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 24 Weeks

NCT04800211

22MAR2017

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Altria Client Services Study No. ALCS-RA-17-11-EV
Final Protocol Date: 22 March, 2017

Sponsor:

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(Signature) (Date)

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27 MAR 2017
(Signature) (Date)

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 24 Weeks

Altria Client Services Study No. ALCS-RA-17-11-EV

Sponsor's Contact:

PROTOCOL SIGNATURE PAGE
Altria Client Services Study No. ALCS-RA-17-11-EV

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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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STUDY SYNOPSIS

ALCS Protocol Number:

ALCS-RA-17-11-EV

Abbreviated Protocol Title:

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

Long Protocol Title:

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 24 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

Study Duration:

The study participants in this extension study will continue to use the Test and Control Products, in the groups assigned, for an additional 12 weeks after completing the 12-week ALCS-RA-16-06-EV [CA20130] study, for a total of 24 weeks. The expected study duration from Screening (of the 12-week ALCS-RA-16-06-EV study) to End of Study for each individual subject is approximately 28 weeks.

Estimated Study Sites:

6-10 study sites

Study Objectives:

The Primary Objective is to:
Compare absolute changes in selected biomarkers[a] from Baseline[b] to Week 24 (EOS) between adult smokers who continue to smoke conventional cigarettes (Control group) ad libitum and adult smokers who have completely[c] switched to ad libitum use of the test

e-vapor products (Test groups) for 24 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] Baseline of the 12-week ALCS-RA-16-06-EV study (CA20130), Week 1, will be used.

[c] Subjects who exclusively use e-vapor products and have exhaled carbon monoxide (eCO) measurements ≤ 8 ppm from Week 3 (of the 12-week ALCS-RA-16-06-EV study) through Week 24 (EOS) and urine N-nitrosonornicotine (NNN) levels from Week 6 (of the 12-week ALCS-RA-16-06-EV study) through Week 24 (EOS) consistent with switching to an e-vapor product.

The Secondary Objectives are to:

- 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 of the 12-week ALCS-RA-16-06-EV study (CA20130) to Week 18 and to Week 24 (EOS) between the Test and Control groups
- Compare changes in selected biomarkers (same as those in the primary objective) from Baseline to Week 18 between Test and Control groups
- Determine the number of cigarettes smoked (Test and Control groups) from Baseline through Week 24 (EOS)
- Assess changes in the amount of test e-vapor product use (Test groups only) from Baseline through Week 24 (EOS)
- Assess adherence to protocol by comparing changes from Baseline through Week 24 (EOS) within the Test groups for eCO and urinary NNN

The Exploratory Objectives are to:

- Assess changes in biomarkers of potential harm (BOPHs) and biomarkers of exposure (BOEs) (same as in the primary objective) from Baseline through Week 24 (EOS) between the subgroups that used different flavored Test e-vapor products
- Assess changes in urine nicotine equivalents (NE) from Baseline through Week 24

(EOS) **within** and **between** Test and Control groups

- Assess changes in the QGEN and TQOLIT questionnaires and the Cough Questionnaire responses from Baseline through Week 24 (EOS) between the Test and Control groups
- Assess reasons for test product use/not-use at EOS and modified Cigarette Evaluation Questionnaire (mCEQ) questionnaires from Baseline to Week 24 (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 parallel-group, open-label, controlled design and will be conducted at multiple study sites. Up to 250 adult male and female (neither gender should account for more than 60% of the population) smokers (30 to 65 years of age, inclusive, determined at Screening [Visit 1] of the 12-week ALCS-RA-16-06-EV study) who completed the 12-week ALCS-RA-16-06-EV study (CA20130), were compliant with the requirements of the 12-week study, and continue to satisfy all inclusion/exclusion criteria of that study, will be invited to enroll into this study and remain in the group into which they were randomized in the 12-week ALCS-RA-16-06-EV study.

Enrolled subjects in Test Product groups will be provided a 3-week supply of the Test Product to which they were randomized in the 12-week ALCS-RA-16-06-EV study and will be given a return date for Visit 2 (Week 15).

