An Open-Label, Parallel-Group, Controlled Study to Evaluate Changes in Biomarkers of Cigarette Smoke Exposure and Biomarkers of Potential Harm in Adult Smokers Who Completely Switch to Using e-Vapor Products for 12 Weeks

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Altria Client Services Study No. ALCS-RA-16-06-EV
Final Protocol Date: 10 November, 2016

Sponsor:

Altria Client Services LLC
601 E. Jackson Street
Richmond, Virginia 23119

[redacted]

11/10/16
(Signature) (Date)

Medical Monitor:

[redacted]

16 Nov 2016
(Signature) (Date)

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Sponsor's Contact:

PROTOCOL SIGNATURE PAGE
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An Open-Label, Randomized, Parallel-Group, Controlled Study to Evaluate Changes in Biomarkers of Cigarette Smoke Exposure and Biomarkers of Potential Harm in Adult Smokers Who Completely Switch to Using e-Vapor Products for 12 Weeks

By signing below, the Investigator agrees to adhere to the protocol as outlined and agrees that any changes to the protocol must be approved by Altria Client Services LLC (ALCS) prior to seeking approval from the Institutional Review Board (IRB).

This study will be conducted in accordance with Good Clinical Practice (GCP) based on the current International Conference on Harmonization (ICH) guidelines for GCP and the corresponding sections of the United States (US) Code of Federal Regulations (CFR) governing Protection of Human Subjects (Title 21 CFR Part 50), Institutional Review Boards (Title 21 CFR Part 56), the Basic Principles of the Declaration of Helsinki, and applicable legal and regulatory requirements.

Principal Investigator:	Phone: Fax: E-mail:
	(Signature) (Date)

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APPENDECES

STUDY SYNOPSIS

ALCS Protocol Number:
ALCS-RA-16-06-EV

Abbreviated Protocol Title:

e-Vapor SWITCHing Study to Assess Health Risks in Adult Smokers(e-SWITCH)

Long Protocol Title:

An Open-Label, Randomized, Parallel-Group, Controlled Study to Evaluate Changes in Biomarkers of Cigarette Smoke Exposure and Biomarkers of Potential Harm in Adult Smokers Who Completely Switch to Using e-Vapor Products for 12 Weeks

Study Products:

Test e-Vapor products (supplied by Altria Client Services LLC):

- Product XLCB = Test EVP (currently marketed by Nu Mark LLC as MarkTen® XL Bold Classic [4.0% NBW]) [CVR2.6.8] Formula: 10381-44-B; Name: "Rosetta"; Label: B44
- Product XLMB = Test EVP (currently marketed by Nu Mark LLC as MarkTen® XL Bold Menthol [4.0% NBW]) [CVR2.6.8] Formula: 10381-40-E; Name: "Spencer"; Label: 40E

Reference product (supplied by subject at their own cost):

- Subject's own brand[1] commercially available conventional cigarettes

[1] own brand: subject's choice, no restriction on brand at any time during the study

Number of Subjects and Groups:

Total number of adult subjects (to randomize): 450 will be randomized in total, with 150 subjects into each of the groups described below to better ensure that a minimum of 120 in each group complete the study.

Three study groups:

- Test 1 Group (n=150): Exclusive ad libitum use of test e-Vapor Product XLCB, without use of any other type of tobacco/nicotine containing product, for the entire 12 weeks
- Test 2 Group (n=150): Exclusive ad libitum use of test e-Vapor Product XLMB, without use of any other type of tobacco/nicotine containing product, for the entire 12 weeks
- Control Group (n=150): Continue smoking under ad libitum use of subjects' own brand of conventional lit-end cigarettes, without use of any other type of tobacco/nicotine containing product, for the entire 12 weeks

Study Duration:

16 weeks (up to 4 weeks for screening + 12 weeks from randomization to the End of Study [EOS])

Estimated Study sites:

6-10 study sites

Study Objectives:

The Primary Objective is to:

Compare absolute changes in selected biomarkers[a] from Baseline to End of Study (EOS) between adult smokers who continue to smoke conventional cigarettes (Control group) ad libitum and adult smokers who have completely[b] switched to ad libitum use of the test e-Vapor products (Test groups) for 12 weeks.

[a] Seleted biomarkers include:

- White Blood Cell Count (WBC)
- High Density Lipoprotein Cholesterol (HDL-C)
- Urinary 8-epi-prostaglandin $F_{2\alpha}$
- Urinary 11 Dehydrothromboxane B_2
- Blood Soluble Intercellular Adhesion Molecule-1 (sICAM-1)
- Urinary 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronides (total NNAL)
- Carboxyhemoglobin (COHb)

[b] Subjects who exclusively use e-Vapor products and with eCO measurements < 8 ppm from Week 3 through EOS

The Secondary Objectives are to:

- Compare changes in selected biomarkers (same as those in the primary objective) from Baseline to Week 6 between Test and Control groups
- Determine the number of cigarettes smoked (Test and Control groups) from Week

2 through EOS

- Assess changes in the amount of test e-Vapor product use (Test groups only) from Week 2 through EOS
- Assess adherence to protocol by comparing changes from Baseline to each post randomization measurement within the Test groups for exhaled CO and urinary NNN

The Exploratory Objectives are to:

- Assess changes in BOPHs and BOEs (same as in the primary objective) from Baseline to Week 6 and EOS in two subgroups that use different flavored e-Vapor products
- Assess changes in forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC) and FEV_1/FVC ratios from Screening/Visit 2 to EOS between the Test and Control groups
- Assess changes in urine nicotine equivalents (NE) from Baseline to Week 6 and EOS **within** and **between** Test and Control groups
- Assess changes in the QGEN and TQOLIT questionnaires and the Cough Questionnaire responses from Baseline to EOS between the Test and Control groups
- Assess reasons for test product use/not-use at EOS and mCEQ questionnaires from Baseline to EOS for the Test groups
- Collect blood and urine samples for future assessment of BOE and or BOPH

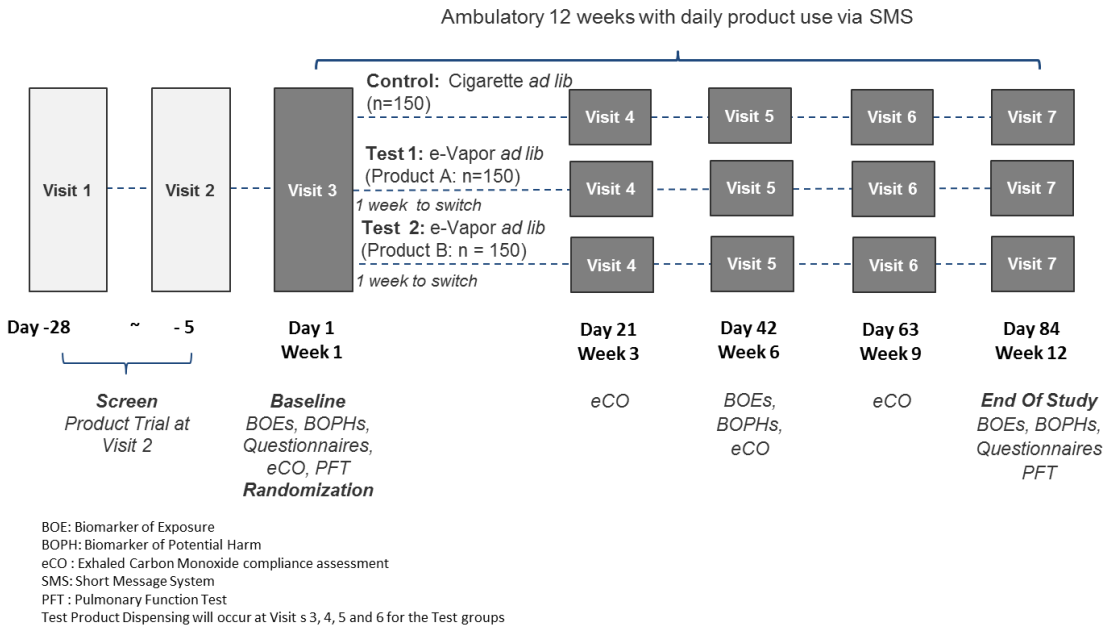
Study Design:

This research study will utilize a randomized, parallel-group, open-label, controlled design and will be conducted at multiple study sites. Up to 450 adult male and female (neither gender should account for more than 60% of the population) smokers (30 to 65 years of age, inclusive) with ≥ 10 years of smoking and an average daily cigarette consumption of ≥ 10 CPD in the 12 months prior to Screening, Visit 1, will be randomized into one of the three study groups at Visit 3. Subjects that pass the initial screening at Visit 1 (Screen Part 1) will be asked to return to the study site for a test product trial at Visit 2 (Screen Part 2). During the test product trial, potential subjects will be allowed to use each of the Test Products for 15 minutes with 30 minutes in

between. Subjects will then complete the Test e-Vapor Product Assessment questionnaire. Subjects who pass all eligibility requirements and are willing to replace all of their cigarettes with one of the test products will be randomized at Visit 3 (Day 1) to one of the study groups.

All subjects will report their cigarettes per day (CPD) (Control and Test groups) and Test product use (Test groups only) daily using a Short Message Service (SMS), i.e., text message, based system (Med-Quest). The self-reported CPD, use of other tobacco products, and measurements of CO and NNN taken during the in-clinic visits after randomization will be used to monitor subject compliance with exclusive use of the test products. All subjects will return to the study sites for four visits at Weeks 3, 6, 9 and 12.

Study Diagram:



BOE: Biomarker of Exposure
BOPH: Biomarker of Potential Harm
eCO : Exhaled Carbon Monoxide compliance assessment
SMS: Short Message System
PFT : Pulmonary Function Test
Test Product Dispensing will occur at Visit s 3, 4, 5 and 6 for the Test groups

Study Visits:

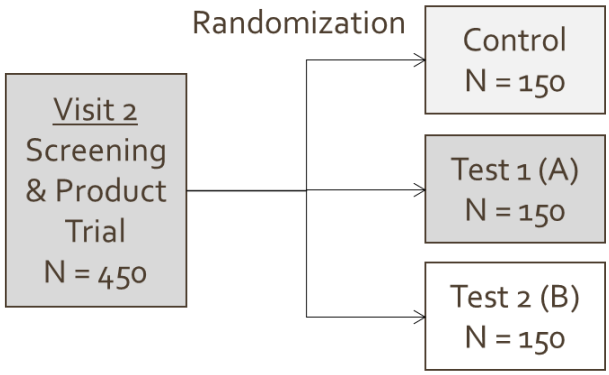
- Visit 1: Screening Part 1 (Day -28 to Day -7)
- Visit 2: Screening Part 2 (Visit 1 to Day -5)
- Visit 3: Randomization (Week 1, Day 1)
- Visit 4: (Week 3, Day 21 +/- 3 days)
- Visit 5: (Week 6, Day 42 +/- 3 days)

- Visit 6: (Week 9, Day 63 +/- 3 days)
- Visit 7: (Week 12, Day 84 +/- 3 days, EOS [or Early Termination])

Number of Subjects per Group:

Up to 450 healthy adult cigarette smokers will be randomized (stratified by body mass index, gender, and age) in a 1:1:1 ratio to Test 1, Test 2 and Control groups to ensure that 120 from each group will complete the study. Neither gender should account for more than 60% of the study population.

Randomization Schema



- Control group: n = 150 (own brand conventional cigarettes)
- Test 1 group: n = 150 (Product XLCB)
- Test 2 group: n = 150 (Product XLMB)

Study Population:

The study population will consist of up to 450 adult (30 – 65 years of age) cigarette smokers who satisfy all inclusion/exclusion criteria.

Inclusion criteria:

Subjects must satisfy the following criteria before being enrolled into the study. Subjects must:

1) sign an IRB-approved informed consent form (ICF) for the study;
2) be between the ages of 30 and 65 years, inclusive, at the time of Screening, Visit 1;
3) have ≥ 500 ng/ml urine cotinine measurement at Screening, Visit 1;
4) have smoked for ≥ 10 years and smoked an average of ≥ 10 manufactured cigarettes per day during the 12 months prior to Screening, Visit 1;
   a) Brief periods [i.e., up to 7 consecutive days] of non-smoking during

the 12 months prior to Screening, Visit 1 due to illness, trying to quit, or participation in a study where smoking was prohibited are acceptable.

5) indicate that he/she is "definitely" or "probably" willing and able to replace their cigarettes for 12 weeks with the assigned test e-Vapor product;

6) have daily access to text messaging capable cellular phone for daily product use reporting;

7) have a negative ethanol breath test and amphetamines, opiates, cannabinoids, and cocaine urine drug screen results at Screening, Visit 1;

a) Subjects with a prescription from a licensed physician will not be exempted from this criterion.

8) if female (**all** females), have a negative serum pregnancy test at Visit 1 and negative urine pregnancy test at Visit 2 through Visit 7, inclusive;

9) if female, heterosexually active, and of childbearing potential (i.e., not surgically sterile or 2 years naturally postmenopausal), must have used a medically accepted method of contraception (listed below in a) and b)) prior to Screening, Visit 1 and must agree to continue to use such method(s) through the End of Study;

a) Surgically sterile includes bilateral tubal ligation, Essure, hysterectomy, or bilateral oophorectomy at least 6 months prior to Screening, Visit 1. Naturally postmenopausal is defined as women having 2 years without menses.

b) Acceptable methods of contraception are: hormonal (i.e., oral, transdermal patch, implant, or injection) consistently for at least 3 months prior to Screening, Visit 1; double barrier (i.e., condom with spermicide or diaphragm with spermicide) consistently for at least 4 weeks prior to Screening, Visit 1; and intrauterine device for at least 3 months prior to Screening, Visit 1; or only have a partner who has been vasectomized for at least 6 months prior to Screening, Visit 1.

10) Be willing and able to comply with the requirements of the study.

Exclusion criteria:

Subjects may be excluded from the study if there is evidence of any of the following criteria. Exceptions may be permitted at the discretion of the Investigator and in consultation with the Sponsor or designee provided there would be no additional risk to the subject. Any exceptions will be documented.

1) History or presence of clinically significant gastrointestinal, renal, hepatic, neurologic, hematologic, endocrine, oncologic, urologic, diabetes, existing

respiratory diseases, 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. (Note: chronic medical conditions controlled and on stable medications [over past 3 months] may not necessarily be exclusionary per Investigator discretion);

2) Currently taking medication for depression, asthma or diabetes;

3) Allergy to menthol;

4) Systolic blood pressure > 140 mmHg and / or diastolic blood pressure > 90 mmHg at Screening Visit 1.

5) Have clinically significant abnormal findings on the physical examination, vital signs, electrocardiogram (ECG), or medical history that would jeopardize the safety of the subject, in the opinion of the Investigator;

6) Positive test for human immunodeficiency virus (HIV), hepatitis B surface antigen (HbsAg), or hepatitis C virus (HCV) at Screening, Visit 1;

7) Current evidence or any history of congestive heart failure;

8) Any acute illness (e.g., upper respiratory infection, viral infection) requiring treatment within 2 weeks before Visit 3 (Day 1);

9) History of drug or alcohol abuse within 24 months of Visit 3 (Day 1) as defined by the Investigator;

10) BMI greater than 40.0 kg/m^2 or less than 18.0 kg/m^2 at Screening, Visit 1;

11) Post-bronchodilator FEV_1:FVC ratio < 0.7 and FEV_1 < 50% of predicted at Screening, Visit 2;

12) Post-bronchodilator FEV1:FVC ratio < 0.75 and FEV1 increase ≥ 12% and > 200 mL from pre- to post-bronchodilator at Screening, Visit 2;

13) Estimated creatinine clearance (by Cockcroft-Gault equation) < 80 mL/min at Screening, Visit 1;

14) Serum alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≥ 1.5 times the upper limit of the reference range at Screening, Visit 1;

15) Female candidates who are pregnant, lactating, or intend to become pregnant from Screening, Visit 1 through End of Study;

16) Use of HDL-C raising medication / supplements (e.g., niacin, gemfibrizole, fenofibrate, etc.) within the past 3 months prior to Screening, Visit 1 or any time during the study;

17) Use of nicotine-containing products other than manufactured cigarettes (e.g., roll-your-own cigarettes, e-cigarette or e-Vapor products, Bidis, snuff, nicotine inhaler, pipe, cigar, smokeless tobacco, nicotine patch, nicotine spray, nicotine lozenge, or nicotine gum) within 14 days prior to

Screening, Visit 1 through Visit 3 (Day 1) except as required for the purpose of this study;

18) Donation of blood or blood products, including plasma, history of significant blood loss in the opinion of the investigator, or receipt of whole blood or a blood product transfusion within 60 days prior to Visit 3 (Day 1);

19) Participation in a clinical study of an investigational drug, medical device, biologic, or of a tobacco product, within 30 days before Visit 3 (Day 1);

20) Participation in more than two ALCS studies within 12 months before Visit 3 (Day 1);

21) Already enrolled or failed screening for the current study at a different study site;

22) Subject or a first-degree relative (i.e., parent, spouse, sibling, or child) is a current or former employee of the tobacco industry or a named party or class representative in litigation with any tobacco company.

Study Duration:

The expected duration of the study, from first subject, first visit through last subject, last visit will be approximately 6 months. The expected study duration from Screening to the End of Study for each individual subject is approximately 16 weeks.

Statistics:

Sample size estimation

The study is designed to detect a statistically significant difference in change from baseline to the end of the study in 5 out of the 7 primary biomarkers between the Test and the Control groups. Total NNAL, COHb, 11-Dehydrothromboxane B_2, 8-epi-prostaglandin $F_{2\alpha}$ WBC and HDL values from a previous PMUSA longitudinal study (Study #: EHCJLI/02/02) for the Electronic Heating Cigarette Smoking System and S-ICAM values from another source (Scott DA et. al. 2000) were used for the sample size calculation. Assuming a two-sided test, 3.5 % Type I error rate (adjusted for multiplicity of detecting statistical significance in 5 out of the 7 biomarkers based on the Hailperion-Ruger approach), 80% power and a 1 to 1 ratio of the Test group over the Control group, a sample size of 120 subjects in the Test group and 120 in the Control group are needed. With a 15% dropout rate expected, 150 subjects are needed in each group. Because there are two test groups and one control group, a total of 450 subjects (300 in the Test and 150 in Control groups) are needed at the randomization. The statistical power for each primary biomarker is provided below.

