venipuncture 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 Study Purpose

This study is being conducted to evaluate the overall performance of the currently-marketed *my*blu™ e-cigarette device and pods, as assessed by nicotine uptake and consumer satisfaction. The endpoints to be assessed are based on the United States (US) Food and Drug Administration (FDA) Electronic Nicotine Delivery Systems Draft Guidance for Industry (FDA 2019), and the data may be included in future premarket tobacco application submissions to the Center for Tobacco Products.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

Primary

1. To characterize nicotine uptake following controlled use of *my*blu™ e-cigarettes.

2. To assess the change-from-baseline differences in the primary tobacco-related BoE following a 9-day use period of myblu™ e-cigarettes.

Secondary

1. To assess the change-from-baseline differences in the primary tobacco-related BoE following a 14-day use period of *my*blu™ e-cigarettes.

2. To assess the change-from-baseline differences in the secondary tobacco-related BoE following 9-day and 14-day use periods of *my*blu™ e-cigarettes.

3. To characterize the change in the primary and secondary tobacco-related BoE and BoPH during a 14-day period of use of *my*blu™ e-cigarettes and compare between exclusive e-cigarette use, exclusive combustible cigarette use and dual (combustible cigarette and e-cigarette) use.

4. To assess the change-from-baseline differences in the primary and secondary tobacco-related BoE between Day 9 and Day 14 in subjects using *my*blu™ e-cigarettes, both exclusively and alongside use of combustible cigarettes.

5. To assess change-from-baseline differences in BoPH following 9-day and 14-day use periods of *my*blu™ e-cigarettes.

6. To assess measures of subjective effects associated with use of *my*blu™ e-cigarettes.

7. To determine puffing topography parameters (puff count, puff duration, puff volume, peak puff flow rate, average puff flow rate, inter puff interval) following an 8-day use period of *my*blu™ e-cigarettes and assess change-from-baseline differences (if applicable).

8. To assess change-from-baseline differences in physiologic endpoints (i.e., BP, HR, and spirometry) following 9-day and 14-day use periods of *my*blu™ e-cigarettes.

9. To characterize product use of *my*blu™ e-cigarettes under short-term controlled and *ad* libitum use conditions.

10. To assess the safety and tolerability of *my*blu™ e-cigarettes following short-term use.

2.2 Study Endpoints

Pharmacokinetics:

For each first (controlled) product use session on Days 2, 4, 6, and 8, plasma nicotine PK parameters (AUC0-180, Cmax, and Tmax) will be computed from the individual plasma concentrations for each study product. Baseline adjustments will be performed.

Nicotine concentrations and PK parameters will be listed by subject and summarized using descriptive statistics.

Biomarkers:

For each of Days -1, 9, and 14, biomarker concentrations will be listed by subject and summarized using descriptive statistics. Absolute and percent change-from-baseline will be determined for the mass excreted and creatinine-adjusted values.

Primary Biomarkers of Exposure:

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

Secondary 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-PGF2α	Urine	Oxidative stress
11-DHTXB2	Urine	Platelet activation

Subjective Effects:

Urge to Smoke (Days 2, 4, 6, and 8)

Responses and derived parameters (Emax, TEmax, and AUEC0-120) will be listed by subject and summarized using descriptive statistics.

Product Liking (Days 2, 4, 6, and 8)

Responses will be listed by subject and summarized using descriptive statistics.

Product Evaluation (Days 2, 4, 6, and 8)

Responses will be considered as a 7-point scale, and will be presented as factors outlined in Section 7.3.3.3.

Descriptive statistics of the subscales will be provided by study product and product use session. Individual responses will be listed.

Future Intent to Use (Days 2, 4, 6, and 8)

Responses recorded as VAS scores will be treated as bipolar categorical variables (-50 to <0, 0, >0 to 50) and summarized by study product using frequency count tables. The bipolar score for the Future Intent to Use questionnaire is calculated by subtracting 50 from the original VAS score. The bipolar scores will also be treated as continuous variables and summarized using descriptive statistics.

QSU-Brief (Days 9 and 14)

Responses to the QSU-brief will be considered as a 7-point scale and treated as a continuous variable and will be presented as two factors as outlined in Section 7.3.3.5.

Descriptive statistics of the subscales will be provided by study day and study arm (Part 2 only). Individual responses will be listed.

MTWS-R (Days 9 and 14)

The total score to the MTWS-R will be summarized by study day and study arm (Part 2 only).

PSCDI/PSECDI (Days 9 and 14)

The total score to the PSCDI/PSECDI will be summarized by study day and study arm (Part 2 only).

Puff Topography:

Topography parameters (puff count, puff duration, puff volume, peak puff flow rate, average puff flow rate, inter-puff interval) will be listed by subject and summarized using descriptive statistics.

Physiological Endpoints:

Blood Pressure and Heart Rate

Unadjusted and change from baseline BP and HR parameters (e.g., AUEC0-t, Emax, and TEmax) will be listed by subject and summarized using descriptive statistics.

Spirometry

Pre- and post-bronchodilator lung function variables (measured and percent of predicted FEV1, measured and percent of predicted FVC, measured and percent of predicted FEV1:FVC ratio, and measured and percent of predicted FEF25-75%) will be listed by subject and summarized using descriptive statistics.

Product Use Behavior:

All product use data, including the number of combustible cigarettes smoked and the difference in pod weights, will be summarized using descriptive statistics.

Safety:

Screening evaluations will include a full physical examination, vital signs measurements, 12-lead ECG, clinical laboratory tests (serum chemistry, hematology, urinalysis, and serology), exhaled CO measurement, urine drug screen, urine/breath alcohol screen, and a serum/urine pregnancy test (females only).

Safety will be monitored on-study through physical examination (symptom-driven), vital signs measurements, ECGs, and clinical laboratory tests (serum chemistry, hematology, and urinalysis).

AEs spontaneously reported by the subjects or observed by the Investigator or other study personnel will be monitored from the time subjects first use a study product until the follow-up.

AEs will be tabulated and summary statistics for vital signs and clinical laboratory tests may be computed and provided, as deemed clinically appropriate.

Incidence of device malfunction(s) will also be tabulated.

3. SUMMARY OF STUDY DESIGN

3.1 Design and Procedures

This will be an open-label, randomized, 2-part study in adult smokers. All subjects will participate in both study parts. Part 2 will begin immediately after Part 1.

Screening procedures will be performed within 28 days prior to study procedures on Day -2.

Forty (40) adult, male and female, self-affirmed smokers (smoke an average of 10 or more manufactured combustible CPD for at least 12 months prior to Screening), who successfully complete the screening procedures and meet the eligibility criteria, will be eligible to check-in to the CRU on Day -2. Every attempt will be made to enroll no more than 60% of either sex.

Following check-in, subjects will complete all subjective effects questionnaires for the purpose of familiarization with the questions, scales, and computerized tablet. Subjects will also participate in a brief trial on Day -2 (approximately 30 minutes) using the *my*blu™ device with a 0% nicotine e-liquid, to familiarize with the use of the device. Baseline study assessments, including BoE, BoPH, spirometry (Day -1 only), BP, HR, and puff topography (in a subset of 16 subjects [2 subjects from each sequence in Part 1] on Day -1 only) will be performed on Days -2 through -1, as appropriate. Subjects will continue to smoke their usual brand combustible cigarette from check-in through Day -1, but will abstain from use of any tobacco- or nicotine-containing products for at least 12 hours prior to the start of product use on Day 1. Subjects will be randomized to 1 of 8 sequences (Part 1) on Day -1.