At Visits 2 and 4 (Week 15 and Week 21, respectively), subjects will return to the study site with all of their used and unused cartridges, which will be counted. Vital signs will be taken and medical history and symptom-driven physical examination will be performed. Compliance with daily tobacco use reporting will be discussed and eCO will be measured; use of non-Test Product and/or eCO measurements > 5 ppm will prompt counceling by clinic staff on the Tobacco and Nicotine Restrictions and, for measurements > 8 ppm, potential for removal from the study. Test Product for the following 3 weeks and a urine collection container will be dispensed. Subjects will receive reminder calls regarding their following clinic visits and need to collect the first void urine prior to returning to the study site (Visits 3 and 5).

At Visit 3 (Week 18), procedures will be as described for Visits 2 and 4 (Weeks 15 and 21, respectively), with the addition of spirometry, questionnaires, and collection of urine and blood for Week 18 biomarkers and future biomarker assessments. A urine collection container will not be dispensed at Visit 3.

At Visit 5 (Week 24), subjects will return to the study site with all of their used and unused cartridges (which will be counted), blood and urine samples will be collected for Week 24 biomarker assessments, questionnaires will be completed, and subjects will undergo EOS

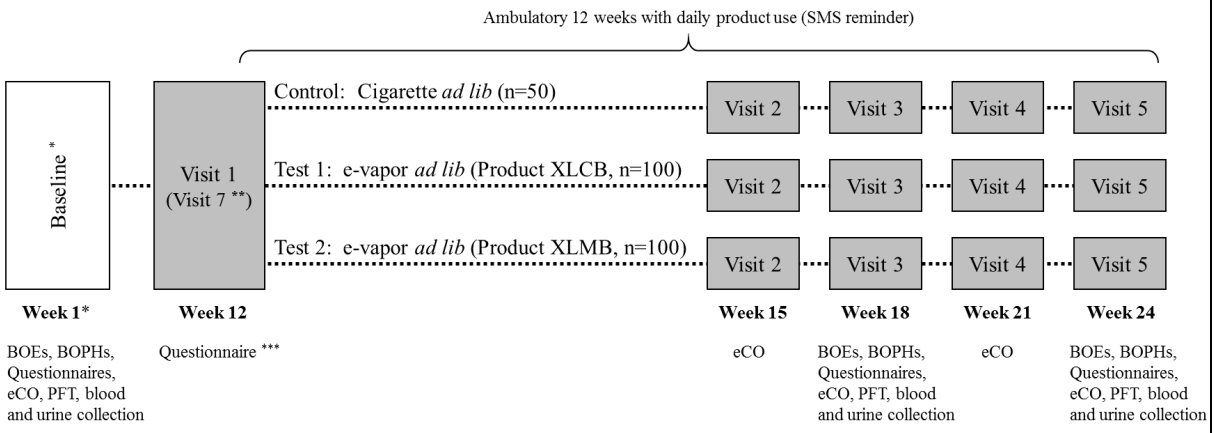
procedures and be discharged from the study.

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 eCO and NNN taken during the in-clinic visits 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 15, 18, 21, and 24.

Throughout this protocol, Screening refers to Visit 1 and/or Visit 2 of the 12-week ALCS-RA-16-06-EV study (CA20130), and study weeks are relative to Week 1 (Visit 3) of the 12-week ALCS-RA-16-06-EV study. Baseline values reported on Day 1 (Week 1) or at Screening (for spirometry only) of the 12-week ALCS-RA-16-06-EV study (CA20130) will be used.

Subjects who completed 24 weeks of product use, in both Test and Control groups, will be asked to provide additional consent (signed) for post-study follow-up at approximately 1, 2, 3, and 6 months after study discharge (Visit 5, Week 24) to determine their smoking status.

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

* Baseline values reported on Day 1 (Week 1) or at Screening (for PFT only) of the 12-week ALCS-RA-16-06-EV study (CA20130) will be used.
** Visit 1 is the same as Visit 7 of the 12-week ALCS-RA-16-06-EV study (CA20130).
*** Changes in Your Health and Well-Being Questionnaire.

Test Products dispensing will occur at Visits 1, 2, 3, and 4 for the Test groups.