Table 1. Approximate power for a preliminary sample size of test=120 and control=120 subjects

Biomarker	Cigarette Smoker (mean, SD)	Electrically Heated Cigarette Smoker or Quitter (mean, SD)	Power (%)

Total NNAL (ng/g Cr)[1]	484.51 (187.50)	86.90 (134.19)	>85
COHb ($AUC_{(7\text{-}23h)}$, % •hr)[2]	3.6 (18.1)	-70.7 (35.4)	>85
8-Epi (ng/g Cr)[3]	1320 (506.78)	1106.28 (456.74)	85
11-Dehydro (mg/g Cr)[1]	1264.00 (533.58)	1011.53 (385.33)	>85
WBC (X1,000/ul)[2]	-0.3 (1.3)	-1.1 (1.3)	>85
HDL (mg/dl)[2]	0 (7.0)	5.0 (10.0)	>85
sICAM-1 (ng/ml)[4]	5 (66.0)	-66.1 (75.0)	>85

All biomarker data except S-ICAM are from the PMUSA EHCSS JLI long term study[21].

1. Week 13 value
2. Change from baseline to Week 13
3. Average value of Week 8 and Week 17 due to potential bioanalytical data issue for Week 13
4. Scott D et. al. (2000)[22].

Hypothesis

If adult cigarette smokers completely switch to the test e-Vapor products for 12 weeks, all of the selected biomarkers will change in a favorable direction, with at least 5 out of 7 biomarkers demonstrating a statistically significant change from baseline compared to cigarette smoking.

Primary Endpoints

The primary endpoints are changes from baseline to the end of study in the following biomarkers measured at Baseline (Day 1) and End of Study (Week 12):

1) WBC in whole blood (10^3 µg/L)

2) HDL-C in serum (mg/dL)

3) 8-epi-prostaglandin $F_{2\alpha}$ in urine with creatinine adjusted (ng/g Cr)

4) 11-dehydrothromboxane B_2 in urine with creatinine adjusted (ng/g Cr)

5) Soluble Intercellular Adhesion Molecule – 1 (sICAM-1) in serum (ng/mL)

6) Total NNAL in urine with creatinine adjusted (ng/g Cr)

7) COHb in whole blood (% sat)

Secondary Endpoints

The secondary endpoints are:

1) Levels of selected biomarkers (same as the primary endpoints) and the following additional biomarkers measured at Baseline/Day 1 (Visit 3), Week 6 (Visit 5) and EOS (Visit 7):

a) Creatinine-adjusted NNN in urine (ng/g Cr) and exhaled CO.

2) The average daily cigarettes smoked and Test Product use reported by subjects during Week 2 through Week 6 and during Week 7 through EOS

a) Test Product The Test Products used per day, the number of new cartridges used, and average number of puffs taken (1 – 20 or >20) will be document through text message.

b) The number of cigarettes smoker per day will be documented by the subjects through the text message.

Exploratory Endpoints

The exploratory endpoints are:

1) Assess changes in BOPHs and BOEs (same as in the primary objective) from Baseline to Week 6 and EOS in two subgroups that use the two Test e-Vapor Products

2) FEV1 (% predicted), FCV, and FEV1/FVC measured at Screening (Visit 2) and EOS

3) Nicotine Equivalents (Nicotine, Cotinine, Trans-3'-Hydroxycotinine, Trans-3'- Hydroxycotinine-O-glucuronide, Nicotine-N-glucuronide, and Cotinine-N-glucuronide) (NE) in urine with creatinine adjustment (mg/g Cr) measured at Baseline/Day 1 (Visit 3), Week 6 (Visit 5) and EOS

4) Responses (Score) to the QGEN and TQOLIT questionnaires and the Cough Questionnaire recorded at Baseline/Day 1 (Visit 3), Week 6 (Visit 5) and EOS

5) Reponses to Reasons for Use and Not-use of Test Product (EOS) and mCEQ questionnaires (Baseline/Day 1 [Visit 3]) (Test group only)

Statistical Analysis Methods

Demographic Variables

Demographic baseline characteristics will be summarized by study group with descriptive statistics (the number of non-missing values, mean, median, standard deviation [SD], minimum, maximum, coefficient of variation [CV], 95% confidence interval) for continuous variables (e.g., BMI) and frequency counts for categorical variables (e.g., gender).

Primary and secondary variables

Primary variable analysis

A linear mixed model for repeated measures (MMRM) analysis will be used for comparing each Test group to the Control group in the mean absolute change from Baseline to EOS in each primary endpoint. In the model, study group, visit, and study group by visit interaction, gender, age class, race and BMI class are the fixed effect factors. The baseline value of the response biomarker is the fixed effect covariate and subject is the random effect factor. The unstructured covariance structure will be used for modeling covariance. The least-square mean difference, 95% confidence interval and p-value will be provided for the group difference. The analysis will be conducted on the MITT population.

To assess the robustness of the primary MMRM analysis to the possible violation of the missing at random (MAR) assumption, the pattern mixture model based on the non-future dependent missing value restriction will be applied. In addition, a supportive analysis based on the per-protocol (PP) population will also be conducted.

Secondary variable analyses

1) The MMRM as used for the primary endpoints will be used to test the differences in the mean absolute change from Baseline to Week 6 for the selected biomarkers (WBCs, HDL-C, COHb, total NNAL, 8-epi-prostaglandin $F_{2\alpha}$, 11-Dehydrothromboxane B_2, and sICAM-1) between each Test group and the Control group.

2) Descriptive statistics (the number of subjects with non-missing data, number of subjects with missing data, mean, standard deviation, median, minimum and maximum) will be used to summarize the average cigarettes per day and daily e-Vapor cartridge consumption amount by group from Week 2 through Week 6 and from Week 7 through EOS. Frequency tables will also be used to summarize the proportions of change categories (reduce, no change, increase or percentage) from baseline to end of study for each study group.

3) A frequency table (n and %) will be used to summarize use of other tobacco products, eCO and NNN for assessment of compliance and noncompliance for each study group.

Exploratory Endpoints/Variable Analyses

The MMRM approach will be used to provide the estimates for:

- changes in BOPHs and BOEs from Baseline to Week 6 and EOS in two subgroups that use different flavored e-Vapor products
- changes in forced expiratory volume in the first second (FEV_1), forced vital

capacity (FVC), and FEV_1/FVC ratios from Baseline to EOS in the Test and Control groups
- changes in urine nicotine equivalents (NE) from Baseline to Week 6 and EOS **within** each test group and **between** the Test and Control groups
- changes in the QGEN and TQOLIT questionnaires and the Cough Questionnaire from Baseline to EOS in the Test and Control groups

Subgroup Analysis

Subgroup analyses will be conducted for the end of study change from baseline in the primary biomarkers by product and gender, product and age class and product and BMI class using the MMRM model.

Clinical Safety

Adverse Events (AE) will be coded with the Medical Dictionary for Regulatory Activities (MedDRA®).

AEs will be listed in by-subject data listings. Frequency counts of AEs will be provided by system organ class and preferred terms, and study group. Frequency counts of AEs will also be listed and summarized by severity and relationship to product.

Clinical safety analyses will include summaries of clinical safety measures (blood pressure, ECG, vital signs, clinical chemistry, and hematology).

More details about the data analysis will be described in the Statistical Analysis Plan (SAP).

All statistical analyses will be performed with SAS® software.

SUMMARY OF EVENTS/ASSESSMENTS

EVENTS/ASSESSMENTS	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
	Screening Part 1 (Day -28 through Day -7)	Screening Part 2 (After the results of Part 1 are assessed through Day -5)	Week 1 Day 1	Week 3 Day 21 (+/- 3)	Week 6 Day 42 (+/- 3)	Week 9 Day 63 (+/- 3)	Week 12 Day 84 (+/- 3) End of Study / Early Term
Age Verification and Photocopy of ID	X						
Informed Consent	X						
Urine Drug Screen and Alcohol Breath Test	X						
Medical History	X						
Demographics and Tobacco Use History Questionnaires	X						
Photocopy Cigarette Pack[1]	X						
Review of Inclusion / Exclusion Criteria	X	X	X	X	X	X	X
Vital Signs[2]	X	X	X	X	X	X	X
Body Weight	X		X				X
Height	X						
Body Mass Index	X		X				X
Spirometry[3]		X					X
Smoking Cessation Information	X						X
Clinical Chemistry (8 hr fasting)	X						X
Hematology (8 hr fasting)	X						X
Urinalysis	X						X
HIV, HbsAg, and HCV Serology	X						
Urine Cotinine Screen	X						
Serum Pregnancy Test (females)	X						
Review of Concomitant Medications	X	X	X	X	X	X	X
Review of Tobacco and Nicotine Restrictions	X	X	X	X	X	X	
Physical Examination		X	X[4]				X[4]
12-Lead ECG[5]		X					X
Urine Pregnancy Test		X	X	X	X	X	X
Test e-Vapor product trial		X					
Test e-Vapor Product(s) Assessment Questionnaire		X					
Review of AEs		X	X	X	X	X	X
QGEN and TQOLIT questionnaires			X		X		X
Cough Questionnaire			X		X		X
mCEQ Questionnaire			X				X
Reasons of Use/Not-Use Test Product							X

EVENTS/ASSESSMENTS	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
	Screening Part 1 (Day -28 through Day -7)	Screening Part 2 (After the results of Part 1 are assessed through Day -5)	Week 1 Day 1	Week 3 Day 21 (+/- 3)	Week 6 Day 42 (+/- 3)	Week 9 Day 63 (+/- 3)	Week 12 Day 84 (+/- 3) End of Study / Early Term
Questionnaire[10]							
Confirm Regular Cigarette Brand		X	X[11]	X[11]	X[11]	X[11]	X[11]
Subject Randomization			X				
Test e-Vapor Product Dispensation			X	X	X	X	
Test e-Vapor Product Collection				X	X	X	X
Subject Instructions for Product Use		X					
Reminder Phone Calls			X	X	X	X	X
Distribute 1st Morning Void Containers		X		X		X	
Urine (1st void of day) for BOEs and BOPHs[6, 7]			X		X		X
Blood Collection for BOPHs[8]			X		X		X
Blood Collection for COHb[8]			X		X		X
BioBanking			X		X		X
–Product Use Reporting Training			X				
Product Use Reporting[9]			X	X	X	X	X
Exhaled CO Measurement			X	X	X	X	X
End of Study Questionnaire							X

AE = adverse event; BOE = biomarker of exposure; BOPH = biomarker of potential harm; CO = carbon monoxide; COHb = carboxyhemoglobin; CPD = cigarettes per day; ECG = electrocardiogram; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; HbsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HDL-C = high-density lipoprotein cholesterol; HIV = human immunodeficiency virus; ID = identification; IVRS = interactive voice response system; NE = nicotine equivalents; NNAL = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; sICAM-1 = Soluble intercellular adhesion molecule-1; WBC = white blood cell.

1 Obtain photocopy at Visit 1. Photocopies are required after Visit 1 only if the subject's regular cigarette has changed.

2 Vital signs (respiratory rate, pulse rate, blood pressure, and oral temperature) in the sitting position after at least 5 minutes of rest and at least 15 minutes after the last conventional cigarette smoked or test e-Vapor product used.

3 Spirometry includes FEV_1, FVC, and FEV_1/FVC ratio measurements.

4 Brief physical examination (symptom driven).

5 After at least 5 minutes resting in supine position.

6 Urinary creatinine will be measured in all urine samples to allow for adjustment of all urine biomarkers.

7 Spot urine (first void of the day, after at least 4 hrs since prior void) collections will be used for the analysis of BOEs (total NNAL, NE, NNN) and BOPHs (11-Dehydrothromboxane B_2, 8-epi-prostaglandin $F_{2\alpha}$).

8 Blood will be collected after overnight fasting (at least 8 hrs) and will be used for the analysis of COHb and BOPHs (WBC, sICAM-1, HDL-C).

9 Daily product use (conventional cigarettes or test e-Vapor product) will be reported daily (Day 1 through Day 84/Week 12) by subjects using a Short Message Service (SMS), i.e., text message, based system (Med-Quest) to assess product use and compliance during the study.

10 Questionnaire given to Test group only.

11 Control group only, photocopy the pack if there has been a change from Screening.

ABBREVIATIONS AND DEFINITIONS

AE	Adverse event
ALCS	Altria Client Services LLC
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
APE	Alleged physical effects
AST	Aspartate aminotransferase
BMI	Body mass index
BOE	Biomarker of exposure
BOPH	Biomarker of potential harm
BUN	Blood urea nitrogen
°C	Degrees Celsius
CDMS	Clinical Data Management System
CFR	Code of Federal Regulations
CLIA-88	Clinical Laboratory Improvement Amendments of 1988
CO	Carbon monoxide
COHb	Carboxyhemoglobin
CPD	Cigarettes per day
CRF	Case report form
CRO	Clinical Research Organization
CSP	Clinical safety population
CV	Coefficient of variation
DMP	Data management plan
ECG	Electrocardiogram
°F	Degrees Fahrenheit
FVC	Forced vital capacity
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in 1 second
GCP	Good Clinical Practice
HbsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HDL-C	High-density lipoprotein cholesterol
HIV	Human Immunodeficiency Virus
ICF	Informed consent form
ICH	International Conference on Harmonization
ID	Identification
LLC	Limited Liability Company
IRB	Institutional Review Board
ITT	Intent to treat
IVRS	Interactive Voice Response System
Kg	Kilogram(s)
LED	Light-emitting diode
M	Meter(s)
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
MITT	Modified intent to treat
mL	Milliliter(s)
MMRM	Mixed model for repeated measures
N	Number, sample size

NBW	Nicotine by weight
NE	Nicotine Equivalents
ng	Nanograms
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
pg	Picogram
PK	Pharmacokinetic
PP	Per-protocol
QA	Quality assurance
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
sICAM-1	Soluble intercellular adhesion molecule-1
SD	Standard deviation
SOP(s)	Standard operating procedure(s)
US	United States
USP	United States Pharmacopoeia
WBC	White blood cell
WHO-DD	World Health Organization Drug Dictionary

1.0 INTRODUCTION AND STUDY RATIONALE

1.1 Background

Innovative and novel tobacco derived nicotine products, like e-Vapor products (EVPs) potentially offer reduced risk alternatives to adult consumers of conventional lit-end cigarettes (CCs)[1]. The proven strategies of prevention and cessation can be complemented by making available tobacco products that have demonstrated lower risks than CCs. There is overwhelming scientific evidence regarding a risk continuum in the range of tobacco products available currently in the market. According to this body of evidence, combustible tobacco products, like CCs, are the most risky and non-combustible tobacco products, like EVPs present relatively lower risks. The Royal College of Physicians' new report, 'Nicotine without smoke: tobacco harm reduction'[2], has concluded that EVPs are significantly less risky than cigarettes and likely to be benefit public health. EVPs deliver nicotine in an aerosol that has a very different composition than a typical aerosol from CCs. There are thousands of chemicals generated from the combustion of tobacco, many of which are carcinogenic[3, 4]. In contrast, far fewer chemicals are generated from heating an e-liquid consisting of carrier ingredients (usually propylene glycol [PG] and/or glycerol), nicotine, water and flavors[5]. The likely reductions in exposure due to large differences in the chemical composition of aerosols between the cigarettes and EVPs presents harm reduction opportunities for adult smokers switching to EVPs. Nu Mark LLC (Nu Mark) is focused on responsibly developing and marketing innovative tobacco products, such as e-Vapor products, that may reduce the risk of tobacco-related disease. Altria Client Services LLC (ALCS) and Nu Mark are undertaking various studies to evaluate the EVPs including the MarkTen® branded e-Vapor products. These studies will provide the scientific evidence in support of a Premarket Tobacco Product Application (PMTA) submission to the Center of Tobacco Products at FDA. Before issuing a marketing order, FDA must determine, based on the contents of the PMTA and other data available to FDA, that marketing the new product that is the subject of the PMTA would be appropriate for the protection of the public health. FDA's Draft PMTA Guidance for Electronic Nicotine Delivery Systems[6] (ENDS or in other words EVPs) (Draft ENDS PMTA Guidance) suggests that applicants include,in addition to other information, results from studies addressing topography and use patterns, an assessment of abuse liability and results from human studies assessing biomarkers and health risks. This study will assess biomarkers and health risks in adult smokers who switch to EVP products or continue smoking cigarettes. This study is one component of a broader comprehensive framework that will provide the totality of evidence for the PMTA.

In the following sections we briefly describe the preclinical studies on the products proposed for testing in this study as well as human studies conducted on earlier versions of MarkTen® branded products.

1.2 Product Safety Information

Preclinical Testing and Toxicological Assessment

ALCS implements an e-Vapor product toxicological assessment ("Product Stewardship [PS]") program based on the concept that, while the use of any tobacco product has an inherent risk, ingredients and components used in Nu Mark's products and any interaction of e-Vapor device and e-liquid to form aerosols should not increase the inherent risk. The toxicological assessment is based on the totality of all of the available scientific evidence and, when appropriate, considers the harm reduction potential of EVPs for cigarette smokers.

Nu Mark uses the highest quality ingredients available, including, food-grade GRAS flavors and USP-grade aerosol formers (propylene glycol and glycerol) and nicotine. The use levels are determined based on estimated consumer usages, material-specific scientific data in the literature, and applicable regulatory information.

Toxicological data are already available for many individual ingredients commonly used in consumer products. However, there is no toxicological data on specific product formulations. Therefore ALCS uses a weight-of-evidence approach in assessing e-Vapor ingredients and products considering the following information:

- Individual material evaluation & risk assessment
- Chemistry analyses of formulations and product aerosols
- Flavor mixtures (prototype formulations): in vivo inhalation study in rats
- Product-specific formulation: in vitro (genotoxicity and cytotoxity) testing

The approach is consistent with FDA's recommendations in the Draft ENDS PMTA Guidance (May 2016)[7], for "a full assessment of the toxicological profile associated with the new product, which includes in vitro and in vivo toxicological studies"[6]. In the assessment of genotoxicity

potential, FDA refers to International Conference on Harmonization (ICH) S2(R1)[7] guidance and Organization for Economic Cooperation and Development (OECD) protocols[8-12].

ALCS has performed the following battery of in vitro tests and if needed, in vivo genotoxicity test for the relevant e-liquid formulations:

1. In vitro bacterial gene mutation test (Ames assay; OECD471)[10]

2. In vitro mammalian cytotoxicity test (Neutral Red Uptake [NRU] assay; OECD129)[9]

3. In vitro mammalian genotoxicity test (micronucleus [MN] assay; OECD487)[8], and

4. (if needed) In vivo mammalian genotoxicity test (micronucleus [MN] assay; OECD 474[11]; Comet assay OECD 489)[12].