Part 1 (Days 1 to 9)

On Days 1, 3, 5, and 7, subjects will use the study product they are assigned to use the following day according to the randomization scheme. Subjects will use the assigned study product *ad libitum* until the start of the abstinence period (i.e., at least 12 hours prior to the start of the first product use session on the next day). A fully charged battery and a fresh pod will be provided on each day. Additional pods will be provided as needed. Pods will be weighed within 24 hours before the start and after completion of product use on each day. On Day 1, puff topography measurements will be performed in the same subset of 16 subjects (2 subjects from each sequence in Part 1) for 1 hour during *ab libitum* product use. Puff topography should be performed within ± 2 hours of the time of the baseline assessment on Day -1.

On Days 2, 4, 6, and 8, subjects will participate in two product use sessions on each day, using the assigned study product according to the randomization scheme. In the first (controlled) product use session, subjects will use the assigned study product under controlled conditions (i.e., 10 puffs taken at 30-second intervals, with puffs 3 seconds in duration). Blood samples for nicotine PK assessment will be collected prior to and for 3 hours following the start of the first product use session. Subjects will complete the Urge to

Smoke questionnaire during and following the first product use session and the Product Liking, PES, and Future Intent to Use questionnaires following the first product use session. Following collection of the last PK blood sample (180-minute time point) and completion of the subjective effects questionnaires, subjects will start the second (*ad libitum*) product use session, during which they will use the same assigned study product *ad libitum* (with no limits on puff duration or inter-puff interval) until approximately 23:00. Subjects will complete the Urge to Smoke, Product Liking, PES, and Future Intent to Use questionnaires at least 6 hours after the start of the second product use session. A fresh pod and fully charged device will be provided for each product use session. Pod weights will be measured before and after each product use session. On Day 8, puff topography measurements will be performed in the same subset of 16 subjects (2 subjects from each sequence in Part 1) for 1 hour during the second (*ab libitum*) product use session. Puff topography will be performed at least 4 hours after the start of the second (*ab libitum*) product use session and should be within ± 2 hours of the time of the baseline assessment on Day -1.

On Day 9, subjects may use all or any of the 4 study products (used previously on Days 1 to 8) *ad libitum* until approximately 23:00. For BoE and BoPH assessments, blood samples will be collected on Day 9 and urine samples will be collected over 24 hours (starting on Day 8 after completion of the second [*ab libitum*] product use session). BP and HR measurements will be taken throughout the period of *ad libitum* product use. Subjects will complete the QSU-Brief, the MTWS-R, and the PSCDI/PSECDI questionnaires at least 6 hours after the start of the *ad libitum* product use session on Day 9. Spirometry measurements will be conducted following completion of all subjective effects questionnaires on Day 9. Fresh pods and a fully charged device will be provided on Day 9 and pod weights will be measured.

Depending on the availability of topography equipment, puff topography may not be performed at all scheduled time points and may not be performed for some or all assigned subjects.

Part 2 (Days 10 to 14)

Subjects will be randomized to 1 of 3 study arms (Part 2) on Day 10. Subjects will use any or all of the 8 study products and/or smoke their usual brand combustible cigarettes *ad libitum* for 5 days (until approximately 23:00 on each day) according to the randomization scheme. For BoE and BoPH assessments, blood samples will be collected on Day 14 and urine samples will be collected over 24 hours (starting on Day 13 after the end of product use for that day). On Day 14, BP and HR measurements will be taken throughout the period of *ad libitum* product use/smoking. The QSU-Brief, MTWS-R, and PSCDI/PSECDI questionnaires will be completed at least 6 hours after the start of the *ad libitum* product use session on Day 14. Spirometry measurements will be conducted following completion of all subjective effects questionnaires on Day 14. Product use behavior will be assessed by documenting the number of cigarettes smoked, the flavor and strength of the *my*blu™ products, and pod weights, per day, as appropriate. On each study day, fresh pods and a fully charged device will be provided, as appropriate.

Subjects will not be forced to use any tobacco/nicotine products at any time during the study.

The overall study design is depicted in Figure 1.

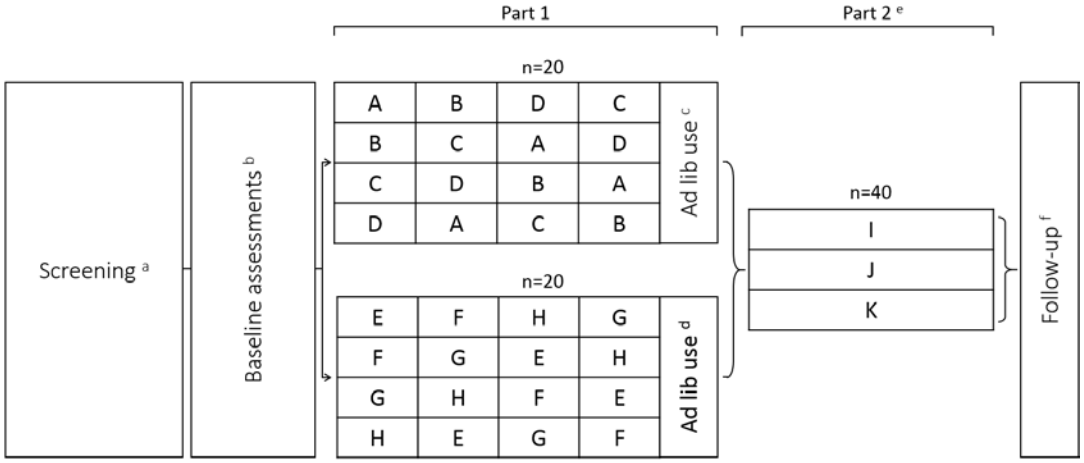
Safety will be monitored through physical examination (symptom-driven), vital signs measurements, ECGs, and clinical laboratory tests (serum chemistry, hematology, and urinalysis).

AEs spontaneously reported by the subjects or observed by the Investigator or other study personnel will be monitored from the time of first use of any study product until the follow-up. Device malfunctions will also be recorded.

The safety monitoring practices employed by this protocol (i.e., vital signs, 12-lead ECGs, clinical laboratory tests, AE questioning, and physical examinations) are adequate to protect the subjects' safety and should detect all expected emergent AEs.

Discontinued subjects may be replaced at the discretion of the Sponsor.

Figure 1. Overall Study Design



Study Days	-2	-1	1 g	2	3 g	4	5 g	6	7 g	8	9	10	11	12	13	14
Randomization		X										X				
PK blood sampling				X		X		X		X						
BoE/BoPH	<-- X -->									<-- X -->					<-- X -->	
Subjective questionnaires	X h			X		X		X		X	X					X
Puff topography i		X	X							X						
Intensive BP and HR		X									X					X
Spirometry		X									X					X

a: To be performed within 28 days prior to study procedures on Day -2.

b: Baseline study assessments will be performed on Days -2 and -1 while subjects continue to smoke their usual brand combustible cigarette.

c: Subjects may use all or any of the 4 study products (i.e., A, B, C, and/or D) *ad libitum* (Ad lib) until approximately 23:00.

d: Subjects may use all or any of the 4 study products (i.e., E, F, G, and/or H) *ad libitum* (Ad lib) until approximately 23:00.

e: Subjects will be randomized to 1 of 3 study arms (Part 2) on Day 10 and will use any or all of the 8 study products (Products A to H) and/or smoke their usual brand combustible cigarettes *ad libitum* for 5 days according to the randomization scheme.

f: The CRU will attempt to contact all subjects who used at least one study product (including subjects who terminate the study early) using their standard procedures approximately 14 days after the last study product used.

g: Subjects will use *ad libitum* the study product they are assigned to use the following day according to the randomization scheme. Subjects will use the assigned study product *ad libitum* until the start of the abstinence period (i.e., at least 12 hours prior to the start of the first product use session on the next day).

h: Subjects will complete one set of questionnaires for the purpose of familiarization with subjective effects questions, appropriate use of the VAS, and use of the computerized tablet system.

i: A total of 16 subjects (2 subjects from each sequence in Part 1) will have puff topography evaluated for 1 hour during *ad libitum* product use.