Study Visits:

- Visit 1: (Week 12, Day 84 +/- 3 days) same visit as Visit 7 of the ALCS-RA-16-06-EV (CA20130) study
- Visit 2: (Week 15, Day 105 +/- 3 days)
- Visit 3: (Week 18, Day 126 +/- 3 days)
- Visit 4: (Week 21 Day 147 +/- 3 days)
- Visit 5: (Week 24, Day 168 +/- 3 days, EOS [or Early Termination])

Number of Subjects and Groups:

Up to 250 adult smokers who completed and were compliant with the requirements of the 12-week ALCS-RA-16-06-EV study (CA20130) will be enrolled as follows:

- Test 1 group (n=100): Exclusive ad libitum use of test e-vapor Product XLCB, without use of any other type of tobacco/nicotine containing product, for the entire additional 12 weeks
- Test 2 group (n=100): Exclusive ad libitum use of test e-vapor Product XLMB, without use of any other type of tobacco/nicotine containing product, for the entire additional 12 weeks
- Control group (n=50): 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 additional 12 weeks

Study Population:

The study population will consist of up to 250 adult (30 – 65 years of age as determined at Screening [Visit 1] of the 12-week ALCS-RA-16-06-EV study) cigarette smokers who were compliant with the requirements and continue to satisfy all inclusion/exclusion criteria of the 12-week ALCS-RA-16-06-EV study (CA20130). In addition, subjects must satisfy the following inclusion/exclusion criteria.

Inclusion criteria:

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

1) have participated in and completed the 12-week ALCS-RA-16-06-EV study and have Baseline biomarker samples collected;
2) demonstrate willingness to participate by signing an IRB-approved informed consent form (ICF) for the study;
3) have demonstrated consistent daily reporting of product use in the 12-week

ALCS-RA-16-06-EV study (≥ 80% reporting compliance);

4) if randomized to a Test group, have reported an average of no more than 10% of Baseline cigarette smoking per day through Week 11 of the 12-week ALCS-RA-16-06-EV study;

5) if randomized to a Test group, have reported use of at least two Test product cartridges per week in the 12-week ALCS-RA-16-06-EV study;

6) if randomized to a Test group, have eCO measurements of ≤ 8 ppm at each post-Baseline time point in the 12-week ALCS-RA-16-06-EV study;

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

8) if female (**all** females), have a negative urine pregnancy test at Week 12 (Visit 1) through Week 24 (Visit 5), 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 of the 12-week ALCS-RA-16-06-EV study and must agree to continue to use such method(s) through Week 24 (EOS);

   a) Surgically sterile includes bilateral tubal ligation, Essure, hysterectomy, or bilateral oophorectomy at least 6 months prior to Screening, Visit 1 of the 12-week ALCS-RA-16-06-EV study. 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 of the 12-week ALCS-RA-16-06-EV study; double barrier (i.e., condom with spermicide or diaphragm with spermicide) consistently for at least 4 weeks prior to Screening, Visit 1 of the 12-week ALCS-RA-16-06-EV study; and intrauterine device for at least 3 months prior to Screening, Visit 1 of the 12-week ALCS-RA-16-06-EV study; or only have a partner who has been vasectomized for at least 6 months prior to Screening, Visit 1 of the 12-week ALCS-RA-16-06-EV study.

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) Have clinically significant abnormal findings on the physical examination, vital signs, or electrocardiogram (ECG) at the EOS visit (Visit 7) of the 12-week

ALCS-RA-16-06-EV study that would jeopardize the safety of the subject, in the opinion of the Investigator;

2) Female subjects who are pregnant (as determined at the EOS visit [Visit 7] of the 12-week study), lactating, or intend to become pregnant from Visit 1 (Week 12) through Week 24 (EOS);
3) Use of any medication for depression, asthma, or diabetes at any time during the study;
4) Use of HDL-C raising medication / supplements (e.g., niacin, gemfibrozil, fenofibrate, etc.) at any time during the study;
5) 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;
6) Subject or a first-degree relative (i.e., parent, spouse, sibling, or child) is a current or former employee of Celerion or any of the clinical study sites.

Statistics:

Sample size estimation

The 12-week ALCS-RA-16-06-EV study (CA20130) was 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 sICAM values from another source[22] were used for the sample size calculation. A total of 450 subjects (300 in the Test groups and 150 in the Control group) were randomized.