Four of six formulations tested, including Bold Menthol, exhibited negative responses in all three in vitro assays (Ames, NRU, and MN assays). Two formulations, including Bold Classic, displayed negative responses in the Ames and NRU assays, but required further evaluation in the MN assay. The MN response for the Bold Classic formulation was "equivocal" (values were higher for the Bold Classic formulation than the negative control but within the historical control values for the assay) whereas the other formulation had a definitive positive response in this in vitro assay. While none of the e-liquid ingredients in these formulations are known mutagens or carcinogens, mixtures of e-liquid could potentially trigger in vitro genotoxic responses in cellular systems. In the absence of OECD guidelines for tobacco products, we rely on the guidelines for pharmaceutical drug candidates which recommends that in vivo genotoxicity assays be used to further investigate genotoxicity detected by an in vitro system" (OECD 474/489[11,12]). Accordingly, ALCS has initiated in vivo genotoxicity testing of Bold Classic and the other formulation, using a conservative approach of including two independent endpoints (in vivo MN and in vivo Comet responses following acute inhalation exposures of e-liquid aerosols in rats) based on the combined OECD guidelines 474[11] and 489[12]. Preliminary results for the other formulation are negative at both endpoints. The results for the Bold Classic formulation are pending, however, it is likely to be negative (to be confirmed) considering a weaker in vitro MN response compared to that of the other formulation.

In addition to an in vitro battery of assays, all flavor ingredients were tested as aerosols via in vivo 90-day inhalation exposures in rats. While not product formulation specific, these investigations allow holistic evaluations of respiratory and systemic responses in rodents

inhaling aerosols of e-Vapor flavor mixtures, similar to the human mode of exposure. Additionally, Werley et al (2016)[13] demonstrated that 90-day inhalation exposures from a prototype e-Vapor product (MarkTen® CVR1.3) did not show meaningful difference in biological endpoints between the vehicle only and the vehicle with flavor groups.

In conclusion, we believe there is no concern for use of these e-Vapor products in future clinical studies based on the above formulation, product-specific testing, and the overall weight-of-evidence toxicological assessment. Both formulations are currently available in the commercial market (since August 8, 2016) based on our initial toxicological assessment.

Human studies on previous Nu Mark e-Vapor Products

In-Clinic Human Studies (n=5)

Pharmacokinetic Studies

Study 1

ALCS sponsored three pharmacokinetic (PK) studies of e-Vapor products since 2012. The first study (CEL-LIQ-01-12) included two prototype e-Vapor products (CVR1.2 NS [PM 10305-54-B] non-menthol and CVR1.2 MS [PM 10305-57-A] menthol flavored) containing 2% tobacco-derived nicotine by weight (Study number CEL-LIQ-01-12). The purpose of this PK study was to characterize the nicotine plasma PK profile from single and multiple (1 use [10 inhalations] each hour over 12 hours) uses of the prototypes. This randomized, single-blind, 4 period crossover PK study was conducted in 27 (14 males, mean age 36.3 years) healthy adult cigarette smokers. Subjects were instructed to use the prototype e-Vapor products by taking ten 5-second puffs over a 5-minute period, repeating the exposure every hour for 12 hours. Six subjects (25%) experienced 11 mild adverse events (AEs) on the day they were using the CVR1.2 NS product, and 7 subjects (29%) reported 13 mild AEs on the day of CVR1.2 MS product use. The most common AE was throat irritation (4 subjects), followed by dyspepsia (2 subjects), and nausea (2 subjects).

Study 2

The second study (CEL-LIQ-01-13) included two prototype e-cigarette products (CVR1.3 NB3 [10305-126-NB3%] containing 3.0% tobacco-derived nicotine by weight (NBW) and CVR1.3 NB5 [10305-126-NB5%] containing 5% tobacco-derived NBW). Twelve adult smokers (6 males

and 6 females) participated in the study. For each product, the subjects took ten 5 second inhalations within a 5 minute period, and repeated the product use episode at 1-hour intervals for a total of 12 product use episodes. One subject reported six adverse events (AEs) (including dry lip, nausea, vomiting, and dizziness) following the use of the CVR1.3 NB3 product, and three subjects experienced 15 AEs (including nausea, vomiting, feeling hot, burning sensation, dizziness, nervousness and hiccups) following the use of the CVR1.3 NB5 product. One subject discontinued due to mild AEs of nausea, vomiting and nervousness during the CVR 1.3 NB5 use period.

Study 3

The third study (ALCS-E45-01-14) included 4 prototype e-Vapor products containing 2.5% to 4.5 % tobacco-derived nicotine by weight. The purpose of the PK study was to characterize the nicotine plasma PK profile from single and multiple (1 use each hour over 10 hours) uses of the prototypes. Adult subjects were instructed to use the prototype e-Vapor products by taking ten puffs over a 10-minute period, repeating the exposure every hour for 10 hours. Five (21%) of the 24 randomized subjects experienced 14 mild AEs that were considered likely related to study product. The most common AE (11 events in two subjects) was throat irritation, followed by 1 dry throat, 1 headache and 1 dizziness.

Puff Topography studies

Study 1

ALCS conducted a study (CRT-LIQ-01-13) to evaluate puffing topography measurements in subjects using a prototype e-Vapor product, CVR1.3 (PM-10305-87A) (Study number: CRT-LIQ-01-13). Thirteen (6 males) adult cigarette smokers and 10 (4 males) adult e-Vapor users were enrolled in this study. Subjects were provided 2 cartridges (2% by weight tobacco-derived nicotine) for ad libitum use over a 7-hour period. Twelve (6 males) of the thirteen cigarette smokers returned to the study site for additional puff measurements using 4 prototypes (2% by weight tobacco-derived nicotine). The subjects were instructed to take ten 5 second puffs over a 5 minute period. The subjects repeated this puff regimen 6 times a day (3 times per prototype) on two separate days. One reported AE of headache (mild) was considered possibly related to study product.

Study 2

ALCS sponsored a study (ALCS-M10-05-14) to evaluate puffing topography measurements in three different groups of tobacco product users: adult smokers, adult smokers and e-Vapor users (dual users) and adult exclusive e-Vapor users. During the study subjects used CVR1.5 e-Vapor products (2.5% tobacco-derived nicotine in both Menthol and Classic flavors) ad libitum over eight consecutive hours. Ninety one generally healthy adult subjects (48 males) were enrolled and eighty nine subjects completed the study. On average, subjects used approximately 2.9 CVR1.5 e-Vapor cartridges over the 8 hours and no adverse advents were reported.

Ambulatory Studies (n=2)

Study 1

ALCS sponsored an Ambulatory Vaping Exposure study (COV-M10-01-14) in 2014. One hundred forty-eight (70 males) healthy adult smokers were enrolled in the randomized control study. One hundred and three (48 males) subjects were allowed to smoke their own brand conventional cigarettes and use an e-Vapor CVR 1.5 (1.5% tobacco-derived nicotine, either Classic or Menthol flavored) product ad libitum and 45 (22 males) smoked their conventional cigarettes ad libitum without using e-Vapor products for four weeks. Of the 103 subjects assigned to the e-Vapor group, 34 reported 44 adverse events, and 9 of the 45 subjects assigned to smoking group reported 13 AEs. Out of the 44 AE reports from the subjects assigned to the CVR 1.5 e-Vapor group, 4 mild AEs were considered to be possibly related to the test products by the investigators (2 Upper Respiratory Tract Infection, 1 Throat Irritation and 1 Headache).

Study 2

ALCS sponsored an ambulatory tobacco product use study (ALCS-M10-02-14). Two hundred and twenty six (104 males) adult cigarette smokers were randomized into five groups investigating the use of cigarettes with the use of CVR1.5 e-Vapor products (1.5% tobacco-derived nicotine, in Classic [C15] or Menthol [M15] flavor and 2.5% tobacco-derived nicotine in Classic [C25] or Menthol [M25] Flavor) for 3 weeks. Two groups were instructed to use their own brand cigarettes and CVR1.5 e-Vapor products (n=51, C15/M15; n=49, C25/M25) ad libitum and two groups were instructed to use their own brand cigarettes ad libitum and at least 1 CVR1.5 e-Vapor cartridge per day (n=52, C15/M15; n=49, C25/M25). The control group (n=25) continued to smoke their own brand cigarettes ad libitum. A total of 26 subjects (11.5% of enrolled subjects) reported 37 post-randomization AEs. In the two hundred and one subjects randomized to CVR1.5 e-Vapor product use groups, 15 mild or moderate AEs from 9 subjects (4.0% of CVR1.5 e-Vapor use groups) were considered as unlikely, possibly or likely related to

the test products by the investigators (no definitely related AEs were reported). Of these 15 unlikely, possibly or likely related AEs, the only AE reported by more than one subject across all of the CVR1.5 use groups was mild oral discomfort (2 subjects, 1% of the CVR1.5 e-Vapor use groups).

Consumer Response Center Data

ALCS continuously monitors consumer calls to the Consumer Response Center regarding e-Vapor products currently marketed as MarkTen® e-Vapor since August 2013. As of March 31, 2016, consumers reported via the Consumer Response Center a total of 538 alleged physical effects (APEs) related to the use of e-Vapor products (estimated 26 million cartridges distributed to consumers). Of the 538 reported APEs, the most common were "burned skin or hair" (42%) and other type of APE reports were "sore or burning mouth or tongue or lips" (12%), "sore or burning throat" (6%), "coughing" (6%), "nausea or vomiting" (4%), "electrical shock" (4%), "headache" (3%), "dizziness or lightheaded" (2%), "after taste" (2%), "blisters in mouth or on lips" (2%) and "stomach ache" (2%). There were 30 other APE symptoms each with less than 2% of the total reports. Majority (74%) of the APEs were categorized as minor. Three of the APE reports – "difficulty breathing" (1), "swelling" (1) and "blacking out, fainting or passing out" (1) were categorized as severe.

Based on the information presented, it is anticipated that Product XLCB and Product XLMB test e-Vapor products will be well-tolerated in this study and the subjects will be informed that the test e-Vapor products used in this research bear the following warning:

> This product is not a smoking cessation product and have not been tested as such. This product is intended for use by persons of legal age or older, and not by children, women who are pregnant or breast feeding, or persons with or at risk of heart disease, high blood pressure, diabetes, or taking medicine for depression or asthma. Nicotine is addictive and habit forming, and it is very toxic by inhalation, in contact with the skin, or if swallowed. Nicotine can increase your heart rate and blood pressure and cause dizziness, nausea, and stomach pain. Inhalation of this product may aggravate existing respiratory conditions. Ingestion of the non-vaporized concentrated ingredients in the cartridges can be poisonous.

For products sold in the State of California, the following warning will be present at points of sale:

> CA Proposition 65 WARNING: This product can expose you to chemicals including glycidol, which is known to the State of California to cause cancer, and nicotine, which is known to the State of California to cause birth defects or other reproductive harm. For more information go to www.P65Warnings.ca.gov.

Glycidol is detected in the aerosols generated from our products. IARC has classified glycidol as "probably carcinogenic to humans (Group 2A)"[14]. Our scientific test data however show that the anticipated human exposures are substantially below the established regulatory limits[15]

1.3 Purpose of this Study

The purpose of the study is to evaluate changes in BOPHs and BOEs in adult cigarette smokers who completely switch to the test e-Vapor products (Product XLCB or Product B) as compared to adult smokers who continue to smoke conventional cigarettes. This study will support the overall assessment of the health risk associated with the use of the e-Vapor products in adult smokers using e-Vapor products exclusively.

1.4 Hypothesis

If adult smokers completely switch to exclusive use of an e-Vapor test product for 12 weeks[a], all selected biomarkers will change in a favorable direction, with at least 5 out of 7 biomarkers demonstrating a statistically significant change from baseline compared to cigarette smoking.

[a] One week of dual use is allowed immediately following randomization

1.5 Rationale

Cigarette smoking produces the predominance of the morbidity and mortality from the use of tobacco products. Cigarette smoking is the leading preventable cause of death in the United States, primarily due to cancers, respiratory, and cardiovascular disease[16]. More than 4,800 different chemical constituents have been identified in cigarette smoke[3], many of these chemicals are present either in the particulate or gas/vapor phase of the smoke aerosol. The test e-vapor products do not produce the vast majority of these compounds, therefore switching from cigarettes to the test e-vapor products should result in large reductions in exposure to many of the chemicals present in cigarette smoke. However we have no evidence of the impact of switching from cigarettes to the test e-vapor products. This study is designed to measure changes in biomarkers of exposure and biomarkers of potential harm when adult smokers switch to the test

e-Vapor products. The results from this study will provide supportive evidence to the overall assessment of the reduced risk potential of test e-Vapor product

2.0 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to compare absolute changes in selected biomarkers[a] from Baseline to End of Study (EOS) between adult smokers who continue to smoke conventional cigarettes (Control group) ad libitum and adult smokers who have completely[b] switched to ad libitum use of the test e-Vapor products (Test groups) for 12 weeks.

[a] Seleted biomarkers include:

- White Blood Cell Count (WBC)
- High Density Lipoprotein Cholesterol (HDL-C)
- Urinary 8-epi-prostaglandin $F_{2\alpha}$
- Urinary 11 Dehydrothromboxane B_2
- Blood Soluble Intercellular Adhesion Molecule-1 (sICAM-1)
- Urinary 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronides (total NNAL)
- Carboxyhemoglobin (COHb)

[b] Subjects who exclusively use e-Vapor products and with eCO measurements < 8 ppm from Week 3 through EOS

2.2 Secondary Objectives

The secondary objectives are to:

- Compare changes in selected biomarkers (same as those in the primary objective) from Baseline to Week 6 between Test and Control groups
- Determine the number of cigarettes smoked (Test and Control groups) from Week 2 through EOS

- Assess changes in the amount of test e-Vapor product use (Test groups only) from Week 2 through EOS
- Assess adherence to protocol by comparing changes from Baseline to each post randomization measurement within the Test groups for exhaled CO and urinary NNN

2.3 Exploratory Objectives

The exploratory objectives are to:

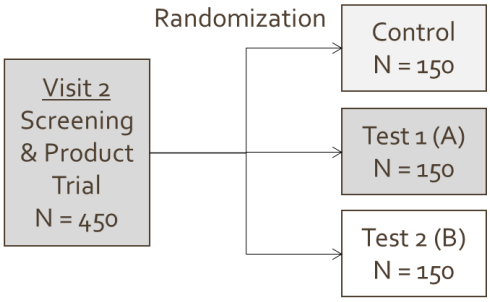
- Assess changes in BOPHs and BOEs (same as in the primary objective) from Baseline to Week 6 and EOS in two subgroups that use different flavored e-Vapor products
- Assess changes in forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC) and FEV_1/FVC ratios from Screening/Visit 2 to EOS within the Test and Control groups
- Assess changes in urine nicotine equivalents (NE) from Baseline to Week 6 and EOS **within** and **between** Test and Control groups
- Assess changes in the QGEN and TQOLIT questionnaires and the Cough Questionnaire from Baseline to EOS within the Test and Control groups
- Assess reasons for test product use/not-use at EOS and mCEQ from Baseline to EOS for the Test groups
- Collect blood and urine samples for future assessment of BOE and or BOPH

3.0 SUMMARY OF STUDY DESIGN

3.1 Design

This research study will utilize a randomized, parallel-group, open-label, controlled design and will be conducted at multiple study sites. Up to 450 adult male and female (neither gender should account for more than 60% of the population) smokers (30 years of age to 65 years of age, inclusive) with ≥ 10 years of smoking and an average daily cigarette consumption of ≥ 10 CPD during the 12 months prior to Screening, Visit 1 will be randomized into one of the three study groups on Day 1. Subjects that pass the initial screening at Visit 1 (Screen Part 1) will be asked to return to the study site for a test product trial at Visit 2 (Screen Part 2). During the Test product trial, potential subjects will be allowed to use each of the Test Products for 15 minutes with 30 minutes in between. Subjects will then complete the Test e-Vapor Product Assessment

questionnaire. Subjects who pass all eligibility requirements and are willing to replace all of their cigarettes with one of the test products will be randomized at Visit 3 (Day 1) to one of the study groups.



- Control Group (n=150): Continue smoking under ad libitum use of subjects' own brand of conventional lit-end cigarettes, without use of any other type of tobacco/nicotine containing product, for the entire 12 weeks

- Test 1 Group (n=150): Stop smoking during Week 1 and ad libitum use of test e-Vapor products (Product XLCB), without use of any other type of tobacco/nicotine containing product, for the entire 12 weeks

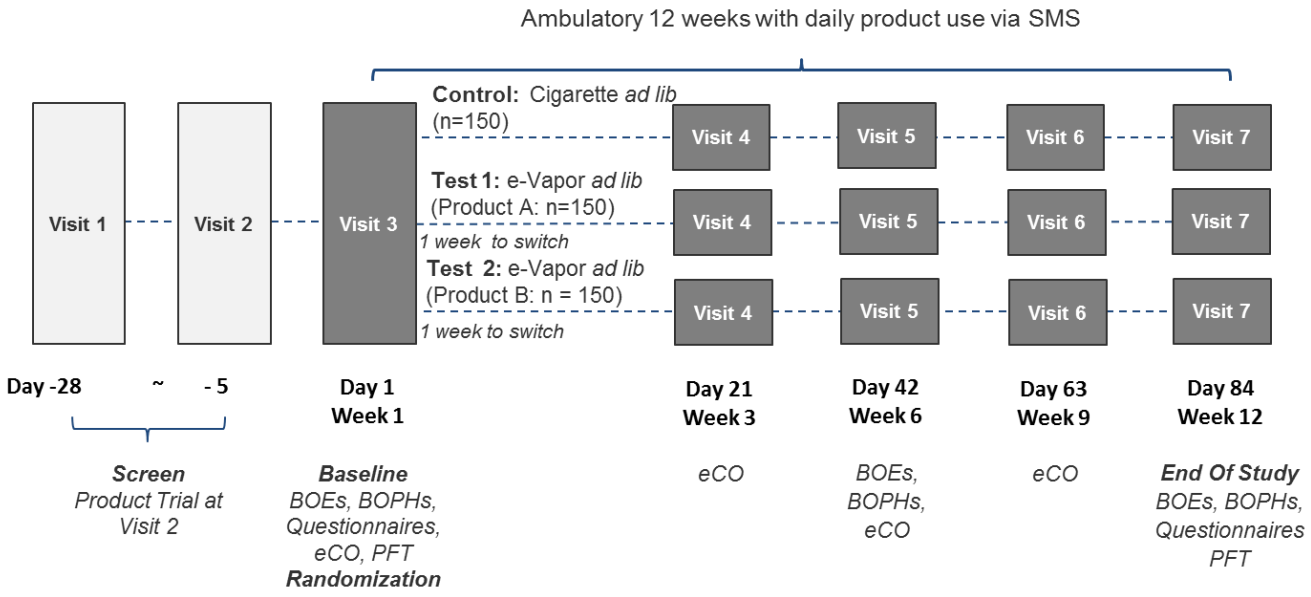
- Test 2 Group (n=150): Stop smoking during Week 1 and ad libitum use of test e-Vapor products (Product XLMB), without use of any other type of tobacco/nicotine containing product, for the entire 12 weeks

Study sites will record the reason for drop out for subjects who leave the study at randomization (e.g., because they do not wish to continue in the group into which they were randomized); such subjects will be replaced.