Study Products in Part 1:

A	*my*blu™ (freebase), Gold Leaf flavor, 2.4%
B	*my*blu™ (freebase), Polar Mint flavor, 2.4%
C	*my*blu™ (freebase), Cherry flavor, 2.4%
D	*my*blu™ (freebase), Vanilla flavor, 2.4%
E	*my*blu™ (freebase), Gold Leaf flavor, 1.2%
F	*my*blu™ (freebase), Polar Mint flavor, 1.2%
G	*my*blu™ (freebase), Menthol flavor, 2.4%
H	*my*blu™ Intense (nicotine salts), Fresh Mint flavor, 2.4%

Study Arms in Part 2:

I (*my*blu™)	Exclusive use of *my*blu™ products *ad libitum*
J (Combustible)	Exclusive smoking of usual brand combustible cigarettes *ad libitum*
K (Dual Use)	Smoking of usual brand combustible cigarettes (up to 50% of the subject's self-reported CPD) and use of *my*blu™ products *ad libitum*

3.2 Confinement and Follow-Up

Subjects will be housed at the CRU on Day -2, at the time indicated by the CRU, until after completion of all study procedures on Day 15. At all times, a subject may be required to remain at the CRU for longer at the discretion of the Investigator or designee.

The CRU will attempt to contact all subjects who used at least one study product (including subjects who terminate the study early) using their standard procedures approximately 14 days after the last study product use to determine if any AE has occurred since the last study visit.

3.3 End of Study Definition

The end of study is defined as the date of the last scheduled study procedure as outlined in the Study Events Flow Chart (Table 1).

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, 21 to 65 years of age, inclusive, at Screening.

2. Reports smoking an average of at least 10 manufactured combustible (menthol or non-menthol) CPD for at least 12 months prior to Screening. Brief periods of non-smoking (e.g., up to ~7 consecutive days due to illness, trying to quit, participation in a study where smoking was prohibited) within 60 days prior to Check-in will be permitted at the discretion of the Investigator.

3. Has a positive urine cotinine (≥ 200 ng/mL) at Screening.

4. Has an exhaled carbon monoxide (CO) > 10 ppm at Screening.

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;
   - double barrier method (e.g., condom with spermicide, diaphragm with spermicide) consistently for at least 14 days prior to Check-in;
   - intrauterine device for at least 3 months prior to Check-in;
   - a partner who has been vasectomized for at least 4 months prior to Check-in;
   - abstinence beginning at least 14 days prior to Check-in.

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:
   - 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 and follicle-stimulating hormone (FSH) levels consistent with postmenopausal status.

7. Is willing to comply with the requirements of the study, including a willingness to use the e-cigarettes.

8. 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 at Screening, Check-in, or during the study as noted, in the opinion of the Investigator:

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 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.

5. Has diabetes mellitus that is not controlled by diet/exercise alone, in the opinion of the Investigator.

6. Has had an acute illness (e.g., upper respiratory infection, viral infection) requiring treatment within 14 days prior to Check-in.

7. Has a fever (> 100.5°F/38.05°C) at Screening or Check-in.

8. Has a body mass index (BMI) > 40 kg/m^2 or < 18 kg/m^2 at Screening.

9. Has a history or presence of drug or alcohol abuse within 24 months of Check-in, as determined by the Investigator.

10. Has a systolic blood pressure < 90 mmHg or > 150 mmHg, diastolic blood pressure < 40 mmHg or > 95 mmHg, or heart rate < 40 bpm or > 99 bpm at Screening.

11. Has a post-bronchodilator FEV1 < 50% of predicted at Screening.

12. Has a post-bronchodilator FEV1 increase ≥ 12% and > 200 mL from pre- to post-bronchodilator at Screening.

13. Is allergic to propylene glycol or glycerin.

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

15. Has a positive urine/breath screen for alcohol or positive urine screen for drugs of abuse at Screening or Check-in.

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

17. Has taken medication for depression or asthma within 12 months prior to Check-in and throughout the study.

18. Has used prescription anti-diabetic medication and/or insulin therapy within 12 months prior to Check-in and throughout the study.

19. 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 and throughout the study.

20. Has used prescription or over-the-counter nonsteroidal anti-inflammatory drugs (e.g., aspirin, ibuprofen) within 7 days prior to Check-in and throughout the study. Medication listed as part of acceptable birth control methods, hormonal replacement therapy, and occasional or seasonal use of over-the-counter products such as analgesics, antihistamines, nasal decongestants, and dietary supplements are permitted at the discretion of the Investigator in consultation with the Sponsor (refer to Section 4.3.2).

21. Has used inhalers to treat any medical condition within 3 months prior to Check-in and throughout the study.

22. Use of prescription or over-the-counter bronchodilator medication (e.g., inhaled or oral β-agonists) for treatment of any illness within 12 months prior to Check-in and throughout the study.

23. Has used other nicotine-containing products other than manufactured combustible 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.

24. Has used any prescription smoking cessation treatments, including, but not limited to, varenicline (Chantix®) or bupropion (Zyban®) within 3 months prior to Check-in.

25. Is a self-reported puffer (i.e., adult smoker who draws smoke from the cigarette into the mouth and throat but does not inhale).

26. Is planning to quit smoking during the study or postponing a quit attempt in order to participate in the study.

27. Has donated plasma within 7 days prior to Check-in.

28. 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.

29. Has participated in a previous clinical study for an investigational drug, device, biologic, or tobacco product within 30 days prior to Check-in.

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

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

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

4.3 Study Restrictions

4.3.1 Food and Beverages

Foods and beverages containing the following substances should not be consumed as indicated below:

- Alcohol should be avoided for 48 hours prior to Screening and Check-in to avoid exclusion for a positive alcohol test and throughout the study.
- Foods containing poppy seeds should be avoided for 48 hours prior to Screening and Check-in to avoid exclusion for a positive urine drug test and throughout the study.
- Food and beverages containing grapefruit for 14 days prior to Check-in and throughout the study.
- Subjects will be advised to avoid eggplant, meats cooked at high temperatures (e.g., barbecued, grilled, pan-fried), cured sandwich meats, bacon, salami, and sausages for 48 hours prior to Check-in and throughout the study.
- Caffeinated beverages will be restricted throughout confinement.

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 Check-in through the end-of-study will be recorded. Except for those medications noted in the exclusion criteria (Section 4.2) and albuterol used during spirometry measurements for this study, prescription or over-the-counter medications required to treat a 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. Occasional or seasonal use of over-the-counter products such as analgesics (e.g., acetaminophen), antihistamines, nasal decongestants, and dietary supplements are permitted. Exceptions may be permitted at the discretion of the Investigator in consultation with the Sponsor, providing the medication in question would have no impact on the study. Any exceptions will be documented.

Decisions to use concomitant medications during the study will be made in the best interest of the health of the subject. If use of a prohibited medication is required during the study, a joint decision will be made by the Investigator and Sponsor to continue or discontinue the subject. 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 Meals/Dietary Considerations

For all subjects, meals and snacks will be provided at the appropriate times during confinement at the CRU. Each meal and/or snacks served at the CRU will be standardized and will be similar in caloric content and composition and will be taken at approximately the

same time on each day. When confined in the CRU, subjects will be required to fast from all food and drink except water between meals and snacks.