In the current study, a total of up to 250 subjects (up to 100 in each of the Test groups and 50 in the Control group) who were compliant with the requirements of the 12-week ALCS-RA-16-06-EV study and continue to satisfy all inclusion/exclusion criteria of that study will be enrolled. The number of subjects is based on the anticipated number of protocol-compliant subjects in the Test groups rather than the power required to discriminate between Test and Control groups.

Primary Endpoints

The primary endpoints are changes from Baseline to Week 24 (EOS) in the following biomarkers measured at Week 24:

- 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)

Secondary Endpoints

The secondary endpoints are:

1) FEV_1 (% predicted), FCV, and FEV_1/FVC measured at Screening (Visit 2 of the 12-week ALCS-RA-16-06-EV study), Week 18, and Week 24 (EOS)
2) Levels of selected biomarkers (same as the primary endpoints) and the following additional biomarkers measured at Baseline, Week 18, and Week 24 (EOS):
    a) Creatinine-adjusted NNN in urine (ng/g Cr) and eCO
3) The average daily cigarettes smoked and Test Product use reported by subjects from Baseline through Week 24 (EOS)
    a) Test Products used per day, as determined by the number of new cartridges used and the average number of puffs taken (1 – 20 or >20), to be documented through text message
    b) The number of cigarettes smoked per day will be documented by the subjects through text message

Exploratory Endpoints

The exploratory endpoints are:

1) Assess changes in BOPHs and BOEs (same as in the primary objective) measured at Baseline, Week 18, and Week 24 (EOS) between the subgroups that used different flavored Test e-vapor products
2) NE (nicotine, cotinine, trans-3'-hydroxycotinine, trans-3'-hydroxycotinine-O-glucuronide, nicotine-N-glucuronide, and cotinine-N-glucuronide) in urine with creatinine adjustment (mg/g Cr) measured at Baseline, Week 18, and Week 24 (EOS)
3) Responses (Score) to the QGEN and TQOLIT questionnaires and the Cough Questionnaire recorded at Baseline, Week 18, and Week 24 (EOS)
4) Reponses to Reasons for Use and Not-use of Test Product (Week 24 [EOS]) and mCEQ questionnaires (Baseline and Week 24) (Test group only)

Statistical Analysis Method:

Subject Demographics and Baseline Characteristics:

Demographics and baseline characteristics will be summarized by study group with descriptive statistics (the number of non-missing values, mean, median, standard deviation [SD], median, minimum, maximum, coefficient of variation [CV], and 95% confidence interval, as appropriate) 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 Week 24 (EOS) for 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 covariate and subject is the random effect factor. The unstructured covariance structure will be used for modeling covariance. The least-squares mean difference, 95% confidence interval, and p-value will be provided for the group difference. The analysis will be conducted on the modified intent to treat (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.

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 raw values (creatinine-adjusted raw values for urine variables) and absolute change from baseline values.

Secondary Variable Analyses

- Changes in FEV_1, FVC, and FEV_1/FVC ratios from Baseline to Week 18 and to Week 24 (EOS) in the Test and Control groups.

- The MMRM as used for the primary endpoints will be used to test the differences in the mean absolute change from Baseline to Week 18 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 the average number of e-vapor cartridge used per day by group from Week 12 through Week 18 and from Week 19 through Week 24 (EOS). Frequency tables will also be used to summarize the number and percent of subjects with a reduction, no change, or increase in cigarette or e-vapor cartridge use from Baseline to Week 24 (EOS) 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.

Exploratory Endpoints/Variable Analyses

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

- changes in BOPHs and BOEs from Baseline to Week 24 (EOS) between the subgroups that used different flavored Test e-vapor products
- changes in urine NE from Baseline to Week 18 and Week 24 (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 Week 24 (EOS) in the Test and Control groups

Subgroup Analysis

Subgroup analyses will be conducted for the Week 24 (EOS) change from Baseline in the primary biomarkers for covariates including gender, age class, race, and BMI that prove to be statistically significant in the MMRM model.