All subjects will report their cigarettes per day (CPD) (Control and Test groups) and Test product use (Test groups only) daily using a Short Message Service (SMS), i.e., text message, based system (Med-Quest). Subjects in the Test groups are allowed up to 1 week (Day 1 through Day 7) to acclimatize to switching to the Test Product. By Day 8, all subjects in the Test group will have completely switched to exclusive use of the Test Product without use of any other tobacco or nicotine products until the end of the study. The self-reported CPD, use of other tobacco products, and eCO measurements, taken during the in-clinic visits after randomization

will be used to monitor subject compliance. All subjects will return to the study sites for four visits at Weeks 3, 6, 9, and 12.

The overall design of the study is shown below.



BOE: Biomarker of Exposure
BOPH: Biomarker of Potential Harm
eCO : Exhaled Carbon Monoxide compliance assessment
SMS: Short Message System
PFT : Pulmonary Function Test
Test Product Dispensing will occur at Visit s 3, 4, 5 and 6 for the Test groups

3.2 Study Duration

The expected duration of the study, from first subject, first visit, through last subject, last visit will be approximately 6 months. The expected study duration from Screening to End of Study for each individual subject is approximately 16 weeks.

3.3 Clinical Safety Evaluations

Clinical safety evaluations will be performed to ensure that subjects meet the requirements of the study and to monitor subject safety. Screening safety evaluations will include the following: physical examination; vital signs; body weight and height; body mass index (BMI); 12-lead electrocardiogram (ECG); human immunodeficiency virus (HIV), hepatitis B surface antigen (HbsAg), hepatitis C virus (HCV) serology; clinical chemistry, hematology, and urinalysis; lung function (FEV1, FVC, and FEV1/FVC ratio); and pregnancy testing (all females). Visit 3 safety evaluations will include the following: physical examination (symptom driven); vital signs; body

weight; BMI; and pregnancy testing (all females). Visits 4, 5 and 6, safety evaluations will include vital signs. Visit 7/EOS (or early termination) safety evaluations will include a physical examination (symptom driven); vital signs; body weight; BMI; 12-lead electrocardiogram (ECG); clinical chemistry, hematology, and urinalysis; and pregnancy testing (all females).

AEs will be monitored and recorded from the time of the test e-Vapor product trial at Screening Part 2, Visit 2 until the End of Study (or upon Early Termination). Events occurring after informed consent signing and before the test e-Vapor product trial will be recorded and considered baseline signs and symptoms.

Any concomitant medications taken from 30 days prior to Screening, Visit 1 through the End of Study (or upon Early Termination) will also be recorded.

4.0 SUBJECT SELECTION

4.1 Inclusion Criteria

Subjects must satisfy the following criteria before being enrolled into the study. Subject must:

1) sign an IRB-approved informed consent form (ICF) for the study;

2) be between the ages of 30 and 65 years, inclusive, at the time of Screening, Visit 1;

3) have $\geq$ 500 ng/ml urine cotinine measurement at screening Visit 1;

4) have smoked for $\geq$10 years and smoked an average of $\geq$ 10 manufactured cigarettes per day during the 12 months prior to Screening, Visit 1;

a) Brief periods [i.e., up to 7 consecutive days] of non-smoking during the 12 months prior to Screening, Visit 1 due to illness, trying to quit, participation in a study where smoking was prohibited are acceptable.

5) indicate that he/she is “definitely” or “probably” willing and able to replace their cigarettes for 12 weeks with the assigned test e-Vapor product;

6) have daily access to text messaging capable cellular phone for daily product use reporting;

7) have a negative ethanol breath test and amphetamines, opiates, cannabinoids, and cocaine urine drug screen results at Screening, Visit 1;

a) Subjects with a prescription from a licensed physician will not be exempted from this criterion.

8) if female (**all** females), have a negative serum pregnancy test at Visit 1 and negative urine pregnancy test at Visit 2 through Visit 7, inclusive;

9) if female, heterosexually active, and of childbearing potential (i.e., not surgically sterile or 2 years naturally postmenopausal), must have used a medically accepted method of contraception (listed below in a) and b)) prior to Screening, Visit 1 and must agree to continue to use such method(s) through the End of Study;

a) Surgically sterile includes bilateral tubal ligation, Essure, hysterectomy, or bilateral oophorectomy at least 6 months prior to Screening, Visit 1. Naturally postmenopausal is defined as women having 2 years without menses.

b) Acceptable methods of contraception are: hormonal (i.e., oral, transdermal patch, implant, or injection) consistently for at least 3 months prior to Screening, Visit 1; double barrier (i.e., condom with spermicide or diaphragm with spermicide) consistently for at least 2 weeks prior to Screening, Visit 1; and intrauterine device for at least 3 months prior to Screening, Visit 1; or only have a partner who has been vasectomized for at least 6 months prior to Screening, Visit 1.

10) Be willing and able to comply with the requirements of the study.

4.2 Exclusion Criteria

Subjects may be excluded from the study if there is evidence of any of the following. Exceptions may be permitted at the discretion of the Investigator and in consultation with the Sponsor or designee provided there would be no additional risk to the subject. Any exceptions will be documented.

1) History or presence of clinically significant gastrointestinal, renal, hepatic, neurologic, hematologic, endocrine, oncologic, urologic, diabetes, existing respiratory diseases, 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. (Note: chronic medical conditions controlled and on stable medications [over past 3 months] may not be exclusionary per Investigator discretion);

2) Currently taking medication for depression, asthma or diabetes;

3) Allergy to menthol;

4) Systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg at Screening Visit 1;

5) Have clinically significant abnormal findings on the physical examination, vital signs, electrocardiogram (ECG), or medical history that would jeopardize the safety of the subject, in the opinion of the Investigator;

6) Positive test for human immunodeficiency virus (HIV), hepatitis B surface antigen (HbsAg), or hepatitis C virus (HCV) at Screening, Visit 1;

7) Current evidence or any history of congestive heart failure;

8) Any acute illness (e.g., upper respiratory infection, viral infection) requiring treatment within 2 weeks before Visit 3 (Day 1);

9) History of drug or alcohol abuse within 24 months of Visit 3 (Day 1) as defined by the Investigator;

10) BMI greater than 40.0 kg/m^2 or less than 18.0 kg/m^2 at Screening, Visit 1;

11) Post-bronchodilator FEV_1:FVC ratio < 0.7 and FEV_1 < 50% of predicted at Screening, Visit 2;

12) Post-bronchodilator FEV1:FVC ratio < 0.75 and FEV1 increase ≥ 12% and > 200 mL from pre- to post-bronchodilator at Screening, Visit 2;

13) Estimated creatinine clearance (by Cockcroft-Gault equation) < 80 mL/min at Screening, Visit 1;

14) Serum alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≥ 1.5 times the upper limit of the reference range at Screening, Visit 1;

15) Female candidates who are pregnant, lactating, or intend to become pregnant from Screening, Visit 1 through End of Study;

16) Use of HDL-C raising medication / supplements (e.g., niacin, gemfibrizole, fenofibrate, etc.) within the past 3 months prior to Screening, Visit 1 or any time during the study;

17) Use of nicotine-containing products other than manufactured cigarettes (e.g., roll-your-own cigarettes, e-cigarette or e-Vapor products, Bidis, snuff, nicotine inhaler, pipe, cigar, smokeless tobacco, nicotine patch, nicotine spray, nicotine lozenge, or nicotine gum) within 14 days prior to Screening, Visit 1 through Visit 3 (Day 1) except as required for the purpose of this study;

18) Donation of blood or blood products, including plasma, history of significant blood loss in the opinion of the Investigator, or receipt of whole blood or a blood product transfusion within 60 days prior to Visit 3 (Day 1);

19) Participation in a clinical study of an investigational drug, medical device, biologic, or of a tobacco product, within 30 days before Visit 3 (Day 1);

20) Participation in more than two ALCS studies within 12 months before Visit 3 (Day 1);

21) Already enrolled or failed screening for the current study at a different study site;

22) Subject or a first-degree relative (i.e., parent, spouse, sibling, or child) is a current or former employee of the tobacco industry or a named party or class representative in litigation with any tobacco company.

4.3 Restrictions

- No participation in other studies or blood donations (other than for this study) or plasma while taking part in this study.
- Subjects will be instructed not to use any tobacco or nicotine-containing products other than manufactured cigarettes and/or test e-Vapor product (according to their group assignment) (e.g., roll-your-own cigarettes, e-cigarette or e-Vapor products, Bidis, snuff, nicotine inhaler, pipe, cigar, chewing tobacco, nicotine patch, nicotine spray, nicotine lozenge, or nicotine gum) following randomization.
- Medications with therapeutic effect on HDL-C, or medications for for depression, asthma or diabetes, are not allowed during the study.

4.4 Concomitant Medications

Any concomitant medications taken from 30 days prior to Screening, Visit 1 through the End of Study (or upon Early Termination) will be recorded.

Stable doses (i.e., no dosage adjustments within 3 months prior to Screen, Visit 1) of prescription or over-the-counter medications required to treat an Investigator-approved disease or condition (e.g., hypertension) are permitted at the discretion of the Investigator. Hormonal contraceptives (e.g., oral, transdermal patch, implant, injection) and hormonal replacement therapy are permitted. Occasional use of over-the-counter analgesics (e.g., acetaminophen, ibuprofen), antihistamines, and nasal decongestants are permitted. Exceptions may be permitted at the discretion of the Investigator in consultation with the Sponsor or designee, providing the medication in question would have no impact on the study. Any exceptions will be documented.

5.0 TEST PRODUCTS

5.1 Test e-Vapor Products

- Product XLCB = Test EVP (currently marketed by Nu Mark LLC as MarkTen® XL Bold Classic [4.0% NBW]) [CVR2.6.8] Formula: 10381-44-B; Name: “Rosetta”; Label: B44
- Product XLMB = Test EVP (currently marketed by Nu Mark LLC as MarkTen® XL Bold Menthol [4.0% NBW]) [CVR2.6.8] Formula: 10381-40-E; Name: “Spencer”; Label: 40E

The test e-Vapor products are identified as Product XLCB for the Rosetta (Bold Classic) flavor and Product XLMB for the Spencer (Bold Menthol) flavor in this study. Each test e-Vapor product consists of a battery and a cartridge. Each cartridge contains approximately 32 mg solution consisting of propylene glycol, glycerol, flavors, and 4.0% USP grade tobacco-derived nicotine by weight. Once the battery is close to being fully discharged, the LED will blink indicating that the battery needs to be recharged. When a cartridge is almost empty there is a noticeable reduction in vapor and flavor.

5.2 Study Material Accountability

5.2.1 Test e-Vapor Products

The test e-Vapor products will be provided and shipped by the Sponsor or designee to each of the study sites. The staff at each study site will coordinate shipping of all test e-Vapor products from the Sponsor or designee. The staff will document the date each shipment was received in the inventory records.

All test e-Vapor products will be stored in a locked, limited-access area in the study site. The test e-Vapor products will be kept at controlled room temperature (defined as 20˚-25˚C [68˚ - 77˚F], with excursions permitted to 15˚C - 30˚C [59˚ - 86˚F] for up to 15 minutes).

The study site will document and reconcile the total number of test e-Vapor products shipped to the study site, the total number of test e-Vapor products dispensed, the total number of used test e-Vapor products collected during the study, and the total number of unused test e-Vapor products remaining at the end of the study.

It is the responsibility of the Investigator to ensure that a current record of test e-Vapor product accountability is maintained at each study site where test e-Vapor product is inventoried and dispensed. Records or logs must include:

- Number received/placed in storage area
- Date dispensed
- Amount dispensed to and returned by each subject, including unique subject identifiers

- Amount re-dispensed to each subject, including unique subject identifiers
- Number dispensed but not returned (e.g., lost by subject)
- Amount returned to Sponsor

Individual test e-Vapor product dispensing records will be maintained by the study site for each subject. Test e-Vapor products will be prepared for use by the study site according to the Study Procedures Manual.

Upon completion or termination of the study, all used and unused test e-Vapor products will be reconciled at the study site. The test products will then be returned to ALCS or designee (return address and instruction will be provided separately). Twenty-four cartridges (one box) of each lot of flavored test e-Vapor product will be retained by each study site until final Clinical Study Report is issued (even if within 1 month of product expiration).

All test e-Vapor products returned to ALCS or designee must be accompanied by the appropriate documentation and be clearly identified by protocol number and study site number on outermost shipping container. If test product is returned and never dispensed to subjects, the supply should be in the original packaging.

5.3 Study Material Dispensing

5.3.1 Test e-Vapor Products

Prior to dispensing, the study site will ensure that the test e-Vapor product packaging is labelled to disclose, at minimum, the protocol number and unique subject identifiers, date it was dispensed, the statements of “For study use only, not for sale” and “Keep out of reach of children”.

Subjects should be reminded at Visit 3/Day 1, Visit 4/Week 3, Visit 5/Week 6, and Visit 6/Week 9, when test e-Vapor products are distributed, to keep test e-Vapor products out of the reach of children and that they must keep all used and unused cartridges from the time of dispensing until the next visit and bring them to the study site at the following visit.

When handling or dispensing test e-Vapor products, study site personnel will be instructed to wear gloves.

5.3.2 Conventional Cigarettes

Subjects randomized to the Control group will need to supply their own conventional cigarettes, at their own cost, for the duration of the study.

The conventional cigarette brand for each subject (Test and Control groups) will be documented by photocopy of the package at Screen Visit 1. Photocopies are required at the visits after Visit 1 only if the subject's regular cigarette has changed. There will be no restrictions on cigarette brand at any time during the study.

6.0 VISIT 1, SCREENING PART 1 (DAY -28 TO DAY -7)

6.1 Age Verification and Photocopy of ID

Each subject must show proof of age with government-issued ID (e.g., driver's license) which will be photocopied as source documentation.

6.2 Informed Consent

All prospective subjects will have the study explained by the Investigator or his/her designee.

All prospective subjects will be required to read, sign, and date the study informed consent form (ICF) prior to any screening/study procedures being performed. Written acknowledgment of the receipt of the full informed consent and the subject's freely tendered offer to participate will be obtained from each subject in the study and documented in the source documents. Each subject will receive a signed and dated copy of his/her ICF.

6.3 Medical History

Medical history will be recorded for each subject.

6.4 Demographics and Tobacco Use History Questionnaires

Subjects will fill out the Demographics and Tobacco Use History Questionnaires (APPENDECES

Appendix 1).

6.5 Review Inclusion / Exclusion Criteria

The study site staff will confirm that the inclusion and exclusion criteria have been met. Subjects who do not meet the inclusion/exclusion criteria will be considered screen failures; data to be captured will include subject demographics and the reason(s) for screen failure.

6.6 Vital Signs

Respiratory rate, pulse rate, blood pressure, and oral temperature in the sitting position after at least 5 minutes of rest and at least 15 minutes after the last conventional cigarette smoked.

6.7 Body Weight, Height, and Body Mass Index

Height (meters) and weight (kg) will be measured in indoor clothing without shoes. BMI will be calculated as weight (kg)/height (meters) squared (kg/m^2).

6.8 Smoking Cessation Information

The Investigator or designee will advise all subjects that to reduce the health effects of smoking and smokeless tobacco products, the best thing to do is to quit. The Investigator or designee also will offer all participants the Quit Assist™ brochure or referral to the Quit Assist™ web site, which contains citations to a number of third-party information sources, including web sites, telephone resources, and other organizations with additional information.

6.9 Clinical Laboratory Tests

All clinical laboratory tests will be conducted by a central laboratory facility accredited by the Centers for Medicare and Medicaid Services (Clinical Laboratory Improvement Amendments of 1988 [CLIA-88]) or at the clinic 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.

6.9.1 Urine Drug Screen and Alcohol Breath Test

Following completion of the ICF, a urine drug screen consisting of, at minimum, amphetamines, opiates, cannabinoids, and cocaine, and an alcohol breath test will be completed. Subjects who test positive for alcohol and/or drugs will be considered screen failures and will not complete the remaining screening assessments at this visit (with the exception of the Demographics and Tobacco Use History questionnaire).

6.9.2 Clinical Chemistry

Clinical chemistry will be performed, after at least 8 hrs fasting, consisting of sodium, potassium, chloride, bicarbonate, ALT, AST, blood urea nitrogen (BUN), alkaline phosphatase, total bilirubin, glucose, creatinine (at screening, creatinine clearance will be calculated using Cockcroft-Gault formula), total protein, uric acid, and albumin.

6.9.3 Hematology

Hematology will be performed, after at least 8 hrs fasting, consisting of hemoglobin, hematocrit, red blood cell count (RBC), white blood cell count (WBC) with differential, and platelet count.

6.9.4 Urinalysis

Routine clinical urinalysis consisting of bilirubin, blood, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, and urobilinogen will be evaluated. Microscopic examination will be conducted if protein, leukocyte esterase, nitrite and/or blood are detected. Microscopic analysis will include RBC, WBC, casts, and bacteria.

6.9.5 HIV, HbsAg, and HCV Serology

A serum test for HIV, HbsAg, and HCV will also be performed.

6.9.6 Urine Cotinine Screen

Study sites will perform a urine screen for cotinine.

6.9.7 Serum Pregnancy Test (Females)

Serum pregnancy test will be performed for **all** female subjects.

6.10 Review of Concomitant Medications

Any concomitant medications taken from 30 days prior to Screening Part 1, Visit 1 will be recorded.

6.11 Review of Tobacco and Nicotine Restrictions

Subjects will be given instructions regarding permissible tobacco and nicotine containing products for this study and the study site staff will advise the subjects of the importance of compliance with study instructions.

7.0 VISIT 2, SCEENING PART 2 (AFTER ASSESSMENT OF SCREENING PART 1 AND ON OR BEFORE DAY -5)

7.1 Review Inclusion / Exclusion Criteria

Brief written assessment (medical/medication questionnaire) to affirm that the inclusion and exclusion criteria/restrictions have not been violated since Screening Visit 1. Subjects who do not meet the inclusion/exclusion criteria will be considered screen failures; data to be captured will include subject demographics and reason(s) for screen failure.