Subjects will fast for at least 1 hour prior to and for at least 4 hours after the start of each first product use session on Days 2, 4, 6, and 8. Subjects will also fast for at least 1 hour prior to each puff topography session and for at least 8 hours prior to blood sample collection for biomarkers (other than COHb).

During confinement, water will be allowed *ad libitum*, except that subjects may not consume beverages of any kind (including water) during the first product use session on Days 2, 4, 6, and 8, and during each puff topography session. An exception to the water restriction can be made if a subject starts coughing uncontrollably while smoking or using the e-cigarettes.

4.3.4 Activity

Subjects will be instructed to refrain from abnormal strenuous physical activity which could cause muscle aches or injury, including contact sports at any time from 48 hours prior to Screening and Check-in, and during confinement.

During each 24-hour urine collection period, specific measures will be taken to prevent the subject from missing a urine collection by strictly controlling and providing access to designated restrooms only. Subjects will be asked to void prior to entering the shower.

4.3.5 Tobacco Use/Considerations

Except as required by the study, consumption of tobacco- or nicotine-containing products will not be permitted from Check-in through discharge.

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:

- AE
- Lost to follow-up
- Non-compliance with study procedures
- Protocol violation
- Study terminated by Sponsor, 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 study product administration will undergo all discharge safety procedures as feasible and as deemed necessary by the Investigator.

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 qualified individual 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.

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

4.5 Subject Randomization

Subjects who complete the study screening assessments and meet all the eligibility criteria and are randomized will be assigned a unique randomization identification number on Day -1 for Part 1 and on Day 10 for Part 2, and will receive study products according to the randomization scheme generated by [redacted]

In Part 1, the sequences to be used in the randomization of Part 1 will be ABDC, BCAD, CDBA, DACB, EFHG, FGEH, GHFE, and HEGF.

In Part 2, subjects will be randomized to 1 of 3 study arms (i.e., I, J, or K).

If replacement subjects are used, the replacement subject number will be 100 more than the original (e.g., Subject No. 101 will replace Subject No. 1).

5. STUDY PRODUCTS/MATERIALS

5.1 Description of Study Products

In Part 1, 20 subjects will be randomized to use Products A to D and 20 subjects will be randomized to use Products E to H.

The following study products will be used in Part 1 of this study:

Product Designation	Study Product Name
A	*my*blu™ (freebase), Gold Leaf flavor, 2.4%
B	*my*blu™ (freebase), Polar Mint flavor, 2.4%
C	*my*blu™ (freebase), Cherry flavor, 2.4%
D	*my*blu™ (freebase), Vanilla flavor, 2.4%
E	*my*blu™ (freebase), Gold Leaf flavor, 1.2%
F	*my*blu™ (freebase), Polar Mint flavor, 1.2%
G	*my*blu™ (freebase), Menthol flavor, 2.4%
H	*my*blu™ Intense (nicotine salts), Fresh Mint flavor, 2.4%

In Part 2, subjects will be randomized to one of the following arms:

Arm	Product Use Description
I (*my*blu™)	Exclusive use of *my*blu™ products *ad libitum*
J (Combustible)	Exclusive smoking of usual brand combustible cigarettes *ad libitum*
K (Dual Use)	Smoking of usual brand combustible cigarettes (up to 50% of the subject's self-reported CPD) and use of *my*blu™ products *ad libitum*

5.1.1 Usual Brand Combustible Cigarette

Subjects will be required to bring with them to the CRU a sufficient supply (i.e., 2-week supply [unopened packs]) of their usual brand combustible cigarettes for personal use throughout confinement.

5.1.2 *my*blu™ E-Cigarettes

*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 3.7 V (maximum 3.9 V). 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 freebase, and a proprietary blend of flavors.

5.2 Study Product Accountability and Dispensing

All *my*blu™ e-cigarettes (devices and all e-liquids including the 0% nicotine e-liquid) will be provided by the Sponsor. The CRU staff will coordinate shipping of e-cigarettes from the Sponsor. The staff will document the date each shipment was received and recorded in the inventory records. The CRU staff will document and reconcile the total number of products shipped to the CRU, the total number of products dispensed during the study, and the total number of products remaining at the end of clinical conduct. Subjects will bring a 2-week supply (unopened packs) of their usual brand combustible cigarettes for personal use at designated times throughout confinement in the CRU.

All products will be stored in a locked, limited-access area at the CRU and kept at controlled room temperature (defined as 20 - 25°C [68 - 77°F], with excursions permitted to 15 - 30°C [59 - 86°F]). Humidity is recorded but not controlled.

Study products for dispensing (including usual brand combustible cigarettes) to subjects will be prepared by the study staff according to instructions provided by the Sponsor. Individual study product dispensing records will be maintained by the CRU staff for each subject. Care should be taken when repackaging the study products for use at the CRU to avoid exposure to air and moisture to the extent possible. The pharmacy will maintain records of the number of cigarettes dispensed for each subject.

The study staff will document the start time and stop time of each product use session. A fresh pod and fully charged device will be used for each product use session and each product use day (as applicable). The number of cigarettes smoked will be documented on Days -2 and -1, and on Days 10 through 14 for subjects in Arms J and K. The flavor and strength of the *my*blu™ products will be documented as appropriate. Pod weights will be documented in grams to 4 decimal places.

Subjects will smoke their usual brand combustible cigarettes and use each assigned product only in designated areas of the CRU.

Opened and unopened packages of e-cigarettes and components will be returned to the Sponsor or destroyed at the direction of the Sponsor. Unopened packages of subject's own

brand combustible cigarettes will be returned to the subjects; opened packages will be destroyed. All returns or destruction of study products will be documented.

6. STUDY PROCEDURES

6.1 Screening

Potential subjects will undergo Screening procedures to ensure that they meet the requirements for inclusion in the study within 28 days prior to study procedures on Day -2.

Screening procedures will be performed as delineated in the Study Events Flow Chart (Table 1).

Pre-screening procedures, if applicable, will be performed as delineated in the Study Events Flow Chart (Table 1).

6.1.1 Informed Consent

All prospective subjects will have the study explained by the Investigator or his/her designee and will be required to read, sign, and date an Institutional Review Board (IRB)-approved ICF prior to completion of screening or other study procedures. This consent form will provide the subjects in non-technical terms with the purpose of the study, procedures to be carried out, and potential hazards. 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. Subjects will be given a copy of their signed ICF.

6.1.2 Medical History/Demographic Data/Record of Concomitant Medication

Medical history and socio-demographic data, including name, sex, age (each subject must show proof of age with government-issued identification [e.g., driver's license]), race, ethnicity, address, and phone number will be recorded at Screening for each subject.

Additional data including social security number or tax identification number will be recorded at Check-in.

Any concomitant medications taken from 30 days prior to Check-in through discharge will be recorded.

6.1.3 Tobacco/Nicotine Product Use History

Subjects will be required to report previous tobacco-product and nicotine-product use histories to satisfy the study inclusion and exclusion criteria.

Details of the subject's usual brand combustible cigarette, including the brand, brand style, flavor, cigarette length, and amount of daily use will be recorded at Screening and updated at Check-in as necessary. A color photocopy or photograph of the subject's usual brand combustible cigarette package will be taken by the CRU staff at Check-in.

6.1.4 Exhaled Carbon Monoxide

Exhaled CO levels will be measured using a Bedfont Micro+ Smokerlyzer or similar device, at Screening.