Clinical Safety

Adverse events (AEs) 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 [1]	Visit 2	Visit 3	Visit 4	Visit 5
	Week 12 Day 84 (+/- 3)	Week 15 Day 105 (+/- 3)	Week 18 Day 126 (+/- 3)	Week 21 Day 147 (+/- 3)	Week 24 Day 168 (+/- 3) End of Study / Early Term
Informed Consent	X				
Review of Inclusion / Exclusion Criteria	X	X	X	X	X
Vital Signs [2]		X	X	X	X
Body Weight					X
Body Mass Index					X
Spirometry [3]			X		X
Smoking Cessation Information					X
Clinical Chemistry (8 hr fasting)					X
Hematology (8 hr fasting)					X
Urinalysis					X
Review of Concomitant Medications	X	X	X	X	X
Review of Tobacco and Nicotine Restrictions	X	X	X	X	
Physical Examination		X [4]	X [4]	X [4]	X [4]
12-Lead ECG [5]					X
Urine Pregnancy Test		X	X	X	X
Review of AEs	X	X	X	X	X
QGEN and TQOLIT [6] questionnaires			X		X
Cough Questionnaire			X		X
mCEQ Questionnaire					X
Reasons of Use/Not-Use Test Product Questionnaire [7]					X
Confirm Regular Cigarette Brand	X [8]	X [8]	X [8]	X [8]	X [8]
Test e-Vapor Product Dispensation	X	X	X	X	
Test e-Vapor Product Collection		X	X	X	X
Reminder Phone Calls	X	X	X	X	X
Distribute 1st Morning Void Containers		X		X	
Urine (1st Void of Day) for BOEs and BOPHs [9, 10]			X		X
Blood Collection for BOPHs [11]			X		X
Blood Collection for COHb [11]			X		X
Bio-Banking			X		X
Product Use Reporting [12]	X	X	X	X	X

EVENTS/ASSESSMENTS	Visit 1 [1]	Visit 2	Visit 3	Visit 4	Visit 5
	Week 12 Day 84 (+/- 3)	Week 15 Day 105 (+/- 3)	Week 18 Day 126 (+/- 3)	Week 21 Day 147 (+/- 3)	Week 24 Day 168 (+/- 3) End of Study / Early Term
Exhaled CO Measurement		X	X	X	X
Changes in Your Health and Well-Being Questionnaire	X				X
End of Study Questionnaire					X
Additional Consent for Post-Study Follow-up [13]					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; HDL-C = high-density lipoprotein cholesterol; hr = hour(s); 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; SMS = Short Message Service; WBC = white blood cell.

1 Visit 1 of the current study is the same visit as Visit 7 of the 12-week ALCS-RA-16-06-EV (CA20130) study. Study procedures scheduled at this visit should be performed only once (with the exception of rechecks).

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 Physical examination (symptom-driven).

5 After at least 5 minutes resting in supine position.

6 All Groups will be given the same QGEN questionnaire but different TQOLIT questionnaires: Appendix 1A for the Control Group, Appendix 1B for the Test Groups

7 Questionnaire given to Test group only.

8 Control group only, photocopy the pack if there has been a change from Screening of the 12-week ALCS-RA-16-06-EV (CA20130) study.

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

10 Spot urine (first void of the day, after at least 4 hours 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 $F_{2\alpha}$).

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

12 Daily product use (conventional cigarettes or test e-vapor product) will be reported daily (Day 84/Week 12 through Day 168/Week 24) by subjects using a SMS, i.e., text message, based system (Med-Quest) to assess product use and compliance during the study.

13 Subjects who completed 24 weeks of product use, in both Test and Control groups, will be asked to provide additional consent (signed) for post-study follow-up contact at approximately 1, 2, 3, and 6 months after study discharge (Visit 5, Week 24) to determine their smoking status.

ABBREVIATIONS AND DEFINITIONS

AE	Adverse event
ALCS	Altria Client Services LLC
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
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
eCO	Exhaled carbon monoxide
eCRF	Electronic case report form
EOS	End of study
°F	Degrees Fahrenheit
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GCP	Good Clinical Practice
HDL-C	High-density lipoprotein cholesterol
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)
MAR	Missing at random
mCEQ	Modified Cigarette Evaluation Questionnaire
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
NNN	N-nitrosonornicotine
PFT	Pulmonary function test
pg	Picogram
PK	Pharmacokinetic
PP	Per-protocol
ppm	Parts per million
QA	Quality assurance
QGEN	Generic Quality of Life
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
sICAM-1	Soluble intercellular adhesion molecule-1
SD	Standard deviation
SMS	Short Message Service
SOP(s)	Standard operating procedure(s)
TQOLIT	Tobacco Quality of Life Impact Tool
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 Purpose of this Study