7.2 Vital Signs

Respiratory rate, pulse rate, blood pressure, and oral temperature in the sitting position after at least 5 minutes of rest and at least 15 minutes after the last cigarette smoked or nicotine-containing product used.

7.3 Physical Examination

General physical exam including observations and questioning by the Investigator or his/her qualified designee.

7.4 12-Lead ECG

A 12-lead ECG will be completed after at least 5 minutes in the supine position.

7.5 Urine Pregnancy Test

Female subjects will complete a urine pregnancy test and only those who have a negative test result will continue to be eligible.

7.6 Spirometry

All subjects will undergo spirometry tests (FEV1, FVC, and FEV1/FVC ratio) at the study site. Spirometry measurements will be conducted in accordance with the 2005 American Thoracic Society / European Respiratory Society Joint Task Force on the standardization of spirometry. The spirometry tests will be performed on a study specific spirometer provided by a central vendor. The spirometry predicted values will be standardized by the Third National Health and Nutrition Examination Survey predicted set. Study site staff performing spirometry tests must receive appropriate training by the central vendor. The quality of the tests will be reviewed by a centralized over-reader, however, the evaluation of the spirometry exclusion criteria for all subjects will be the responsibility of the Investigator. The spirometry tests should be performed at least one hour from the last cigarette smoked or last e-Vapor product use and in sitting position. The subjects will be instructed on how to correctly perform spirometry tests prior to the measurements being recorded by appropriately trained study staff. 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 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. Spirometry results will be captured in the source document and eCRF.

7.7 Review of Concomitant Medications

Subjects will be asked about any medications they are taking and the results will be documented.

7.8 Confirm Cigarette Brand / Photocopy Cigarette Pack

The study site staff will record the subject's brand name of conventional cigarettes in the subject source document and a color photocopy of the pack will be made.

7.9 Review of Tobacco and Nicotine Restrictions

Subjects will be asked about any tobacco or nicotine containing products they are using and the results will be documented. If non-permissible tobacco or nicotine containing products have been used, the study site staff will remind the subjects of the importance of compliance with study instructions.

7.10 Test e-Vapor product trial

Subjects will use both the Rosetta (Bold Classic) and Spencer (Bold Menthol) test e-Vapor products (for approximately 15 minutes each with approximately 30 minutes in between each test e-Vapor product use), following an assigned sequence in an open label fashion (i.e., subjects will be informed of the flavors of the product that he/she is using). Study personnel will alternate between administering each subject with the Rosetta (Bold Classic) or Spencer (Bold Menthol) flavor first (e.g., Subject 1: Spencer (Bold Menthol) – Rosetta (Bold Classic), Subject 2: Rosetta (Bold Classic) – Spencer (Bold Menthol), Subject 3: Spencer (Bold Menthol) – Rosetta (Bold Classic), etc).

7.11 Test e-Vapor Product Assessment Questionnaire

Subjects will fill out a Product Assessment Questionnaire (Appendix 4) on both of the test e-Vapor products following completion of product trial (Section 7.10).

Subjects that pass all other eligibility requirements and indicate they would "definitely" or "probably" be willing and able to replace their cigarettes with a test e-Vapor product for the duration of the study will be eligible for enrollment.

7.12 Review of Adverse Events

All AEs occurring from the time of the test e-Vapor product trial until the End of Study (or upon Early Termination) must be recorded in the eCRF. Events that occur after informed consent signing and before the test e-Vapor product trial will be recorded in the eCRF and considered baseline signs and symptoms.

7.13 Subject Instructions for Product Use

Subjects will be instructed to continue to smoke their reported average CPD until returning to the study site for Visit 3.

7.14 Dispense First Urine Void Collection Containers

Study site personnel will dispense first void of the day urine collection containers to all qualifying subjects at Visits 2, 4, and 6, and instruct subjects on collection, storage, and returning the sample at the subsequent visit; subjects will be instructed that urine collection should occur at least 4 hours after the prior void. Subjects who misplace their collection materials will be required to return to the clinic for additional supplies prior to the collection days.

7.15 Reminder Calls

Study site personnel should make a phone call within 24 – 72 hours to subjects prior to their Visits to remind them the date and time of the visits (Visits 3 – 7), and collecting and bringing the first void of day urine samples to study site and fasting for at least 8 hours prior to the study visit (Visits 3, 5 and 7). Subjects should be reminded to maintain their usual smoking/vaping behavior during the morning of the study visits; abstinence is not required.

8.0 VISIT 3, BASELINE, RANDOMIZATION (DAY 1)

Visit 3 should be arranged in the morning to accommodate fasting blood sampling. Subjects should be reminded to maintain their usual smoking behavior during the morning of the study visit; abstinence is not required.

8.1 Review of Inclusion / Exclusion Criteria

A brief assessment (medical/medication questionnaire) to affirm that the applicable inclusion and exclusion criteria/restrictions have not been violated since the Screening Visits will be performed. Subjects who do not meet the inclusion/exclusion criteria required at Visit 3 (Day 1) will be considered screen failures; data to be captured will include subject demographics and reason(s) for screen failure.

8.2 Vital Signs

Respiratory rate, pulse rate, blood pressure, and oral temperature in the sitting position after at least 5 minutes of rest and at least 15 minutes after the last cigarette smoked or nicotine-containing product used.

8.3 Body Weight and Body Mass Index

Weight (kg) recorded in indoor clothing without shoes. BMI will be calculated as weight (kg)/height (meters) squared (height from Screening, Visit 1 will be used to calculate BMI).

8.4 Physical Examination (Symptom Driven)

A brief, symptom-driven physical exam will be conducted on all subjects.

8.5 Urine Pregnancy Test

Female subjects will complete a urine pregnancy test and only those who have a negative test result will continue to be eligible.

8.6 Review of Concomitant Medications

The study site staff will document any concomitant medications taken by subjects.

8.7 Review of Tobacco and Nicotine Restrictions

Subjects will be asked about any tobacco / nicotine containing products they are using and the results will be documented. If non-permissible tobacco or nicotine containing products have been

used, the study site staff will remind the subjects of the importance of compliance with study instructions.

8.8 Review of Adverse Events

All AEs occurring during this clinical trial after the subject has signed the ICF and completed the test e-Vapor product trial must be recorded in the eCRF.

8.9 Confirm Cigarette Brand / Photocopy Cigarette Pack

The study site staff will confirm the previously reported subject's brand name of conventional cigarettes in the subject source and a new color photocopy of the pack will be made, if applicable.

8.10 QGEN and TQOLIT questionnaires (before product use – Day 1 only)

Subjects will complete the QGEN and TQOLIT questionnaires (Appendix 2).

8.11 Cough Questionnaire (before product use – Day 1 only)

Subjects will complete the Cough Questionnaire (Appendix 3).

8.12 mCEQ Questionnaire

Subjects will complete the appropriate mCEQ Questionnaire (Appendix 5b).

8.13 Subject Randomization

Prior to product use, subjects will be randomized (stratified by BMI, gender, and age) into one of the following randomization groups (n=450):

- Test 1 Group (n=150): Exclusive ad libitum use of test e-Vapor product (Product XLCB), for the entire 12 weeks

- Test 2 Group (n=150): Exclusive ad libitum use of test e-Vapor product (Product XLMB), for the entire 12 weeks

- Control Group (n=150): Continue to smoke ad libitum subject's own brand lit-end conventional cigarettes, without use of any other type of tobacco/nicotine containing product, for the entire 12 weeks

For subjects who elect to drop out of the study due to the Group into which they were randomized, the study sites will record the reason for drop out; such subjects will be replaced.

8.14 Test e-Vapor Product Dispensation

Subjects randomized to the Test group will be given enough of their assigned Test e-Vapor Product to last until they return to the study site at Visit 4. This will consist of 3 batteries, 3 battery chargers and a 3-week supply of cartridges (66 cartridges assuming **3 per day**). Subjects should be instructed to contact the study site to make arrangements to pick up additional supplies if it looks like they will run out prior to the next scheduled visit. All test e-Vapor product dispensed and returned must be documented by the study site.

Prior to dispensing, the study site will ensure the test e-Vapor product packaging is labelled to disclose, at minimum, the protocol number and unique subject identifiers, date it was dispensed, the statements of "For study use only, not for sale" and "Keep out of reach of children".

Subjects will be asked to bring back all used and unused products (cartridges) at each subsequent study visit. Study sites will perform accountability on the returned product.

Only unused cartridges with the seal intact and at least 1 month to the expiration date should be dispensed to the subject.

During product dispensing, subjects will be reminded to keep the product out of reach of children.

The subjects will be instructed to store the cartridges in a cool and dry place preferably between 15 and 25^{o}C (59 – 77 ^{o}F) and not to leave the product(s) in extreme conditions (e.g. in a car parked in the heat/cold, freezer, etc.).

8.15 Subject Instructions for Product Use

Subjects in the Control group will be instructed to continue to smoke their cigarette of choice, ad libitum, for the entire 12 week study duration. Subjects in the Test group will be instructed to use only the assigned test e-Vapor product for the study duration. Subjects in the Test group will be allowed 7 days to completely switch to using the test e-Vapor product without any further cigarette consumption for the remainder of the study duration.

8.16 SMS System Training for Reporting At-Home Product Use

Subjects will be instructed on use of the SMS system for reporting the number of cigarettes or test e-Vapor products used each day. Product use reporting will begin on Day 1.

8.17 Exhaled CO Measurement

Exhaled CO (eCO) measurements will be performed by the clinic staff using the Micro+ basic™ Smokerlyzer® monitor (coVita). Study site staff performing eCO tests must receive appropriate training. The subjects will be instructed on how to correctly perform the tests prior to the measurements being recorded by appropriately trained study staff.

8.18 BOE and BOPH Urine Sample Collection (before dispensing study product)

First Urine Void for BOEs and BOPHs

On the morning of Visit 3, subjects will collect their first urine void of the day, between 4:00am and 7:00am, and at least 4 hours after the prior void, in the dispensed container as instructed and bring it with them to the study site. Sample should be kept refrigerated until packed for transport to the study site. An ice pack should be placed in the package with the urine sample at the same time. Upon receipt, study staff should document the volume (mL) of the urine sample, status of the ice pack (present – not/or partially melted; present – fully melted; not present).

Blood Collection for BOPH and COHb

Blood will be collected after overnight fasting (at least 8 hrs).

9.0 VISIT 4 (WEEK 3 / DAY 21 ± 3)

Subjects should be reminded to maintain their usual smoking/vaping behavior during the day of the study visit; abstinence is not required.

9.1 Review of Inclusion / Exclusion Criteria

A brief assessment (medical/medication questionnaire) to affirm that the applicable inclusion and exclusion criteria/restrictions have not been violated since the Screening Visits will be performed.

9.2 Vital Signs

Respiratory rate, pulse rate, blood pressure, and oral temperature in the sitting position after at least 5 minutes of rest and at least 15 minutes after the last cigarette smoked or nicotine-containing product used.

9.3 Urine Pregnancy Test

Female subjects will complete a urine pregnancy test and only those who have a negative test result will continue to be eligible.

9.4 Review of Concomitant Medications

The study site staff will document any concomitant medications taken by subjects.

9.5 Review of Tobacco and Nicotine Restrictions

Subjects will be asked about any tobacco / nicotine containing products they are using and the results will be documented. If non-permissible tobacco or nicotine containing products have been used, the study site staff will remind the subjects of the importance of compliance with study instructions.

9.6 Review of Adverse Events

All AEs occurring during this clinical trial after the subject has signed the ICF and completed the test e-Vapor product trial must be recorded in the eCRF.

9.7 Confirm Regular Cigarette Brand / Photocopy Cigarette Pack

The study site staff will confirm that the subject's regular brand of cigarettes (Control group) has not changed. If the regular brand has changed, the change will be documented and a photocopy of the pack made.

9.8 Test e-Vapor Product Collection

The study site staff will collect and document all used and unused products (cartridges). The study site will perform accountability on the returned product.

9.9 Test e-Vapor Product Dispensation

Subjects randomized to the Test group will be given enough of their assigned test e-Vapor product to last until they return to the study site at Visit 5 based on previous use (estimated to be approximately 3 batteries, 3 battery chargers and 66 cartridges assuming **3 per day**). Subjects should be instructed to contact the study site to make arrangements to pick up additional supplies if it looks like they will run out of supplies prior to the next scheduled visit. All test e-Vapor product dispensed and returned must be documented by the study site.

Prior to dispensing, the study site will ensure the test e-Vapor product packaging is labelled to disclose, at minimum, the protocol number and unique subject identifiers, date it was dispensed, the statements of "For study use only, not for sale" and "Keep out of reach of children".

Subjects will be asked to bring back all used and unused products (cartridges) at each subsequent study visit. Study sites will perform accountability on the returned product.

Unused cartridges may be re-dispensed to the same subject. Only unused cartridges with the seal intact and at least 1 month to the expiration date should be dispensed to the subject.

During product dispensing, subjects will be reminded to keep the product out of reach of children.

The subjects will be instructed to store the cartridges in a cool and dry place preferably between 15 and 25°C (59 – 77 °F) and not to leave the product(s) in extreme conditions (e.g. in a car parked in the heat/cold, freezer, etc.).

9.10 Exhaled CO Measurement

Exhaled CO measurements will be performed by the clinic staff. Subjects in the Control and Test groups are expected to have exhaled CO measurements consistent with recent cigarette smoking or e-Vapor use, respectively. Subjects in the Test groups with exhaled CO measurements >5 ppm will be counseled on the importance of study compliance. Subjects in the Test groups with exhaled CO measurements >8 ppm will be recorded as non-compliant at the Visit.

9.11 SMS System Use

Subjects will be instructed to continue to record their daily cigarette or test e-Vapor product use via the SMS system. Compliance and the need for retraining may be performed as necessary.

9.12 Dispense First Urine Void Collection Containers

Study site personnel will dispense first void of the day urine collection containers to all subjects still qualifying for the study at Visit 4 for collecting the first void urine sample in the morning of Visit 5, and instruct subjects on collection, storage, and returning the sample at the subsequent visit; subjects will be instructed that urine collection should occur at least 4 hours after the prior void.

10.0 VISIT 5 (WEEK 6 / DAY 42 ± 3)

Visit 5 should be arranged in the morning to accommodate fasting blood sampling. Subjects should be reminded to maintain their usual smoking/vaping behavior during the morning of the study visit; abstinence is not required.

10.1 Review of Inclusion / Exclusion Criteria

A brief assessment (medical/medication questionnaire) to affirm that the applicable inclusion and exclusion criteria/restrictions have not been violated since the Screening Visits will be performed.

10.2 Vital Signs

Respiratory rate, pulse rate, blood pressure, and oral temperature in the sitting position after at least 5 minutes of rest and at least 15 minutes after the last cigarette smoked or nicotine-containing product used.

10.3 Urine Pregnancy Test

Female subjects will complete a urine pregnancy test and only those who have a negative test result will continue to be eligible.

10.4 Review of Concomitant Medications

The study site staff will document any concomitant medications taken by subjects.

10.5 Review of Tobacco and Nicotine Restrictions

Subjects will be asked about any tobacco / nicotine containing products they are using and the results will be documented. If non-permissible tobacco or nicotine containing products have been used, the study site staff will remind the subjects of the importance of compliance with study instructions.

10.6 Review of Adverse Events

All AEs occurring during this clinical trial after the subject has signed the ICF and completed the test e-Vapor product trial must be recorded in the eCRF.

10.7 Confirm Regular Cigarette Brand / Photocopy Cigarette Pack

The study site staff will confirm that the subject's regular brand of cigarettes (Control group) has not changed. If their regular brand has changed, the change will be documented and a photocopy of the pack made.

10.8 QGEN and TQOLIT questionnaires

Subjects will complete the QGEN and TQOLIT questionnaires (Appendix 2).

10.9 Cough Questionnaire

Subjects will complete the Cough Questionnaire (Appendix 3).

10.10 Test e-Vapor Product Collection

The study site staff will collect and document all used and unused products (cartridges) at each study visit. The study site will perform accountability on the returned product.

10.11 Test e-Vapor Product Dispensation

Subjects randomized to the Test group will be given enough of their assigned test e-Vapor product to last until they return to the study site at Visit 6 based on previous use (estimated to be approximately 3 batteries, 3 battery chargers and 66 cartridges assuming **3 per day**). Subjects should be instructed to contact the study site to make arrangements to pick up additional supplies if it looks like they will run out prior to the next scheduled visit. All test e-Vapor product dispensed and returned must be documented by the study site.

Prior to dispensing, the study site will ensure the test e-Vapor product packaging is labelled to disclose, at minimum, the protocol number and unique subject identifiers, date it was dispensed, the statements of "For study use only, not for sale" and "Keep out of reach of children".

Subjects will be asked to bring back all used and unused products (cartridges) at each subsequent study visit. Study sites will perform accountability on the returned product.

Unused cartridges may be re-dispensed to the same subject. Only unused cartridges with the seal intact and at least 1 month to the expiration date should be dispensed to the subject.

During product dispensing, subjects will be reminded to keep the product out of reach of children.

The subjects will be instructed to store the cartridges in a cool and dry place preferably between 15 and 25^{o}C (59 – 77 ^{o}F) and not to leave the product(s) in extreme conditions (e.g. in a car parked in the heat/cold, freezer, etc.).

10.12 Exhaled CO Measurement

Exhaled CO measurements will be performed by the clinic staff. Subjects in the Control and Test groups are expected to have exhaled CO measurements consistent with recent cigarette smoking or e-Vapor use, respectively. Subjects in the Test groups with exhaled CO measurements >5 ppm will be counseled on the importance of study compliance. Subjects in the Test groups with exhaled CO measurements >8 ppm will be recorded as non-compliant at the Visit.

10.13 SMS System Use

Subjects will continue to record their daily cigarette or test e-Vapor product use via the SMS system. Compliance and the need for retraining may be performed as necessary.

10.14 BOE and BOPH Urine Sample Collection

First Urine Void for BOEs and BOPHs

On the morning of Visit 5, subjects will collect their first urine void of the day, between 4:00am and 7:00am, at least 4 hours after the prior void, in the dispensed container and bring it with them to the study site. Sample should be kept refrigerated until packed for transport to the study site. An ice pack should be placed in the package with the urine sample at the same time. Upon receipt, study staff should document the volume (mL) of the urine sample, status of the ice pack (present – not/or partially melted; present – fully melted; not present).

10.15 BOPH and COHb Blood Sample Collection

Blood Collection for BOPH and COHb

Blood will be collected after overnight fasting (at least 8 hrs).