6.2 Check-in and Confinement

Subjects will check in to the CRU on Day -2 at a time specified by the CRU. Check-in procedures will be performed as delineated in the Study Events Flow Chart (Table 1).

After check-in, subjects will complete one set of questionnaires for the purpose of familiarization with subjective effects questions, appropriate use of the VAS, and use of the computerized tablet system. Data collected from the training session will not be used for any analysis.

Subjects will also participate in a brief trial on Day -2 (approximately 30 minutes) using the *my*blu™ device with a 0% nicotine e-liquid, to familiarize with the use of the device. Instructions on the proper use of the *my*blu™ products will be provided prior to use.

Subjects will have their personal belongings thoroughly checked during Check-in. All subjects will be required to shower and will receive clean articles of clothing prior to the start of the first study product use on Day 1.

Subjects will be confined from Check-in on Day -2 through completion of scheduled study events on Day 15.

A subject may be required to remain at the CRU for longer at the discretion of the Investigator or designee.

6.2.1 Baseline Assessments (Days -2 and -1)

Subjects will continue to smoke their usual brand combustible cigarette from Check-in through Day -1, but will abstain from use of any tobacco- or nicotine-containing products for at least 12 hours prior to the start of product use on Day 1.

The number of usual brand combustible cigarettes smoked per day will be documented.

Baseline assessments will be performed as delineated in the Study Events Flow Chart (Table 1). Urine samples will be collected for biomarkers over a 24-hour period from the start of the overnight abstinence on Day -2. On Day -1, blood samples for biomarkers will be collected, BP and HR measurements will be taken throughout the period of *ad libitum* smoking, and spirometry will be performed.

Subjects will be randomized to 1 of 8 sequences on Day -1 and 2 subjects from each sequence will have puff topography measurements (Section 6.4.4) performed on Day -1.

6.3 Product Use

6.3.1 Days 1, 3, 5, and 7

On Days 1, 3, 5, and 7, subjects will use the study product they are assigned to use the following day according to the randomization scheme. Subjects will use the assigned study product *ad libitum* until the start of the abstinence period (i.e., at least 12 hours prior to the start of the first product use session on the next day).

Each subject will be provided with a fully charged battery and a fresh pod on each day. Additional pods will be provided as needed. The clinic staff will document the time each product is dispensed. Pods will be weighed within 24 hours before the start and after completion of product use on each day. Products that stop functioning should be replaced as soon as possible, with the failure documented and the pod weighed within 24 hours.

6.3.2 Days 2, 4, 6, and 8

On Days 2, 4, 6, and 8, subjects will participate in two product use sessions on each day.

During the first product use session on each day, subjects will use the assigned e-cigarette under controlled conditions by taking 10 puffs at 30-second intervals, with puffs 3 seconds in duration. During the second product use session on each day, subjects will use the same assigned e-cigarette *ad libitum* with no limits on puff duration or inter-puff interval.

The first product use session will start following an abstention from use of any tobacco- or nicotine-containing products for at least 12 hours. The second product use session will begin following collection of the last PK blood sample (180-minute time point) and completion of the subjective effects questionnaires, and will end at approximately 23:00.

Subjects will be provided with a fully charged battery and a fresh pod for each product use session. The clinic staff will document the time the product is dispensed, the start and stop time of each product use session, the number of inhalations (first product use session only), the duration of each inhalation (first product use session only), and reasons for missed puffs during the first product use session. Pods will be weighed within 24 hours before and after each product use session. Products that stop functioning should be replaced as soon as possible, with the failure documented and the pod weighed within 24 hours. No product use of any kind will be allowed between the first and second product use sessions.

6.3.3 Day 9

Subjects may use all or any of the 4 study products (used previously on Days 1 through 8) *ad libitum* until approximately 23:00.

Each subject will be provided with a fully charged battery and will be assigned a fresh pod of each of the 4 study products. The clinic staff will document the time each product is dispensed. Pods will be weighed within 24 hours before the start and after completion of product use on Day 9. Products that stop functioning should be replaced as soon as possible, with the failure documented and the pod weighed within 24 hours.

6.3.4 Days 10 to 14

Subjects randomized to Arm I (*my*blu™) will exclusively use any or all of the 8 study products *ad libitum* until approximately 23:00 on each day.

Subjects randomized to Arm J (Combustible) will exclusively smoke their usual brand combustible cigarette *ad libitum* until approximately 23:00 on each day.

Subjects randomized to Arm K (Dual Use) will be allowed to smoke their usual brand combustible cigarette *ad libitum* (up to 50% of their self-reported CPD) and use any or all of the 8 study products *ad libitum* until approximately 23:00 on each day.

Subjects assigned to Arms I and K will be provided with a fully charged battery and will be assigned a fresh pod of each e-liquid on each day.

The clinic staff will document the time each study product/combustible cigarette is dispensed. As applicable, pods will be weighed within 24 hours before the start and after completion of product use on each day, 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 and the pod weighed within 24 hours. The number of combustible cigarettes smoked on each day will be documented, as applicable.

6.4 Study Assessments

All study assessments will take place at the times delineated in the Study Events Flow Chart (Table 1) unless otherwise noted below.

When scheduled during the same product use session on the same day, the following study procedures will be performed in the order indicated below, with regard to the prescribed time:

a. Puff topography
b. Blood pressure and heart rate
c. Subjective effects questionnaires
d. Spirometry

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

6.4.1 Nicotine Pharmacokinetics

On each of Days 2, 4, 6, and 8, a 4 mL blood sample for plasma nicotine analysis will be drawn into a plastic K_2-EDTA (lavender top) vacutainer tube at the time points delineated in the Study Events Flow Chart (Table 1). Allowable deviation windows for PK sampling are: ± 30 seconds for samples collected from 3 - 15 minutes, ± 1 minute for samples collected from 20 - 60 minutes, and ± 3 minutes for all other samples.

PK blood samples will be collected by direct venipuncture or through an intravenous catheter port as determined by the clinical staff.

Additional blood (typically up to approximately 1 mL) may be drawn between the blood draws during the first 15 minutes for the purpose of keeping the needle patent, if required. The blood from the 1 mL draws will be discarded. In total, approximately 192 mL of blood will be drawn from each subject during the entire study for nicotine PK analysis.

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

Samples will be analyzed using a validated liquid chromatography coupled to tandem mass spectrometry detection analytical method with the appropriate quality controls in accordance with FDA Good Laboratory Practice regulations (Title 21 Code of Federal Regulations [CFR] Part 58).

6.4.2 Biomarkers Sample Collection

6.4.2.1 Blood

Blood samples for COHb in whole blood (2 x 4 mL), sICAM in plasma (1 x 4 mL), WBCs in whole blood (1 x 4 mL), HDL-C in serum (1 x 3.5 mL), and MCP-1 in serum (1 x 3.5 mL), will be collected at the time points delineated in the Study Events Flow Chart (Table 1). Samples for COHb will be collected in the afternoon and samples for the other biomarkers will be collected following an overnight fast of at least 8 hours.

Up to approximately 69 mL of blood will be required for the planned biomarker assessments during the entire study.

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

6.4.2.2 Urine

Urine for biomarker measurements will be collected over a 24-hour period on the days indicated in the Study Events Flow Chart (Table 1). Each 24-hour urine collection will begin at the start of abstinence from tobacco- or nicotine-containing products and will end at the same time ± 30 minutes the following day. The start time of each urine collection should be within ± 1 hour of the start time on Day -2.

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:

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

All aliquots will be prepared within 120 minutes from the end of the collection interval 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.