In section VI (H) (2) of the FDA draft guidance for industry, Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems, it states: "To evaluate the acute and chronic health effects associated with the product, FDA recommends including studies, other scientific evidence, or both, that identify biomarkers of exposure, biomarkers of harm, and health outcome measurements or endpoints." The current study is an extension of the 12-week ALCS-RA-16-06-EV (CA20130) study and its purpose 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 XLMB) for 24 weeks. Changes will be evaluated compared to Baseline values reported on Day 1 (Week 1) of the 12-week ALCS-RA-16-06-EV (CA20130) study.

1.2 Hypothesis

If adult smokers completely switch to exclusive use of an e-vapor test product for 24 weeks, 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.

1.3 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[1]. More than 4,800 different chemical constituents have been identified in cigarette smoke[2], 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, there is currently 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 for 24 weeks. The results from this study will provide supportive evidence to the overall assessment of the reduced risk potential of test e-vapor products.

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[b] to Week 24 (EOS) between adult smokers who continue to smoke conventional cigarettes (Control group) ad libitum and adult smokers who have completely[c] switched to ad libitum use of the test e-vapor products (Test groups) for 24 weeks.

[a] Seleted biomarkers include:

- WBC
- HDL-C
- Urinary 8-epi-prostaglandin $F_{2\alpha}$
- Urinary 11-dehydrothromboxane B_2
- Blood sICAM-1
- Urinary 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronides (total NNAL)
- COHb

[b] Baseline of the 12-week ALCS-RA-16-06-EV study (CA20130), Week 1, will be used.

[c] Subjects who exclusively use e-vapor products and have eCO measurements $\leq$ 8 ppm from Week 3 (of the 12-week ALCS-RA-16-06-EV study) through Week 24 (EOS) and urine NNN levels from Week 6 (of the 12-week ALCS-RA-16-06-EV study) through Week 24 (EOS) consistent with switching to an e-vapor product.

2.2 Secondary Objectives

The secondary objectives are to:

- Assess changes in FEV_1, FVC and FEV_1/FVC ratios from Screening/Visit 2 of the 12-week ALCS-RA-16-06-EV study (CA20130) to Week 18 and to Week 24 (EOS) between the Test and Control groups
- Compare changes in selected biomarkers (same as those in the primary objective) from Baseline to Week 18 between Test and Control groups
- Determine the number of cigarettes smoked (Test and Control groups) from Baseline through Week 24 (EOS)
- Assess changes in the amount of test e-vapor product use (Test groups only) from Baseline through Week 24 (EOS)

- Assess adherence to protocol by comparing changes from Baseline through Week 24 (EOS) within the Test groups for eCO 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 through Week 24 (EOS) between the subgroups that used different flavored Test e-vapor products
- Assess changes in urine NE from Baseline through Week 24 (EOS) **within** and **between** Test and Control groups
- Assess changes in the QGEN and TQOLIT questionnaires and the Cough Questionnaire responses from Baseline through Week 24 (EOS) between the Test and Control groups
- Assess reasons for test product use/not-use at EOS and mCEQ questionnaires from Baseline to Week 24 (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 parallel-group, open-label, controlled design and will be conducted at multiple study sites. Up to 250 adult male and female (neither gender should account for more than 60% of the population) smokers (30 to 65 years of age, inclusive, determined at Screening [Visit 1] of the 12-week ALCS-RA-16-06-EV study) who completed the 12-week ALCS-RA-16-06-EV study (CA20130), were compliant with the requirements of the 12-week study, and continue to satisfy all inclusion/exclusion criteria of that study, will be invited to enroll into this study and remain in the group into which they were randomized in the 12-week ALCS-RA-16-06-EV study.

- Control Group (n=50): 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 additional 12 weeks

- Test 1 Group (n=100): Continue ad libitum use of test e-vapor products (Product XLCB), without use of any other type of tobacco/nicotine containing product, for the entire additional 12 weeks

- Test 2 Group (n=100): Continue ad libitum use of test e-vapor products (Product XLMB), without use of any other type of tobacco/nicotine containing product, for the entire additional 12 weeks

Enrolled subjects in Test Product groups will be provided a 3-week supply of the Test Product to which they were randomized in the 12-week ALCS-RA-16-06-EV study and will be given a return date for Visit 2 (Week 15).