11.0 VISIT 6 (WEEK 9 / DAY 63 ± 3)

Subjects should be reminded to maintain their usual smoking/vaping behavior during the day of the study visit; abstinence is not required.

11.1 Review of Inclusion / Exclusion Criteria

A brief assessment (medical/medication questionnaire) to affirm that the applicable inclusion and exclusion criteria/restrictions have not been violated since the Screening Visits will be performed.

11.2 Vital Signs

Respiratory rate, pulse rate, blood pressure, and oral temperature in the sitting position after at least 5 minutes of rest and at least 15 minutes after the last cigarette smoked or nicotine-containing product used.

11.3 Urine Pregnancy Test

Female subjects will complete a urine pregnancy test and only those who have a negative test result will continue to be eligible.

11.4 Review of Concomitant Medications

The study site staff will document any concomitant medications taken by subjects.

11.5 Review of Tobacco and Nicotine Restrictions

Subjects will be asked about any tobacco / nicotine containing products they are using and the results will be documented. If non-permissible tobacco or nicotine containing products have been

used, the study site staff will remind the subjects of the importance of compliance with study instructions.

11.6 Review of Adverse Events

All AEs occurring during this clinical trial after the subject has signed the ICF and completed the test e-Vapor product trial must be recorded in the eCRF.

11.7 Confirm Regular Cigarette Brand / Photocopy Cigarette Pack

The study site staff will confirm that the subject's regular brand of cigarettes (Control group) has not changed. If the regular brand has changed, the change will be documented and a photocopy of the pack made.

11.8 Test e-Vapor Product Collection

The study site staff will collect and document all used and unused products (cartridges) at each study visit. The study site will perform accountability on the returned product.

11.9 Test e-Vapor Product Dispensation

Subjects randomized to the Test group will be given enough of their assigned test e-Vapor product to last until they return to the study site at Visit 7 based on previous use (estimated to be approximately 3 batteries, 3 battery chargers and 66 cartridges assuming **3 per day**). Subjects should be instructed to contact the study site to make arrangements to pick up additional supplies if it looks like they will run out of supplies prior to the next scheduled visit. All test e-Vapor product dispensed and returned must be documented by the study site.

Prior to dispensing, the study site will ensure the test e-Vapor product packaging is labelled to disclose, at minimum, the protocol number and unique subject identifiers, date it was dispensed, the statements of "For study use only, not for sale" and "Keep out of reach of children".

Subjects will be asked to bring back all used and unused products (cartridges) at each subsequent study visit. Study sites will perform accountability on the returned product.

Unused cartridges may be re-dispensed to the same subject. Only unused cartridges with the seal intact and at least 1 month to the expiration date should be dispensed to the subject.

During product dispensing, subjects will be reminded to keep the product out of reach of children.

The subjects will be instructed to store the cartridges in a cool and dry place preferably between 15 and 25^{o}C (59 – 77 ^{o}F) and not to leave the product(s) in extreme conditions (e.g. in a car parked in the heat/cold, freezer, etc.).

11.10 Exhaled CO Measurement

Exhaled CO measurements will be performed by the clinic staff. Subjects in the Control and Test groups are expected to have exhaled CO measurements consistent with recent cigarette smoking or e-Vapor use, respectively. Subjects in the Test groups with exhaled CO measurements >5 ppm will be counseled on the importance of study compliance. Subjects in the Test groups with exhaled CO measurements >8 ppm will be recorded as non-compliant at the Visit.

11.11 SMS System Use

Subjects will be instructed to continue to record their daily cigarette or test e-Vapor product use via the SMS system. Compliance and the need for retraining may be performed as necessary.

11.12 Dispense First Urine Void Collection Containers

Study site personnel will dispense first void of the day urine collection containers to all subjects still qualifying for the study at Visit 6 for collecting the first void urine sample in the morning of Visit 7, and instruct subjects on collection, storage, and returning the sample at the subsequent visit; subjects will be instructed that urine collection should occur at least 4 hours after the prior void.

12.0 VISIT 7, END OF STUDY (WEEK 12 / DAY 84 ± 3)

Visit 7 should be arranged in the morning to accommodate fasting blood sampling. Subjects should be reminded to maintain their usual smoking/vaping behavior during the morning of the study visit; abstinence is not required.

12.1 Review of Inclusion / Exclusion Criteria

A brief assessment (medical/medication questionnaire) to affirm that the applicable inclusion and exclusion criteria/restrictions have not been violated since the Screening Visits will be performed.

12.2 Vital Signs

Respiratory rate, pulse rate, blood pressure, and oral temperature in the sitting position after at least 5 minutes of rest and at least 15 minutes after the last cigarette smoked or nicotine-containing product used.

12.3 Body Weight and Body Mass Index

Weight (kg) will be recorded in indoor clothing without shoes. BMI will be calculated as weight (kg)/height (meters) squared (height measured at Screening will be used to calculate BMI).

12.4 Spirometry

All subjects will undergo spirometry tests (FEV1, FVC, and FEV1/FVC ratio) at the study site. Spirometry measurements will be conducted in accordance with the 2005 American Thoracic Society / European Respiratory Society Joint Task Force on the standardization of spirometry. The spirometry tests will be performed on a study specific spirometer provided by a central vendor. The spirometry predicted values will be standardized by the Third National Health and Nutrition Examination Survey predicted set. Study site staff performing spirometry tests must receive appropriate training by the central vendor. The quality of the tests will be reviewed by a centralized over-reader. The spirometry tests should be performed at least one hour from the last cigarette smoked or last e-Vapor product use and in sitting position. The subjects will be instructed on how to correctly perform spirometry tests prior to the measurements being recorded by appropriately trained study staff. 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 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. Spirometry results will be captured in the source document and eCRF.

12.5 Physical Examination (Symptom Driven)

A brief, symptom-driven physical exam will be conducted on all subjects.

12.6 Smoking Cessation Information

The Investigator or designee will advise all subjects that to reduce the health effects of smoking, the best thing to do is to quit. The Investigator or designee also will offer all participants the Quit Assist™ brochure or referral to the Quit Assist™ web site, which contains citations to a number of third-party information sources, including web sites, telephone resources, and other organizations with additional information.

12.7 Clinical Laboratory Tests

All clinical laboratory tests will be conducted by a central laboratory facility accredited by the Centers for Medicare and Medicaid Services (Clinical Laboratory Improvement Amendments of 1988 [CLIA-88]) or at the clinic study site using CLIA-waived kits or procedures. Values for the laboratory parameters are to be within the laboratory normal ranges or deemed not clinically significant in the opinion of the Investigator; clinically significant findings will be followed up as described for Adverse Events (Section 13.2).

12.7.1 Clinical Chemistry

Clinical chemistry will be performed, after at least 8 hrs fasting, consisting of sodium, potassium, chloride, bicarbonate, ALT, AST, blood urea nitrogen (BUN), alkaline phosphatase, total bilirubin, glucose, creatinine (at screening, creatinine clearance will be calculated using Cockcroft-Gault formula), total protein, uric acid, and albumin.

12.7.2 Hematology

Hematology will be performed, after at least 8 hrs fasting, consisting of hemoglobin, hematocrit, red blood cell count (RBC), white blood cell count (WBC) with differential, and platelet count.

12.7.3 Urinalysis

Routine clinical urinalysis consisting of bilirubin, blood, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, and urobilinogen will be evaluated. Microscopic examination will be conducted if protein, leukocyte esterase, nitrite and/or blood are detected. Microscopic analysis will include RBC, WBC, casts, and bacteria.

12.8 Urine Pregnancy Test

All female subjects will complete a urine pregnancy test.

12.9 Review of Concomitant Medications

Any concomitant medications taken through the End of Study (or upon Early Termination) will be recorded.

12.10 12-Lead ECG

A 12-lead ECG will be completed after at least 5 minutes in the supine position.

12.11 Review of Adverse Events

All AEs occurring during this clinical trial after the subject has signed the ICF and completed the test e-Vapor product trial must be recorded in the eCRF.

12.12 Confirm Cigarette Brand / Photocopy Cigarette Pack

The study site staff will confirm that the subject's regular brand of cigarettes (Control group) has not changed. If the regular brand has changed, the change will be documented and a photocopy of the pack made.

12.13 QGEN and TQOLIT questionnaires

Subjects will complete the QGEN and TQOLIT questionnaires (Appendix 2).

12.14 Cough Questionnaire

Subjects will complete the Cough Questionnaire (Appendix 3).

12.15 Test e-Vapor Product Collection

The study site staff will collect and document all used and unused products (cartridges) at each study visit. The study site will perform accountability on the returned product.

12.16 Exhaled CO Measurement

Exhaled CO measurements will be performed by the clinic staff.

12.17 SMS System Use

The day prior to the End of Study Visit will be the final product use entry.

12.18 BOE and BOPH Urine Sample Collection

First Urine Void for BOEs and BOPHs

On the morning of Visit 7, subjects will collect their first urine void of the day, between 4:00am and 7:00am, at least 4 hours after the prior void, in the dispensed container and bring it with them to the study site. Sample should be kept refrigerated until packed for transport to the study site. An ice pack should be placed in the package with the urine sample at the same time. Upon receipt, study staff should document the volume (mL) of the urine sample, status of the ice pack (present – not/or partially melted; present – fully melted; not present).

12.19 BOPH and COHb Blood Sample Collection

Blood Collection for BOPH and COHb

Blood will be collected after overnight fasting (at least 8 hrs).

12.20 Reasons of Use/Not-Use Test Product Questionnaire (Test group only)

Subjects will fill out the Reasons of Use/Not-Use Test Product Questionnaire (Appendix 6).

12.21 mCEQ Questionnaire

Subjects will complete the appropriate mCEQ Questionnaire (Appendix 5a for Test groups, 5b for the Control group).

12.22 End of Study Questionnaire

Subjects will fill out the End of Study Questionnaire Appendix 7a (Control group) and Appendix 7b (Test group)

13.0 ADVERSE EVENTS

The following is the definition for an **AE**:

> Any unfavorable or unintended sign (including an abnormal laboratory finding[a]), symptom, or disease[b] temporally associated with the use of a study products, **whether or not** related to the study products.(ICH Guidelines, references 17 and 18)
>
> [a] For this study, a laboratory AE is defined as an abnormal laboratory finding that is determined by the Investigator to be clinically significant for that subject.
>
> [b] 'Disease' includes a newly developed, worsened preexisting, recurring intermittent or intercurrent illness, injury, or condition.

All AEs occurring during this clinical trial after the subject has signed the ICF document and after trial product use during Screening must be recorded in the eCRF, including the date and time of onset and outcome of each event. Events captured between ICF signing and prior to trial product use during Screening will be documented as baseline signs and symptoms in the eCRF.

Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an AE. **Planned** surgery permitted by the clinical study protocol and the condition(s) leading to this surgery are not AEs.

No causal relationship with the study products or with the clinical study itself is implied by the use of the term "adverse event."

The Investigator will review each event and rate each reported sign or symptom on a 3-point severity scale. The following definitions for **rating severity** (ICH Guideline for Clinical Safety Data Management) will be used:

Mild: The AE is easily tolerated and does not interfere with daily activity.

Moderate: The AE interferes with daily activity, but the subject is still able to function.

Severe: The AE is incapacitating and requires medical intervention. Note: This is not the same as "serious," which is based on the outcome or action criteria usually associated with events that pose a threat to life or functioning.

Each AE will also be assessed by the Investigator for relationship to study product (causality) using the following grades of certainty [the strength of a causal association may be revised as more information becomes available]:

Not related: Clearly and definitely due to extraneous cause (e.g., disease, environment)

Unlikely:
a. Does not follow a probable temporal (i.e., time) sequence from use of study product.
b. Does not follow a known pattern of response to the study product.
c. Could plausibly have been produced by the subject's clinical state/underlying disease or other drugs or chemicals the subject received.
d. Does not reappear or worsen when the study product is re-administered.

Possible:
a. Follows a reasonable temporal (i.e., time) sequence from use of study product.
b. Follows a known pattern of response to the study product.
c. Could also have been produced by the subject's clinical state/concurrent disease or other drugs or chemicals the subject received.

Likely:
a. Follows a reasonable temporal (i.e., time) sequence from use of study product.
b. Follows a known pattern of response to the study product.
c. Could not readily have been produced by the subject's clinical state/concurrent disease or other drugs or chemicals.
d. Follows a clinically reasonable response on withdrawal (dechallenge), i.e., disappears or decreases when the study product is stopped or reduced.

e. Rechallenge information is **not** required to fulfill this definition.

Definitely: a. Follows a reasonable temporal (i.e., time) sequence from use of study product.

b. Follows a known pattern of response to the stduy product.

c. Cannot be explained by the subject's clinical state/concurrent disease or other drugs or chemicals.

d. Follows a clinically reasonable response on withdrawal (dechallenge), i.e., disappears or decreases when the study product is stopped or reduced.

e. Recurs with re-exposure to study product (rechallenge). NOTE: Re-exposure of the subject is NOT required, but the "certainly/definitely related" category may only be used when recurrence is observed.

13.1 Serious Adverse Events

The following is the definition for a serious adverse event (SAE):

> An SAE is any adverse study experience that results in any of the following outcomes:
>
> - death
> - a life-threatening adverse study experience[a]
> - in-patient hospitalization or prolongation of existing hospitalization
> - a persistent or significant disability/incapacity[b]
> - a congenital anomaly/birth defect (ICH Guideline for Good Clinical Practice[18]).
>
> [a] "Life-threatening" means that the subject was at immediate risk of death at the time of the SAE; it does not refer to a SAE that hypothetically might have caused death if it were more severe.
>
> [b] "Persistent or significant disability/incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.

Important medical events that may or may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. An example is allergic bronchospasm requiring intensive treatment in an emergency room or at home.

All SAEs, **whether or not** considered study product-related, must be reported by telephone to the Medical Monitor within 24 hours of the study site's learning of the SAE or, at the latest, on

the following workday. The Medical Monitor must inform ALCS within 24 hours of Medical Monitor's notification. The sponsor designated Medical Monitor to contact about this study is:

Dr. Kathy Smith
Drug Safety Solutions
Raleigh, NC 27613 USA
Phone: +1 (919) 844-5687
Fax: +1 (919) 844-6948
Email: ksmith@drugsafety.biz

Additionally, an SAE Report Form must be completed for all SAEs with as much information as is available and e-mailed or faxed within 24 hours of the event to Medical Monitor at email or phone. **The Investigator must also inform the IRB**, in compliance with GCP reporting guidelines, **and the study site monitor of an SAE, whether or not** considered study-related. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the study product. Information not available at the time of the initial report (e.g., end date, laboratory values) must be documented on a follow-up SAE form. SAEs will be reported for up to 48 hours following a subject's completion of the study and followed for 30 days from onset or to a final outcome. Final outcome may be classified as resolved, improved, unchanged, worse, fatal, or unknown (lost to follow-up).

13.2 Adverse Events / Serious Adverse Events Follow Up

AEs, including clinically significant laboratory abnormalities, will be followed for up to 7 days or to a final outcome, regardless of whether the subject is still participating in the study. SAEs will be followed for up to 30 days from onset or to a final outcome, regardless of whether the subject is still participating in the study. Final outcome may be classified as resolved, improved, unchanged, worse, fatal, or unknown (lost to follow-up). Where appropriate, medical tests and examinations will be performed to document the outcome of the AE. Appropriate supportive and/or definitive therapy will be administered as required.

13.3 Pregnancy

Pregnancy occurring in a female study subject before test e-Vapor product use at Screening, Visits 1 and 2, or at Baseline at Visit 3, will be documented as a screen fail. Pregnancy occurring after test e-Vapor product use in the study will be documented on a pregnancy form, as a protocol deviation, and reported in accordance with IRB guidance. Pregnancy itself is not a SAE.

Pregnancies occurring after test e-Vapor product use at Screening, Visit 2 must be reported by telephone to the sponsor designated Medical Monitor within 24 hours of the study site's learning of the pregnancy or, at the latest, on the following workday. The Medical Monitor must inform ALCS within 24 hours of Medical Monitor's notification. 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. The Investigator also will offer all participants the Quit Assist™ brochure or referral to the Quit Assist™ web site, which contains citations to a number of third-party information sources, including web sites, telephone resources and other organizations with additional information. Advice given will be documented in the subject's source document.

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

14.0 SUBJECT SCREEN FAILURES

Subjects may screen fail at Screening Visit 1, Part 1; Screening Visit 2, Part 2; and at Baseline, Visit 3. Subjects who screen fail at any point will be ineligible to continue with the study and will not be permitted to re-screen. Rechecks of borderline values are allowed at the Investigator's discretion. Screen fail data to be captured will include subject demographics and reason(s) for screen failure.

15.0 SUBJECT EARLY TERMINATION

Subjects will be advised that they are free to withdraw from the study at any time. The Investigator may remove a subject if s/he feels this action is in the best interest of the subject. At the discretion of the Investigator, and in consultation with the Sponsor, a subject may be removed for failure to adhere to the requirements of the protocol.

Following randomization on Day 1, if a subject terminates early from the study and has used test e-Vapor product provided by the Sponsor, all used and unused test products (cartridges) should be returned if assigned to the Test group, and all of the safety data normally required at the End of Study, Visit 7 (Week 12) should, if possible, be obtained. Subjects with AEs will be followed per Section 12.

Subjects who terminate early from the study, through their own choice to withdraw or at the discretion of the Investigator, will be considered dropouts and will not be replaced.

16.0 SUBJECT DISCONTINUATION

Subjects will be advised that they are free to not participate or withdraw from the study at any time and for any reason. The Investigator may remove a subject if s/he feels this action is in the best interest of the subject.

Investigators are urged to enroll only those eligible subjects who are likely to complete the entire study and who are willing to comply with the requirements of the protocol. Subjects are discontinued from the study for any reason (including study completion) cannot re-enter.

Subjects will be informed during the informed consent process that all biologic samples collected up to the point of withdrawal are intended for analysis but that they may notify the Investigator if they choose to withdraw consent for analysis of these samples prior to use.

Subject Discontinuation Criteria

Subject participation in this trial may be discontinued for any of the following reasons:

- withdrawal of informed consent;
- clinical AE, laboratory abnormality, or other medical condition (including pregnancy) that indicates to the Investigator that continued participation is not in the best interest of the subject;
- failure to meet Inclusion/Exclusion criteria;
- noncompliance with study procedures, e.g.;
    - failure to comply with daily CPD/cartridge recording requirements (>5 consecutive days without recording).
    - failure to appear within required window for study visits

- eCO > 8 ppm on consecutive visits (Test groups only)

- termination of the study by the Sponsor, US Food and Drug Administration (FDA), or other regulatory authorities; or

- lost to follow-up.