6.4.2.3 Future Research

No additional analysis is planned to be performed on the blood or urine samples for possible future research. Any additional research on these samples unspecified by this protocol will require approval from the subjects.

6.4.3 Subjective Effects Questionnaires

The Urge to Smoke (VAS), Product Liking (VAS), PES (7-point scale), Future Intent to Use (VAS), QSU-Brief, MTWS-R, and PSCDI/PSECDI questionnaires will be completed using a computerized tablet device. All relevant software and staff training specific to the electronic questionnaires will be provided by the vendor. Any electronic device used must meet all regulatory requirements, including FDA 21 CFR Part 11.

All questionnaires will be completed at the time points delineated in the Study Events Flow Chart (Table 1).

When scheduled at the same time as a PK blood draw, the Urge to Smoke questionnaire will be completed approximately 30 seconds prior to the scheduled blood draw (except for the one scheduled at Time 0, which will be performed approximately 10 minutes prior to the start of the first product use session), and all other questionnaires will be completed within approximately 2 minutes after the scheduled blood draw, as applicable.

6.4.4 Puff Topography

Puff topography will be evaluated during *ad libitum* product use on the days indicated in the Study Events Flow Chart (Table 1). Subjects will engage in a 1-hour *ad libitum* product use with their usual brand combustible cigarette (Day -1) or the assigned study product (Days 1 and 8), using the topography device (SPA-M). The topography session should start at least 4 hours after the start of the *ad libitum* product use of that day.

The puff topography session on Days 1 and 8 should be within ± 2 hours of the time of the Day -1 session.

The topography device will be monitored to ensure the device is actively recording during each session.

Additional details and instructions for puff topography procedures will be provided separately.

Depending on the availability of topography equipment, puff topography may not be performed at all scheduled time points and may not be performed for some or all assigned subjects.

6.4.5 Spirometry

Subjects will undergo lung function testing at Screening to affirm eligibility (FEV1, FEV1:FVC ratio) and as a safety endpoint (FEV1, FVC, FEV1:FVC ratio, and forced expiratory flow [FEF]25-75%) on the days indicated in the Study Events Flow Chart (Table 1).

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 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 combustible cigarette smoked or last *my*blu™ product use. Spirometry must be performed after exhaled CO 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.

The CRU 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.

6.4.6 Safety Assessments

Safety assessments in addition to those below may be obtained as necessary at the discretion of the Investigator. In the case of an early subject withdrawal, discharge safety assessments should be collected to the extent possible.

6.4.6.1 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 as deemed appropriate by the Investigator (Table 1).

6.4.6.2 Body Weight, Height, and BMI

Body weight and body height will be measured as delineated in the Study Events Flow Chart (Table 1). BMI will be recorded as kg/m^2.

6.4.6.3 Electrocardiogram

Single 12-lead ECGs will be performed as outlined in the Study Events Flow Chart (Table 1). ECGs will be taken following resting in the supine position for at least 5 minutes. All ECG tracings will be reviewed by the Investigator or a qualified designee.

6.4.6.4 Vital Signs

Single measurements of vital signs (respiratory rate, HR, BP, and oral temperature) will be performed as outlined in the Study Events Flow Chart (Table 1). Additional vital signs may be taken at any other times, if deemed necessary.

BP and HR measurements will be taken following a rest period of at least 5 minutes in a seated position. Vital signs are to be measured at least 15 minutes after the last tobacco- or nicotine-containing product used. When BP and HR measurements are scheduled at the same time or immediately after a puff topography session, subjects may not have abstained from

tobacco- or nicotine-containing product use for 15 minutes prior to the BP and HR measurements.

On Days 2, 4, 6, 8, and 10 through 12, vital signs measurements will be taken within 2 hours prior to the start of the first product use session.

6.4.6.5 Clinical Laboratory

All clinical laboratory tests (with the exception of the urine cotinine test) will be conducted by a laboratory accredited by the Centers for Medicare and Medicaid Services (Clinical Laboratory Improvement Amendments of 1988 [CLIA-88]) or at the study site using CLIA-waived kits or procedures. 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. All tests listed below will be performed as delineated in the Study Events Flow Chart (Table 1). Up to approximately 50 mL of blood will be drawn from each subject during the entire study for clinical laboratory tests.

Serum Chemistry [1]
- Albumin
- Alkaline phosphatase
- Alanine aminotransferase
- Aspartate aminotransferase
- Bicarbonate
- 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
- Serum/urine pregnancy test [3]
- Serum FSH [4]
- Urine cotinine
- Urine drug screen
  - Amphetamines
  - Cannabinoids
  - Cocaine
  - Opiates
- Urine/breath alcohol

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

[1] Serum chemistry tests will be performed after at least an 8-hour fast; however, in case of dropouts or rechecks, subjects may not have fasted for 8 hours prior to the serum chemistry sample being taken.
[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] For postmenopausal females only.

6.4.7 Adverse Events

An AE is any untoward medical occurrence associated with the use of the 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.

6.4.7.1 Monitoring

The subjects will be instructed to inform the Investigator or staff of any AEs and intercurrent illnesses experienced during the study. Additionally, a specific inquiry regarding AEs will be conducted prior to each product use and at discharge (or upon early withdrawal). 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 qualified individual 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).

6.4.7.2 Reporting

All AEs occurring during this clinical trial after the subject has received the first study product must be recorded on the eCRF, including 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 listed.

Events captured between Screening and the first study product use will be documented as baseline signs and symptoms.

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.

6.4.7.3 Serious Adverse Events

A serious adverse event (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 CRU'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 and on the Sponsor signature page. The Investigator must also inform the IRB, in compliance with GCP reporting guidelines, and the site monitor of any SAE.

6.4.7.4 Pregnancy

A pregnancy occurring in a female study subject during the study will be documented in the clinical conduct study report to the IRB. Pregnancy itself is not an AE. 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. Advice given will be documented in the subject's source document.

The CRU staff will request the pregnant subject to notify the CRU of the outcome of the pregnancy (e.g., birth, loss, termination). To help ensure this, the CRU staff will follow up with the subject until the end of pregnancy, if in compliance with the CRU'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.

6.4.7.5 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, and will be encouraged to contact a qualified medical professional for advice on smoking cessation.

7. DATA ANALYSIS

Data will be handled and processed according to [redacted] and/or the site's SOPs, as appropriate, 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

The sample size chosen for this study was selected without statistical considerations. It has been determined adequate to meet the study objectives.

7.2 Analysis Populations

7.2.1 Safety Population

The Safety Population will include all subjects who have successfully completed eligibility requirements after checking in to the CRU and used at least one study product.

7.2.2 Outcomes Population

The Outcomes Population is a subset of the safety population and will consist of subjects who used a study product and have evaluable PK, biomarkers, subjective effects, BP, HR, spirometry, or topography data. This population will be used in the summary and analysis of PK, subjective effects, topography, biomarkers, spirometry, and product use, and all available data will be included in the summary tables to the extent possible.

7.3 Data Analysis, Summarization, and Statistical Methods

SAS software (version 9.3 or higher) will be used for all data presentation and summarization including summary tables, graphs, and data listings. In general, all data will be listed by subject and time point and summarized by study product, time point, and sex using descriptive statistics appropriate for the endpoint. Figures will be used to display the data graphically.

Missing data will not be imputed. Where individual data points are missing because of dropouts or other reasons, the data will be considered missing at random and summarized based on reduced denominators.