At Visits 2 and 4 (Week 15 and Week 21, respectively), subjects will return to the study site with all of their used and unused cartridges, which will be counted. Vital signs will be taken and medical history and symptom-driven physical examination will be performed. Compliance with daily tobacco use reporting will be discussed and eCO will be measured; use of non-Test Product and/or eCO measurements > 5 ppm will prompt counceling by clinic staff on the Tobacco and Nicotine Restrictions and, for measurements > 8 ppm, potential for removal from the study. Test Product for the following 3 weeks and a urine collection container will be dispensed. Subjects will receive reminder calls regarding their following clinic visits and need to collect the first void urine prior to returning to the study site (Visits 3 and 5).

At Visit 3 (Week 18), procedures will be as described for Visits 2 and 4 (Weeks 15 and 21, respectively), with the addition of spirometry, questionnaires, and collection of urine and blood for Week 18 biomarkers and future biomarker assessments. A urine collection container will not be dispensed at Visit 3.

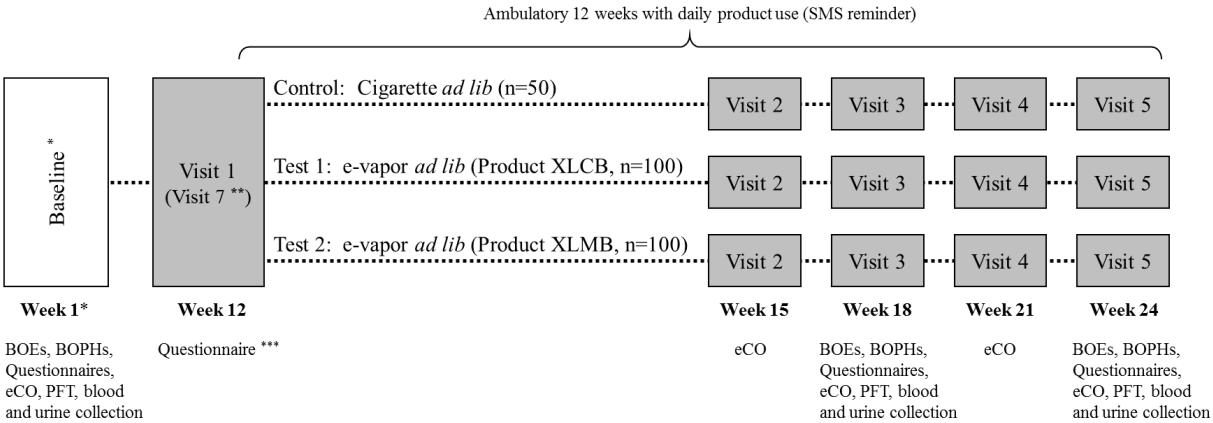
At Visit 5 (Week 24), subjects will return to the study site with all of their used and unused cartridges (which will be counted), blood and urine samples will be collected for Week 24 biomarker assessments, questionnaires will be completed, and subjects will undergo EOS procedures and be discharged from the study.

All subjects will report their CPD (Control and Test groups) and Test product use (Test groups only) daily using a SMS, i.e., text message, based system (Med-Quest). The self-reported CPD, use of other tobacco products, and measurements of eCO and NNN taken during the in-clinic visits 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 15, 18, 21, and 24.

Throughout this protocol, Screening refers to Visit 1 and/or Visit 2 of the 12-week ALCS-RA-16-06-EV study (CA20130), and study weeks are relative to Week 1 (Visit 3) of the 12-week ALCS-RA-16-06-EV study. Baseline values reported on Day 1 (Week 1) or at Screening (for spirometry only) of the 12-week ALCS-RA-16-06-EV study (CA20130) will be used.

Subjects who completed 24 weeks of product use, in both Test and Control groups, will be asked to provide additional consent (signed) for post-study follow-up at approximately 1, 2, 3, and 6 months after study discharge (Visit 5, Week 24) to determine their smoking status.