Protocol deviations 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. Subject compliance with study product use and reporting is a critical component of this study; however, given the duration and ambulatory nature of the study 100% compliance is an unrealistic expectation. During each study visit, the study site staff will stress the importance of compliance with the study requirements and honestly reporting product use. Subjects who regularly fail to complete the daily product use entries or who have eCO measurements inconsistent with use of the study product assigned may be identified by the Investigator as individuals whose noncompliance may jeopardize the integrity of the study data. Disqualification for noncompliance with product use may occur with consultation with the Sponsor.

Discontinuation Procedures

If premature withdrawal from the study occurs for any reason, the Investigator must determine the primary reason and record this information in the case report form (eCRF). Subjects withdrawing or dismissed by the Investigator after randomization will be instructed to return all used and unused test products (if assigned to one of the Test groups) and will undergo EOS safety procedures as feasible.

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

Subjects who are discontinued from the study for any reason after randomization will not be replaced.

17.0 CLINICAL LABORATORY SAMPLES

Values for the clinical laboratory parameters will be determined by a central laboratory facility accredited by the Centers for Medicare and Medicaid Services (CLIA-88). Hematology, clinical chemistry, and urinalysis will be analyzed using standard clinical laboratory procedures.

18.0 BIOANALYTICAL LABORATORY

Biomarkers (BOEs and BOPHs) as noted below will be analyzed using validated analytical methods, and if applicable, with appropriate quality controls according to the FDA Guidance for Industry: Bioanalytical Method Validation (May, 2001)[19] and in accordance with SOPs which are written to meet applicable portions of Good Laboratory Practice regulations (21 CFR Part 58)[18].

Full sample collection methods, processing, storage, and shipping instructions will be provided in the sample handling manual. An overview of sample requirements is as follows:

Urine markers:

Biomarker	**Number of Aliquots/Volume Required**	**Container Type**
Total NNAL / NNN	2 aliquots of 10 mL each	UV shielded HDPP
Creatinine	2 aliquots of 5 mL each	HDPP
8-epi-prostaglandin $F_{2\alpha}$	2 aliquots of 5 mL each	HDPP
11-Dehydrothromboxane B_2	2 aliquots of 5 mL each	HDPP
Nicotine equivalents	2 aliquots of 5 mL each	HDPP
Bio-banking	Remaining volume after	HDPE

	aliquots above have been taken	

All aliquots will be prepared within 120 minutes from the time that the subject presents the sample and then stored at -20 ± 10°C until shipped to Celerion for analysis.

Blood markers:

Biomarker	**Volume and Collection Tube**	**Comments**
COHb	4 ml sodium heparin	store refrigerated until shipped
sICAM	4 ml sodium heparin	centrifuge and freeze plasma at -20°C
WBC	4 ml EDTA	standard whole blood
HDL	3.5 ml SST	allow to clot for 30 minutes, centrifuge, and freeze serum at -20°C
Bio-banking	3.5 ml SST	allow to clot for 30 minutes, centrifuge, and freeze serum at -20°C

Approximately 85 mL of blood will be required for the planned assessments during the entire study. Details regarding the processing, storage, and shipping instructions for the bio-banking samples will be provided in the sample handling guidance document prepared by Celerion.

18.1 BOEs Urine (1st void of the day):

1) Total NNAL in urine with creatinine adjusted (ng/g Cr)

2) NNN in urine with creatinine adjusted (ng/g Cr)

3) Nicotine equivalents (mg/g Cr)

Samples of all BOE urine collections will be banked for potential future additional BOE and/or BOPH assessments

18.2 BOE Blood (after overnight fasting, at least 8 hrs):

1) COHb in whole blood (% sat)

18.3 BOPHs Urine (1st void of the day):

1) 8-epi-prostaglandin $F_{2\alpha}$ in urine with creatinine adjusted (ng/g Cr)

2) 11-Dehydrothromboxane B_2 with creatinine adjusted (ng/g Cr)

18.4 BOPHs Blood (after overnight fasting, at least 8 hrs):

1) WBC in whole blood ($10^3\mu$/L)

2) HDL-C in serum (mg/dL)

3) Soluble Intercellular Adhesion Molecule-1 (sICAM-1) in serum (ng/mL)

Samples of all BOPH blood collections will be banked for potential future BOPH and/or BOE assessments

18.5 Urine Creatinine (1st void of the day)

Urine Creatinine levels (mg/mL) will also be measured for each urine sample and used to adjust for all urinary biomarkers.

19.0 STATISTICAL METHODS

19.1 Statistical Analysis Plan

The contents of this section are the basis for the SAP of this study. The SAP may be revised during the study to accommodate potential amendments of the clinical study protocol that are needed to adapt to unexpected issues in study conduct and may affect the planned SAP.

19.2 Sample Size Estimation

The study is designed to detect a statistically significant difference in change from baseline to the end of the study in 5 out of the 7 primary biomarkers between the Test and the Control groups. Total NNAL, COHb, 11-Dehydrothromboxane B_2, 8-epi-prostaglandin $F_{2\alpha}$ WBC and HDL values from a previous PMUSA longitudinal study (Study #: EHCJLI/02/02)[21] for the Electronic Heating Cigarette Smoking System and S-ICAM values from another source (Scott DA et. al. 2000)[22] were used for sample size calculation. Assuming a two-sided test, 3.5 % Type I error rate (adjusted for multiplicity of detecting statistical significance in 5 out of the 7 biomarkers based on the Hailperion-Ruger approach), 80% power and a 2 to 1 ratio of the Test group over the Control group, a sample size of 240 subjects in the Test group and 120 in the Control group are needed. With a 15% dropout rate expected, a total of 450 subjects (300 in the Test and 150 in Control groups) are needed at the randomization. The statistical power for each primary biomarker is provided below.

Table 1. Approximate power for a preliminary sample size of test=120 and control=120 subjects

Biomarker	Cigarette Smoker (mean, SD)	Electrically Heated Cigarette Smoker or Quitter (mean, SD)	Power (%)
Total NNAL (ng/g Cr)[1]	484.51 (187.50)	86.90 (134.19)	>85
COHb ($AUC_{(7\text{-}23h)}$, % •hr)[2]	3.6 (18.1)	-70.7 (35.4)	>85
8-Epi (ng/g Cr)[3]	1320 (506.78)	1106.28 (456.74)	85
11-Dehydro (mg/g Cr)[1]	1264.00 (533.58)	1011.53 (385.33)	>85
WBC (X1,000/ul)[2]	-0.3 (1.3)	-1.1 (1.3)	>85
HDL (mg/dl)[2]	0 (7.0)	5.0 (10.0)	>85
S-ICAM (ng/ml)[4]	5 (66.0)	-66.1 (75.0)	>85

1. Week 13 value[21]
2. Change from baseline to Week 13[21]
3. Average value of Week 8 and Week 17 due to potential bioanalytical data issue for Week 13[20]
4. Scott D et. al. 2000[22].

19.3 Randomization

This is a multicenter clinical study and a central randomization will be used across the study sites. Randomization will be stratified by gender, age class and BMI classes:

	BMI <25	**BMI ≥25**	**BMI <25**	**BMI ≥25**
<45 years	Male	Male	Female	Female
≥45 years	Male	Male	Female	Female

Further details will be provided in the Statistical Analysis Plan.

19.4 Criteria for Evaluation

19.4.1 Primary Endpoints

The primary endpoints are the following biomarkers measured at Baseline (Day 1) and End of Study (Week 12):

- WBC in whole blood (10^3 µg/L)
- HDL-C in serum (mg/dL)
- 8-epi-prostaglandin $F_{2\alpha}$ in urine with creatinine adjusted (ng/g Cr)
- 11-dehydrothromboxane B_2 in urine with creatinine adjusted (ng/g Cr)
- Soluble Intercellular Adhesion Molecule – 1 (sICAM-1) in serum (ng/mL)
- Total NNAL in urine with creatinine adjusted (ng/g Cr)
- COHb in whole blood (% sat)

19.4.2 Secondary Endpoints

The secondary endpoints are:

1) Levels of selected biomarkers (same as the primary endpoints) and the following additional biomarkers measured at Baseline/Day 1 (Visit 3), Week 6 (Visit 5) and EOS (Visit 7):

   a) NNN in urine with creatinine adjusted (ng/g Cr) and exhaled CO.

2) The average daily cigarettes smoked and Test Product use reported by subjects during Week 2 through Week 6 and for Week 7 through EOS

   a) Test Products used per day, the number of new cartridges used, and average number of puffs taken (1 – 20 or >20) will be document through text message.

   b) The number of cigarettes smoker per day will be documented by the subjects through the text message.

19.4.3 Exploratory Endpoints

1) Assess changes in BOPHs and BOEs (same as in the primary objective) from Baseline to Week 6 and EOS in two subgroups that use the two Test e-Vapor Products

2) FEV1 (% predicted), FCV, and FEV1/FVC measured at Screening (Visit 2) and EOS

3) Nicotine Equivalents (Nicotine, Cotinine, Trans-3'-Hydroxycotinine, Trans-3'-Hydroxycotinine-O-glucuronide, Nicotine-N-glucuronide, and Cotinine-N-glucuronide) (NE) in urine with creatinine adjustment (mg/g Cr), measured at Baseline/Day 1 (Visit 3), Week 6 (Visit 5) and EOS

4) Responses (Score) to the QGEN and TQOLIT questionnaires and the Cough Questionnaire recorded at Baseline/Day 1 (Visit 3), Week 6 (Visit 5) and EOS

5) Reponses to Reasons for Use and Not-use of Test Product at EOS and mCEQ questionnaires from Baseline to EOS (Test group only)

19.4.4 Clinical Safety Endpoints

Clinical safety analyses will be conducted on the clinical safety population. Clinical safety endpoints are:

- AEs and SAEs

- Blood pressure, ECG, vital signs, clinical chemistry, urinalysis, and hematology

19.5 Analyses Data Set

The intent to treat (ITT) population includes every subject who is randomized according to the randomization schedule.

The modified intent to treat (MITT) population includes those subjects in the ITT population for which there is a baseline and at least one post-baseline biomarker measure.

The clinical safety population (CSP) will consist of all subjects who are randomized and record at least one use of study products (i.e., conventional cigarettes or test e-Vapor products) after randomization.

The per-protocol (PP) population is defined as a subset of the MITT population, which is comprised of subjects who completed the study without any major protocol violations, which are defined as:

- Control group: subjects who quit smoking

- Test groups: subjects who self-report use of $\geq$ 10% of baseline CPD over the course of the study, subjects with an eCO > 8 ppm at Visits 4 – 7, or subjects whose NNN levels are consistent with smoking cigarettes

The ITT and PP populations will be used for the analyses of subject demographics, baseline characteristics and tobacco product use.

The MITT and PP populations will be used for the analyses of the primary endpoint, secondary endpoints of biomarkers, and exploratory endpoints.

The CSP will be used for the analyses of AEs, vital signs, clinical laboratory findings and other study safety related variables.

Deviations from the approved SAP will be reported in the final study report.

19.5.1 Demographics and Baseline Characteristics

Demographic baseline characteristics collected at Screening will be summarized by study group with descriptive statistics (the number of non-missing values, the number of missing values mean, median, standard deviation [SD], minimum, maximum, 95% confidence interval) for continuous variables (e.g., BMI) and frequency counts for categorical variables (e.g., gender).

19.5.2 Endpoint Analyses

Descriptive statistics will be provided for all analysis variables by study group and visit. The number of subjects with non-missing data, number of subjects with missing data, mean, standard deviation, median, minimum and maximum will be provided for continuous variables, and counts and percentages for categorical variables

All statistical analyses will be performed with SAS® software version 9.3 or above.

19.5.2.1 Primary Endpoint Analyses

A linear mixed model for repeated measures (MMRM) analysis will be used for comparing each Test group to the Control group in the mean absolute change from Baseline to End of Study in each primary endpoint. In the model, study group, visit, and study group by visit interaction, gender, age class, race, and BMI class are the fixed effect factors. The baseline value of the response biomarker will be the fixed effect covariate and subject will be the random effect factor. The unstructured covariance structure will be used to model the covariance. The least-square mean difference, 95% confidence interval and p-value will be provided for the group difference. The analysis will be conducted on the MITT population.

To assess the robustness of the primary MMRM analysis to the possible violation of the missing at random (MAR) assumption, the pattern mixture model based on the non-future dependent missing value restriction will be applied. In addition, a supportive analysis based on the per-protocol (PP) population will also be conducted.

19.5.2.2 Secondary Endpoint Analyses

- The MMRM as used for the primary endpoints will be used to test the differences in the mean absolute change from Baseline to Week 6 for the selected biomarkers (WBCs, HDL-C,

COHb, total NNAL, 8-epi-prostaglandin $F_{2\alpha}$, 11-Dehydrothromboxane B_2 and sICAM-1) between each Test group and the Control group.

- Descriptive statistics (the number of subjects with non-missing data, number of subjects with missing data, mean, standard deviation, median, minimum and maximum) will be used to summarize the average cigarettes per day and daily e-Vapor cartridge consumption amount by group from Week 2 through Week 6 and from Week 7 through EOS. Frequency tables will also be used to summarize the proportions of change categories (reduce, no change, increase or percentage) from baseline to end of study for each study group.

- A frequency table (n and %) will be used to summarize use of other tobacco products, eCO and NNN for assessment of compliance and noncompliance for each study group

19.5.2.3 Exploratory Endpoints Analyses

The MMRM approach will be used to provide the estimates for:

- changes in BOPHs and BOEs from Baseline to Week 6 and EOS in two subgroups that use different flavored e-Vapor products
- changes in forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC ratios from Baseline to EOS in the Test and Control groups
- changes in urine nicotine equivalents (NE) from Baseline to Week 6 and EOS **within** each test group and **between** the Test and Control groups
- changes in the QGEN and TQOLIT questionnaires and the Cough Questionnaire from Baseline to EOS in the Test and Control groups

19.6 Dealing with Missing Data

In general, missing data will remain as missing in data description, i.e., no attempt will be made to impute missing values and only observed values will be used in descriptive statistics. For the primary endpoint analyses, missing data will be handled using the MMRM. Likewise, for all other endpoints using the MMRM analysis, missing data will be handled by the model. For sensitivity analyses using ANCOVA models, missing data will be imputed using multiple imputation with pattern-mixture model. For secondary or exploratory analyses using the missing data will not be imputed. Details about missing data imputation for the primary endpoints will be provided in the statistical analysis plan.

19.7 Subgroup Analysis

A subgroup analysis will be conducted for change from Baseline to End of Study in the primary biomarkers for those covariates including gender, age class, race and BMI that proved to be significant in the MMRM model.

All subgroup analyses are exploratory in nature.

20.0 DATA MANAGEMENT

Every effort will be made to ensure that data management practices adhere to ethical and scientific quality standards of clinical data management procedures. The sponsor will contract with Celerion to manage the data for this investigation. Details about the data management activities will be specified in the Data Management Plan (DMP).

20.1 Database Design and Creation

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

20.2 Data Coding

Upon completion of the eCRF data entry by the study site, a secondary clinical review will be conducted by Celerion. Adverse events and medical history coding will be undertaken using MedDRA®. Concomitant medications coding will be undertaken using WHO-DD. Each dictionary version will remain the same throughout the trial.

20.3 Data Entry and Verification

Data will be entered directly or transmitted from other sources by the Investigator or Investigator's staff into the eCRF. Ancillary data received from clinical and analytical laboratories (clinical laboratory results) will be integrated into the Clinical Data Interchange Standards Consortium study data tabulation model datasets.

20.4 Study Results Data Transfer

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

20.5 Data Validation

After the data have been entered and verified, various edit checks will be performed to ensure the accuracy, integrity and validation of the database against the eCRF.

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

20.6 Database Lock

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

The final transfer of all study data (without subject personally identifying information) to the study sponsor will be in SAS format.

21.0 MONITORING THE STUDY

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

It will be the monitor or designee's responsibility to review the eCRFs to verify the adherence to the protocol and the completeness, consistency, and accuracy of the data being entered. The monitor will verify that each subject has consented in writing. Where the terms of the informed consent, GCP, and all other applicable state and federal laws permit, the monitor should have access to laboratory test reports and other subject records needed to verify the entries in the

eCRF. The Investigator (or his/her designee) agrees to co-operate with the monitor to ensure that any problems detected in the course of these reviews are resolved.

22.0 REPORTING FOR THE STUDY

22.1 Case Report Forms

Electronic CRFs will be used for each screened subject whether or not he/she has completed the study. All eCRFs will be reviewed and signed by the Investigator.

22.2 Study Report

A clinical study report will be written consistent with ICH guidelines and will include a description of the clinical conduct of the study, safety evaluation, analytical methods and results, and the statistical analysis described in the statistical methodology section of the protocol and the SAP.

The clinical study report will be audited against the SAS data and the raw data. At the completion of the audit, a QA report will be issued allowing any findings to be addressed.

23.0 GENERAL

23.1 Confidentiality

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

Celerion will not supply to the Sponsor any subject names, initials, date of birth (except year), or other personal identifiers.[23] 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. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed during the consenting process that representatives of the Sponsor, IRB, or regulatory authorities may inspect their medical records to verify the

information collected, and that all personal information made available for inspection will be handled in the strictest confidence and in accordance with local data protection laws.

23.2 Responsibility of the Investigator

The Investigator is responsible for ensuring that the clinical study is performed in accordance with the Declaration of Helsinki and in a manner consistent with the ICH Guideline for GCP and the corresponding section of the US CFR governing Protection of Human Subjects (Title 21 CFR Part 50)[15], and Institutional Review Boards (Title 21 CFR Part 56)[17].

The Investigator should ensure that all persons assisting with the study are qualified for the duties assigned, adequately informed and trained about the protocol and amendments to the protocol, the test e-Vapor products, and their study-related duties and functions.

The Investigator will maintain a list, including signatures, of sub-investigators and other appropriately qualified persons to whom significant study-related duties are delegated. Any personnel change in this list during the course of the study will be documented. All study related training will be documented.

23.3 Procedure for Amendments to Protocol

No deviations from this protocol will be permitted, except in a medical emergency, without the approval of the Sponsor. If agreement is reached concerning the need for modification, this agreement will be made in a formal amendment to the protocol.

All revisions and/or amendments to the protocol must be approved in writing by the IRB, if applicable.

All persons who are affected by the amendment to the protocol will be retrained if deemed necessary.