7.3.1 Nicotine Pharmacokinetic Analysis

Individual nicotine concentrations will be adjusted for baseline nicotine ("baseline-adjusted") and all PK parameters will be calculated based on the adjusted concentrations. Baseline adjustment will be performed by subtraction of the pre-existing nicotine concentration from each nicotine concentration obtained after test product administration in that period/day for each subject using the following equation:

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

where C_t is the adjusted concentration at time t, $C_{t\ unadjusted}$ is the observed concentration at time t, C_0 is the pre-product use concentration (-5 minutes), $Kel = \frac{\ln(2)}{t½}$, $t½$ is 2 hours (average nicotine half-life), t is the actual sampling time since product administration, and t1

is the actual sampling time since the time of the pre-product use sample. Any resulting negative concentration values following the baseline adjustment will be set to 0.

Nicotine PK parameters will be determined from the adjusted individual subject plasma concentration-time profiles by applying a non-compartmental approach using appropriate validated PK software (e.g., Phoenix® WinNonlin® version 6.3 or higher).

For each study product and each first product use session on Days 2, 4, 6, and 8, the following PK parameters will be calculated from the baseline-adjusted nicotine concentration-time data:

AUC0-180 Area under the nicotine concentration-time curve from time 0 (defined as the start of the first product use session) to the 180-minute time point as calculated by the linear trapezoidal method

Cmax Maximum baseline-adjusted plasma concentration.

Tmax Time to reach the maximum baseline-adjusted plasma concentration. If the maximum value occurs at more than one time point, Tmax is defined as the first time point with this value.

Plasma concentrations below the limit of quantitation will be set to one-half of the lower limit of quantitation for the calculation of descriptive statistics of unadjusted plasma nicotine concentrations and for the calculation of baseline-adjusted nicotine concentrations.

Nicotine concentrations and PK parameters will be listed by subject and summarized by study product, by sex and overall using descriptive statistics.

7.3.1.1 Analysis of Variance

A linear mixed model for analysis of variance will be performed on the log-transformed PK parameters Cmax and AUC following the first product use session on each of Days 2, 4, 6, and 8. The model will include sequence, study product, and period as fixed effects and subject-nested-within-sequence as a random effect. Sequence will be tested using subject-nested-within-sequence as the error term. Geometric least-squares means (LSM) and 95% confidence intervals (CIs) will be provided for the PK parameters of Cmax and AUC by study product. Geometric LSM ratio, 95% CIs of geometric LSM ratio, and p-values will be provided for the study product comparisons in Cmax and AUC. The comparisons of interest will include each of the study products compared to each other.

The above statistical analyses will be performed using the appropriate SAS procedure.

Non-parametric analysis (Wilcoxon Signed Rank test) will be performed for the comparisons of Tmax.

Details of the statistical methods will be provided in the SAP.

7.3.2 Biomarkers

Biomarker concentrations reported as below the limit of quantitation (BLQ) 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.

7.3.2.1 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 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

7.3.2.2 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.

7.3.2.3 Creatinine Adjustments

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

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

7.3.2.4 Data Summary and Analysis

Comparisons of the Day 9 primary BoE change-from-baseline values between study products and comparisons of the Day 14 primary BoE change-from-baseline values between study arms will be made using a linear mixed model analysis of variance (ANOVA).

An approach similar to that used for the primary endpoints will be used to make Day 9 and Day 14 change-from-baseline comparisons between study products and study arms for the applicable secondary BoE, BoPH, physiologic endpoints, and subjective measure endpoints as described in the SAP.

Comparisons of the primary and secondary BoE change-from-baseline values at each time point between study products and study arms will also be made using a linear mixed model ANOVA.

The comparisons of interest will include each of study products compared to each other (Part 1) and comparisons between study arms (Part 2).

7.3.3 Subjective Effects

7.3.3.1 Urge to Smoke Parameters

The following parameters will be calculated for the urge to smoke assessments:

Emax The maximum change from baseline VAS score (VASpre-use - VASpost-use).

TEmax Time of the Emax. If the maximum value occurs at more than one time point, TEmax will be defined as the first time point with this value.

AUEC0-120 The area under the change from baseline VAS score versus time curve from time 0 to 120 minutes, calculated using the linear trapezoidal method with linear interpolation using actual sample times.

Responses and derived parameters will be listed by subject and summarized by study product, by sex and overall using descriptive statistics.

An appropriate statistical method, similar to the PK analysis detailed above, will be used to compare Urge to Smoke parameters (no data transformation).

7.3.3.2 Product Liking

Responses will be listed by subject and summarized by study product, by sex and overall using descriptive statistics.

7.3.3.3 Product Evaluation

Product Evaluation will be considered as a 7-point scale. Responses will be presented as the following factor scores:

a) Satisfaction: average of the response scores from questions 1, 2, 3, and 12;

b) Psychological reward: average of the response scores from questions 4 to 8;

c) Aversion: average of the response scores from questions 9, 10, 16, and 18;

d) Relief: average of items 11, 13, 14, 15, and reversed for item 20 (i.e., not at all = 7, extremely = 1);

e) Items 17, 19, 21 will be summarized as individual item scores.

Descriptive statistics of the subscales will be provided by study product, by sex and overall. Individual responses will be listed by subject.

7.3.3.4 Future Intent to Use

Responses recorded as VAS scores will be treated as bipolar categorical variables (-50 to <0, 0, >0 to 50) and summarized by study product, by sex and overall using frequency count tables. The bipolar score for the Future Intent to Use questionnaire is calculated by subtracting 50 from the original VAS score.

The bipolar scores will also be treated as continuous variables and summarized by study product, by sex and overall using descriptive statistics.

7.3.3.5 QSU-Brief

QSU-Brief will be considered as a 7-point scale. Responses will be presented as the following 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

Descriptive statistics of the subscales will be provided by study product, study arm (as applicable), study day, and by sex and overall. Individual responses will be listed by subject.

7.3.3.6 MTWS-R

Total scores will be listed by subject and summarized by study product, study arm (as applicable), study day, and by sex and overall using descriptive statistics.

7.3.3.7 Penn State (Electronic) Cigarette Dependence Index (PSCDI/PSECDI)

Total scores will be listed by subject and summarized by study product, study arm (as applicable), study day, and by sex and overall using descriptive statistics.

7.3.4 Puff Topography

The following topography parameters will be assessed:

- Puff count
- Puff duration
- Puff volume
- Peak puff flow rate

- Average puff flow rate
- Inter-puff interval

Topography parameters will be listed by subject and summarized by study product, study day, overall and by sex, usual brand cigarette flavor (non-menthol or menthol), age, number of years smoking, CPD, and time point using descriptive statistics.

An appropriate statistical method, similar to the PK analysis detailed above, will be used to compare topography parameters.

7.3.5 Physiological Endpoints

7.3.5.1 Blood Pressure (BP) and Heart Rate (HR)

The following parameters will be calculated from the BP and HR measurements:

AUEC0-t	The area under the change from baseline versus time curve from time 0 to the last measureable time point, calculated using the linear trapezoidal method with linear interpolation using actual sample times.
Emax	The maximum change from baseline.
TEmax	Time of the Emax. If the maximum value occurs at more than one time point, TEmax will be defined as the first time point with this value.

An ANOVA will be performed on the natural log (ln)-transformed AUEC0-t and Emax, using the appropriate statistical procedure. Ninety (90)% CIs for the ratios will be obtained for the difference between the comparison of interest LSMs resulting from the analyses on the ln-transformed AUEC0-t and Emax.

The potential relationship between BP and HR change from baseline and plasma nicotine concentrations may be assessed.

Unadjusted and change from baseline BP and HR parameters will be listed by subject and summarized by study product, study arm (as applicable), study day, and by sex and overall using descriptive statistics.