23.4 Institutional Review Board

Before study initiation and shipment of test e-Vapor product to a study site, the Investigator must have written and dated approval from the IRB for the protocol, ICF, subject recruitment materials/process (e.g., advertisements), and any other written information that will be provided

to subjects. The IRB approval should be obtained in writing, clearly identifying the trial, the documents reviewed, and the date of the review.

As applicable, amendments to the above stated documents must also be submitted and receive approval from the IRB prior to implementation at the study site. The IRB approval should be obtained in writing, clearly identifying the trial, the documents reviewed, and the date of the review.

The Investigator or Sponsor should also provide the IRB with a copy of other information according to regulatory requirements or Institution procedures.

23.5 Termination of Study

The Sponsor reserves the right to discontinue this study at any time. The Investigator, in collaboration with the Sponsor, reserves the right to discontinue the study for safety reasons at any time.

23.6 Study Records Retention

Investigator-specific essential documents and all primary data, or copies thereof (e.g., eCRFs, laboratory records, data sheets, correspondence, photographs, computer records, photocopied government-issued ID to verify subject age), which are a result of the original observations and activities of the study and are necessary for the reconstruction and evaluation of any study report will be retained in the investigative study site's archives for a **minimum** of 20 years after the completion or termination of the study. It is the responsibility of the Sponsor to inform the Investigator as to when these documents no longer need to be retained. The study report and final database will be retained in CRO NAME's archives for a **minimum** of 20 years after the completion or termination of the study and will be available for inspection at any time by the Sponsor. At completion of the study (i.e., at issuance of final study report), the final database will be transferred to the Sponsor. Subject names, initials, date of birth (except year), and other personal identifiers (including photocopied government issued ID) will be redacted from this data transfer file; any such information removed will be documented at the time of transfer.

24.0 REFERENCES

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Adult Smokers Switching From Conventional Cigarettes to a Second-Generation Electrically Heated Cigarette Smoking System. J Clin Pharmacol. 48: 580 -591.

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APPENDECES

Appendix 1: Demographics and Tobacco Use History Questionnaires

A01.1 Demographic Information

1. What is your date of birth?

   _____

2. What is your gender?

   ❍ Male
   ❍ Female

3. Are you Hispanic or Latino?

   ❍ Yes
   ❍ No

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

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

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

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

6. What is the highest grade or year of school you completed?

   ❍ Never attended school or only attended kindergarten
   ❍ Grades 1 through 8 (elementary)
   ❍ Grades 9 through 11 (some high school)
   ❍ Grade 12 or GED (high school graduate)
   ❍ College 1 year to 3 years (some college or technical school)
   ❍ College 4 years or more (college graduate)
   ❍ Postgraduate/masters/doctorate/law/MD
   ❍ Other

❍ I do not wish to answer

7. Are you currently…?

❍ Employed for wages
❍ Self-employed
❍ Out of work for more than 1 year
❍ Out of work for less than 1 year
❍ A homemaker
❍ A student
❍ Retired
❍ Unable to work
❍ I do not wish to answer

8. If you work outside of the home, what setting best describes your place of work…(Please check one)
❍ Office
❍ Manufacturing
❍ Food Service
❍ Transportation
❍ Construction
❍ Other

9. Have you ever served on active duty in the U.S. Armed Forces, military Reserves, or National Guard? Active duty does not include training in the Reserves or National Guard, but DOES include activation, for example, for the Persian Gulf War. **[Select only one answer]**

❍ Yes, now on active duty
❍ Yes, on active duty in the last 12 months but not now
❍ Yes, on active duty in the past, but not in the last 12 months
❍ No, not on active duty but training for Reserves or National Guard only
❍ No, never served in the military
❍ I do not wish to answer

10. What is your marital status?

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

11. Do you think of yourself as….?

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

A01.2 **Tobacco/Nicotine Use History**

1. How long have you smoked cigarettes on a CONSISTENT BASIS? By consistent basis we mean using cigarettes routinely or with some type of regularity. Examples might include using the product every day, a few times a week, only on the weekend, etc.

   If less than 12 months, indicate number of months _____

   If 12 months or more, indicate number of years _____

2. During the past 12 months did you smoke cigarettes every day, some days, rarely, or not at all?

   ❍ Every Day
   ❍ Some Days
   ❍ Rarely
   ❍ Not At All

3. During the past 12 months, how many cigarettes did you smoke per day, on average?

   Number of Cigarettes Per Day: _____**[Please provide a single number]**

4. How soon after you wake up do you smoke your first cigarette?

   ❍ Within 5 minutes
   ❍ 6 – 30 minutes
   ❍ 31 – 60 minutes
   ❍ After 60 minutes

5. During the PAST 12 MONTHS, have you stopped smoking for more than one day BECAUSE YOU WERE TRYING TO QUIT SMOKING?

   ❍ Yes
   ❍ No

6. Are you planning to quit smoking cigarettes in the next 30 days?

   ❍ Yes
   ❍ No

7. There are many different types of tobacco products. Please read the description on the left, and then indicate with check marks the tobacco products that (1) you have ever used, even once, and (2) now use every day, some days, rarely or not at all.

Tobacco Product	Check the box next to each tobacco product that you have **EVER** used, even once	Of the tobacco products that you have ever used, check whether you used the product in the past 30 days			
		Every day	Some days	Rarely	Not at all
ELECTRONIC CIGARETTES or E-VAPOR products ("e-cigarettes") An electronic cigarette (e-cigarette) is a battery-powered device that is puffed like a cigarette					
BIDIS OR KRETEKS Popular in other parts of the world. Bidis are small hand-rolled cigarettes. Kreteks are clove-flavored cigarettes. An example of a kretek brand is **DJARUM BLACK**					
PREMIUM CIGARS Come in different sizes and shapes. Some examples of premium cigar brands are **MACANUDO, ARTURO FUENTE AND ROMEO Y JULIETA.**					
LARGE CIGARS Not premium cigars; generally wider and longer than cigarillos. **PHILLIES** BLUNT cigars is an example of a large cigar brand.					
CIGARILLOS (INCLUDING BLACK & MILD) Generally narrower and shorter than premium cigars; they may come with plastic or wooden tips. **BLACK & MILD** is an example of a cigarillo brand. Other examples include **SWISHER SWEETS** and **DUTCH MASTERS**.					
LITTLE CIGARS Look similar to cigarettes, except they are brown and have a filter like a cigarette. Some examples of little filtered cigar brands are **WINCHESTER, CAPTAIN BLACK and WRANGLER.**					
CHEWING TOBACCO Coarsely shredded and sold in pocket-sized packs of loose tobacco leaves or in a "plug" or "twist" form. Brands include **RED MAN, LEVI GARRETT and BEECH-NUT**.					
SNUFF (DIP) Finely ground form of tobacco that is usually sold in a tin. Brands include **GRIZZLY, COPENHAGEN and SKOAL.**					
SNUS Spitless tobacco product that comes in small pouches and is usually sold in a tin. **CAMEL SNUS** is an example of a snus brand.					

Tobacco Product	Check the box next to each tobacco product that you have **EVER** used, even once	Of the tobacco products that you have ever used, check whether you used the product in the past 30 days			
		Every day	Some days	Rarely	Not at all
OTHER NEW ORAL TOBACCO OR TOBACCO-DERIVED NICOTINE PRODUCTS Meant to be chewed or dissolved in the mouth. Examples include **CAMEL ORBS, STRIPS, or STICKS; ARIVA or STONEWALL and VERVE DISCS.**					
HOOKAH Or "narghile" pipe, is a type of water pipe used to smoke tobacco.					
PIPE A regular smoking pipe has a bowl for tobacco, stem and mouthpiece.					

8. Have you used a nicotine patch, gum, inhaler, nasal spray or lozenge in the past 30 days?

   ❍ Yes
   ❍ No

QGEN & TQOLIT

This survey asks about your health. For each of the following questions, please mark the one box that best describes your answer.

1. **Overall, how would you rate your health?**

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. **How easy or hard is it for you to do your usual physical activities (such as walking or climbing stairs)?**

Very easy	Easy	Hard	Very hard	Unable to do
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. **In the past 4 weeks, how much did pain limit your everyday activities or your quality of life?**

Not at all	A little	Some	A lot	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4. **In the past 4 weeks, did your physical health make it easy or hard for you to make the effort you needed to do your daily activities (at work or at home)?**

Very easy	Easy	Hard	Very hard	Unable to do
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. **How often during the past 4 weeks were you discouraged by your health problems?**

Very often	Often	Sometimes	Rarely	Never
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. **In the past 4 weeks, has your health made it easy or hard for you to have a social life?**

Very easy	Easy	Hard	Very hard	Unable to do
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. **In the past 4 weeks, on average, did you feel tired or energetic most of the time?**

Tired, all of the time	Tired, most of the time	Both equally often	Energetic, most of the time	Energetic, all of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

8. **How happy and satisfied have you been with your life during the past 4 weeks?**

Extremely happy, could not have been more satisfied	Very happy, satisfied most of the time	Mixed, sometimes happy and sometimes unhappy	More often unhappy, dissatisfied	Very unhappy, dissatisfied most of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. **In the past 4 weeks, was it easy or hard to do your usual work, school or other daily activities because of how you felt emotionally?**

Very easy	Easy	Hard	Very hard	Unable to do
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. **In the past 4 weeks, did your health make it easy or hard for you to do your daily work or activities, both at home and away from home?**

Very easy	Easy	Hard	Very hard	Unable to do
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for answering these questions!

How easy or hard is it for you to:

	Very easy	Easy	Hard	Very hard	Unable to do
Walk more than a mile?	O	O	O	O	O
Run errands and shop?	O	O	O	O	O
Do your usual physical activities (such as walking or climbing stairs)?	O	O	O	O	O
Do strenuous activities (such as backpacking, skiing, playing tennis, bicycling or jogging)?	O	O	O	O	O

How TRUE or FALSE is each of the following for you?

	Definitely true	Mostly true	Not sure	Mostly false	Definitely false
I am very confident in my health	O	O	O	O	O
I am confident in having good health in the future	O	O	O	O	O
I have doubts about having good health in the future	O	O	O	O	O

How often do you have:

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
Bad breath?	O	O	O	O	O
Yellowing of teeth?	O	O	O	O	O
Cold hands and feet?	O	O	O	O	O
Loss of taste and smell?	O	O	O	O	O

How often do you have:

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
Nicotine-stained fingers and teeth?	O	O	O	O	O
Smoker's cough (loose cough that often produces phlegm)?	O	O	O	O	O
A hoarse voice?	O	O	O	O	O
Smell of smoke in clothes and hair?	O	O	O	O	O

In the past 4 weeks, how much did smoking limit your everyday activities or your quality of life?

Not at all	A little	Some	A lot	Extremely
O	O	O	O	O

In the past 4 weeks, how often:

	Never	Rarely	Sometimes	Often	Very often
Did smoking limit your usual physical activities?	O	O	O	O	O
Did you have difficulty doing work or other daily activities because of smoking?	O	O	O	O	O
Did smoking make you worn out or too tired to work or do daily activities?	O	O	O	O	O

In the past 4 weeks, how often:

	Never	Rarely	Sometimes	Often	Very often
Did smoking limit your usual social activities with family, friends, or others close to you?	O	O	O	O	O
Did you feel frustrated or fed up because of smoking?	O	O	O	O	O
Did smoking make you worry about your health or future health problems?	O	O	O	O	O

Appendix 3: Cough Questionnaire

I. Did you have a cough in the past 30 days?
   1. Yes – PROCEED TO QUESTION II.
   2. No – STOP. DO NOT ANSWER THE REST OF THE QUESTIONS.

II. How long have you had the cough? (provide a number)
   1. ____ Days
   2. ____ Weeks
   3. ____ Months
   4. ____ Years

III. When does the cough occur? (choose one)
   1. Middle of the night
   2. Daytime
   3. Anytime

IV. Do you have a cough that comes mainly from your chest and NOT from your throat
   1. Yes, cough mainly comes from my chest
   2. No

V. Do you cough up phlegm?
   1. Never
   2. Seldom
   3. Sometimes
   4. Often
   5. Always

VI. Do you cough more than the average person?
   1. Yes
   2. No

VII. Have you taken medications for your cough?
   1. Yes
   2. No

VIII. Have you sought the help of a health care provider to treat your cough?
   1. Yes
   2. No

IX. In the last 24-hours, has your cough disturbed your sleep?
   1. All of the time
   2. Most of the time
   3. A good bit of the time
   4. Some of the time
   5. A little of the time
   6. Hardly any of the time
   7. None of the time

X. In the last 24-hours, how many times have you had coughing bouts?

1. All the time (continuously)
2. Most times of during the day
3. Several times during the day
4. Some times during the day
5. Occasionally through the day
6. Rarely
7. None

Appendix 4: Test e-Vapor Product Assessment Questionnaire

Now that you have tried the e-Vapor products, how likely are you to be willing and able to use this product to **replace all** of your conventional cigarettes for **3 months** during the study? (CHECK ONE RESPONSE ONLY)

A. ____ Definitely
B. ____ Probably
C. ____ Might or might not
D. ____ Probably not
E. ____ Definitely not

Appendix 5a: mCEQ-E Questionnaire (Test groups only)

Please mark the number that best represents how using the test e-Vapor product made you feel (1—not at all, 2—very little, 3—a little, 4—moderately, 5—a lot, 6—quite a lot, 7—extremely).

---

1. Was using the test e-Vapor product satisfying? ____ (1….7)

2. Did the test e-Vapor product taste good? ____ (1….7)

3. Did you enjoy the sensations in your throat and chest? ____ (1….7)

4. Did using the test e-Vapor product calm you down? ____ (1….7)

5. Did using the test e-Vapor product make you feel more awake? ____ (1….7)

6. Did using the test e-Vapor product make you feel less irritable? ____ (1….7)

7. Did using the test e-Vapor product help you concentrate? ____ (1….7)

8. Did using the test e-Vapor product reduce your hunger for food? ____ (1….7)

9. Did using the test e-Vapor product make you dizzy? ____ (1….7)

10. Did using the test e-Vapor product make you nauseous? ____ (1….7)

11. Did using the test e-Vapor product immediately relieve your craving for a cigarette?

____ (1….7)

12. Did you enjoy using the test e-Vapor product? ____ (1….7)

Appendix 5b: mCEQ-C Questionnaire (Both Groups at Baseline, Control group only at EOS)

Please mark the number that best represents how using the test e-Vapor product made you feel (1—not at all, 2—very little, 3—a little, 4—moderately, 5—a lot, 6—quite a lot, 7—extremely).

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1. Is smoking cigarettes satisfying? ____ (1….7)

2. Does smoking cigarettes taste good? ____ (1….7)

3. Do you enjoy the sensations in your throat and chest? ____ (1….7)

4. Does smoking cigarettes calm you down? ____ (1….7)

5. Does smoking cigarettes make you feel more awake? ____ (1….7)

6. Does smoking cigarettes make you feel less irritable? ____ (1….7)

7. Does smoking cigarettes help you concentrate? ____ (1….7)

8. Does smoking cigarettes reduce your hunger for food? ____ (1….7)

9. Does smoking cigarettes make you dizzy? ____ (1….7)

10. Does smoking cigarettes make you nauseous? ____ (1….7)

11. Does smoking cigarettes immediately relieve your craving for a cigarette? ____ (1….7)

12. Do you enjoy smoking cigarettes? ____ (1….7)

Appendix 6: Reasons of Use/Not-Use Test Product Questionnaire (Test group only)

1. **How likely are you to use e-cigarettes exclusively in the next 30 days?**
   Strongly Likely Quite Likely Somewhat Likely Neutral/Neither
   Strongly Unlikely Quite Unlikely Somewhat Unlikely

2. **How likely would you be to use the test product exclusively in the next 30 days?**
   Strongly Likely Quite Likely Somewhat Likely Neutral/Neither
   Strongly Unlikely Quite Unlikely Somewhat Unlikely

3. **Why would you use the test product <u>NOW</u>? (CLICK ALL THAT APPLY)**

<u>Smoking/Other Tobacco-Related Reasons</u>

To satisfy my nicotine cravings ❍1
To help cut back or quit smoking/using other tobacco products ❍1
To help prevent relapse/return to smoking/using other tobacco products ❍1
To use in places where I cannot or should not smoke/use other tobacco products ❍1
To not smell like smoke ❍1
To not bother other people with smoke/smell of cigarettes/other tobacco products ❍1
It might be less harmful than cigarettes/other tobacco products ❍1
To reduce negative smoking related health symptoms ❍1
So I would not have to quit using tobacco products altogether ❍1
It might be less harmful for other people around me ❍1
More affordable than cigarettes/other tobacco products ❍1

<u>General Reasons</u>

Curiosity ❍1
Offered/given/used by a friend/family member ❍1
Enjoy the taste ❍1
Enjoy the effects ❍1
Advertising or promotion (e.g., magazine ad, in-store, coupon) ❍1
To meet other people or be part of a larger group ❍1
To suppress appetite for food ❍1
Other reason ❍1
Don't know (SP) ❍1

Appendix 7a: End of Study Questionnaire (Control group only)

The following questions are to help in the interpretation of this study and design of future studies, please be **completely honest.** Your answers will **not** affect your compensation or eligibility for future studies in any way.

1. When you collected your 1st void of the day urine collections, were you able to always collect the first void of the day at least 4 hours since the prior void?

   _____Yes
   _____No

2. Were you able to continue to smoke your average cigarettes per day every day over the past 3 months?

   _____Every day
   _____Most days
   _____Some days
   _____Rarely
   _____Not at all

3. Did you smoke more than your average cigarettes per day over the past 3 months?

   _____Every day
   _____Most days
   _____Some days
   _____Rarely
   _____Not at all

4. Did you smoke less than your average cigarettes per day over the past 3 months?

   _____Every day
   _____Most days
   _____Some days
   _____Rarely
   _____Not at all

5. Were there any days when you did not smoke at all?

   _____Yes: If yes, how many days _____ (please provide a single number)
   _____No

Appendix 7b: End of Study Questionnaire (Test groups only)

The following questions are to help in the interpretation of this study and design of future studies, please be **completely honest.** Your answers **will not** affect your compensation or eligibility for future studies in any way.

1. When you collected your 1st void of the day urine collections, were you able to always collect the first void of the day at least 4 hours after the prior void?

   _____Yes

_____No

2. Have you smoked cigarettes since you were instructed to **completely replace** your cigarettes with the test e-Vapor product?

_____Yes: If yes, on how many days? _____ (please provide a single number)

On the days that you smoked what was the average number of cigarettes?_____

_____No

3. Did you use the test e-Vapor product…

_____Every day
_____Most days
_____Some days
_____Rarely
_____Not at all