7.3.5.2 Spirometry

The following pre- and post-bronchodilator lung function variables will be listed by subject and summarized by study day, study arm (as applicable), and by sex and overall using descriptive statistics:

- Measured and percent of predicted FEV1
- Measured and percent of predicted FVC
- Measured and percent of predicted FEV1:FVC ratio
- Measured and percent of predicted FEF25-75%

An appropriate statistical method, similar to the PK analysis detailed above, may be used to compare spirometry parameters.

7.3.6 Product Use Behavior

The number of puffs and duration of each puff (first product use session), and the difference in pod weights before and after each product use session (first and second product use sessions) will be listed by subject and summarized by study product, product use session, study arm (as applicable), study day, and by sex and overall using descriptive statistics.

The amount of nicotine delivery for each study product may be estimated using an appropriate method to correct for nicotine strength. If estimated, the amount of nicotine delivery will be listed by subject and summarized using descriptive statistics.

Correlation analyses may be performed to determine the potential relationship between puff topography parameters and pod weight change.

7.3.7 Safety

Safety data including single vital signs assessments, ECGs, and clinical laboratory results will be listed and summarized by subject and time point as appropriate.

All AEs captured in the database will be listed in by-subject data listings. However, only study product use-emergent AEs will be summarized. 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.

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 serious AEs 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 concomitant medications recorded will be listed by subject.

Incidence of device malfunction(s) will be tabulated.

8. STUDY ADMINISTRATION

8.1 Ethics

8.1.1 Institutional Review Board

This protocol will be reviewed by the IntegReview 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 to International Council for Harmonisation (ICH) guidelines, and may be reached at:

IntegReview IRB
3815 S. Capital of Texas Hwy, Suite 320
Austin, Texas 78704, USA
Tel.: +1 512 817-1130
Fax: +1 512 697-0085
Email: clientservices@integreview.com

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 Consolidated Guidance, April 1996).

8.1.3 Subject Information and Consent

The purpose of the study, the procedures to be carried out, and the potential hazards will be described to the subjects in non-technical terms. Subjects will be required to read, sign, and date an ICF summarizing the discussion prior to Screening, and will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

Subjects will be given a copy of their signed ICF.

8.2 Confidentiality

All clinical sites and vendors will have signed confidentiality agreements with [redacted] By signing this protocol, the Investigator and [redacted] staff will regard all information provided by the Sponsor and all information obtained during the course of the study as confidential.

Neither the clinical site nor [redacted] will supply to the Sponsor any subject names, initials, date of birth (except year), or other personal identifiers (HIPAA 2015). 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. As required, in the case of an event where medical expenses are the responsibility of the Sponsor, personal information i.e., full name, social security details etc. may be released to the Sponsor. 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.

8.3 Termination of the Study

The Investigator reserves the right to terminate the study in the interest of subject welfare.

The Sponsor reserves the right to suspend or terminate the study at any time.

8.4 Data Quality Assurance

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.

Standard operating procedures are available for all activities performed at [redacted] relevant to the quality of this study. Designated personnel of [redacted] will be responsible for implementing and maintaining quality assurance (QA) and quality control systems to ensure that the study is conducted, and that data are reported in compliance with the study protocol, GCP and Good Laboratory Practice requirements as well as applicable regulatory requirements and local laws, rules and regulations relating to the conduct of the clinical study.

The Clinical Study Report will be audited by the QA department and the QA audit certificate will be included in the study report.

8.5 Direct Access to Source Data/Documents

All clinical sites and vendors will ensure that the Sponsor, IRB and inspection by domestic and foreign regulatory authorities will have direct access to all study-related sites, source data/documents, and reports for the purpose of monitoring and auditing (ICH[E6][R2] 5.1.2 & 6.10). In the event that other study-related monitoring should be done by other parties, they will be required to sign a confidentiality agreement prior to any monitoring and auditing.

8.5.1 Monitoring the Study

The responsible study monitor or Sponsor's designee 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).

8.6 Reporting for the Study

8.6.1 Case Report Forms

eCRFs 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. The final signed eCRFs are provided to the Sponsor in the format as decided upon between [redacted] and the Sponsor (e.g., compact disc, flash drive, secure file transfer protocol). This will be documented in the DMP (if applicable).

8.6.2 Data Coding

AEs will be coded using MedDRA®. Concomitant medications will be coded using the World Health Organization Drug Dictionary. Each dictionary version will remain the same throughout the trial. Coding will be completed by qualified members of the [redacted] staff.

8.6.3 Report Format

According to the ICH Harmonized Tripartite Guideline (Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use M4 and the ICH M2 Expert Working Group), the final report will be written according to the ICH E3 Guideline (Structure and Content of Clinical Study Reports).

8.6.4 Record Keeping

All raw data generated in connection with this study, together with the original copy of the final report, will be retained by the clinical site and/or [redacted] (as appropriate) until at least 5 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 5 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/Institution as to when these documents no longer need to be retained.

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.

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10. APPENDICES

Appendix 1. Urge to Smoke Questionnaire

Appendix 2. Product Liking Questionnaire

Appendix 3. Product Evaluation Scale (PES)

Appendix 4. Future Intent to Use Questionnaire

Appendix 5. Questionnaire of Smoking Urges-Brief (QSU-Brief)

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

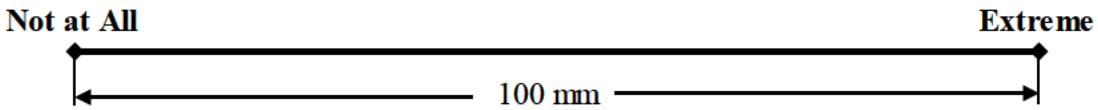
Appendix 7. Penn State [Electronic] Cigarette Dependence Index (PSCDI/PSECDI)

Appendix 1: 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 making a vertical mark anywhere along the horizontal line.

How strong is your urge to smoke right now?

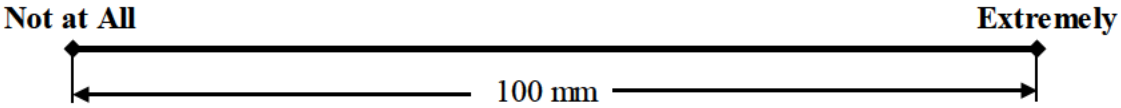


Appendix 2: Product Liking Questionnaire

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.

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

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



Appendix 3: Product Evaluation Scale (PES)

(Hatsukami 2013)

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

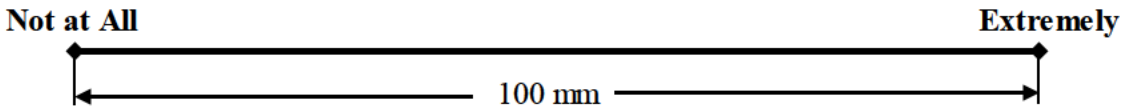
Four multi-item subscales will be derived from "Satisfaction" (items 1, 2, 3, and 12); "Psychological Reward" (items 4 through 8); "Aversion" (items 9, 10, 16, and 18); and "Relief" (items 11, 13, 14, 15, and reversed for item 20) and single items 17, 19, and 21 will be summarized.

Appendix 4: 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.

Please respond to each phrase by making 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 5: Questionnaire of Smoking Urges-Brief (QSU-Brief)

(Cox 2001)

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)

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: Penn State [Electronic] Cigarette Dependence Index (PSCDI/PSECDI)

(Foulds 2015)

Note: For the PSECDI, 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 approximately 15 puffs or lasts approximately 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.