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

* Baseline values reported on Day 1 (Week 1) or at Screening (for PFT only) of the 12-week ALCS-RA-16-06-EV study (CA20130) will be used.
** Visit 1 is the same as Visit 7 of the 12-week ALCS-RA-16-06-EV study (CA20130).
*** Changes in Your Health and Well-Being Questionnaire.

Test Products dispensing will occur at Visits 1, 2, 3, and 4 for the Test groups.

3.2 Study Duration

The expected duration of this study, from first subject, first visit (Visit 1, Week 12), through last subject, last visit will be approximately 12 weeks. The expected study duration from Screening (of the 12-week ALCS-RA-16-06-EV study) to End of Study for each individual subject is approximately 28 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. Visit 1 (Week 12, which is the same as Visit 7 of the 12-week ALCS-RA-16-06-EV study) safety evaluations will include the following: physical examination (symptom-driven); vital signs; body weight, BMI; 12-lead ECGs; clinical chemistry, hematology, and urinalysis; and pregnancy testing (all females). At Visits 2, 3, and 4, safety evaluations will include vital signs and physical examination (symptom-driven). Visit 5/EOS (or early termination) safety evaluations will include a physical examination (symptom-driven); vital signs; body weight; BMI; 12-lead 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, Visit 2 of the 12-week ALCS-RA-16-06-EV study until Week 24/EOS (or upon early termination). Events occurring after the initial informed consent signing at

Screening, Visit 1 of the 12-week ALCS-RA-16-06-EV study 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 of the 12-week ALCS-RA-16-06-EV study through Week 24/EOS (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) have participated in and completed the 12-week ALCS-RA-16-06-EV study and have Baseline biomarker samples collected;

2) demonstrate willingness to participate by signing an IRB-approved ICF for the study;

3) have demonstrated consistent daily reporting of product use in the 12-week ALCS-RA-16-06-EV (≥ 80% reporting compliance);

4) if randomized to a Test group, have reported an average of no more than 10% of Baseline cigarette smoking per day through Week 11 of the 12-week ALCS-RA-16-06-EV study;

5) if randomized to a Test group, have reported use of at least two Test product cartridges per week in the 12-week ALCS-RA-16-06-EV study;

6) if randomized to a Test group, have eCO measurements of ≤ 8 ppm at each post-Baseline time point in the 12-week ALCS-RA-16-06-EV study;

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

8) if female (**all** females), have a negative urine pregnancy test at Week 12 (Visit 1) through Week 24 (Visit 5), 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 of the 12-week ALCS-RA-16-06-EV study and must agree to continue to use such method(s) through Week 24 (EOS);

a) Surgically sterile includes bilateral tubal ligation, Essure, hysterectomy, or bilateral oophorectomy at least 6 months prior to Screening, Visit 1 of the 12-week ALCS-RA-16-06-EV study. 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 of the 12-week ALCS-RA-16-06-EV study; double barrier (i.e., condom with spermicide or diaphragm with spermicide) consistently for at least 4 weeks prior to Screening, Visit 1 of the 12-week ALCS-RA-16-06-EV study; and intrauterine device for at least 3 months prior to Screening, Visit 1 of the 12-week ALCS-RA-16-06-EV study; or only have a partner who has been vasectomized for at least 6 months prior to Screening, Visit 1 of the 12-week ALCS-RA-16-06-EV study.

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) Have clinically significant abnormal findings on the physical examination, vital signs, or ECG at the EOS visit (Visit 7) of the 12-week ALCS-RA-16-06-EV study that would jeopardize the safety of the subject, in the opinion of the Investigator;

2) Female subjects who are pregnant (as determined at the EOS visit [Visit 7] of the 12-week study), lactating, or intend to become pregnant from Visit 1 (Week 12) through Week 24 (EOS);

3) Use of any medication for depression, asthma, or diabetes at any time during the study;

4) Use of HDL-C raising medication / supplements (e.g., niacin, gemfibrozil, fenofibrate, etc.) at any time during the study;

5) 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;

6) Subject or a first-degree relative (i.e., parent, spouse, sibling, or child) is a current or former employee of Celerion or any of the clinical study sites.

4.3 Restrictions

- No participation in other studies or blood (other than for this study) or plasma donations 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) during the study.

- Medications with therapeutic effect on HDL-C, or medications for depression, asthma or diabetes, are not allowed during the study.

4.4 Concomitant Medications

Any concomitant medications taken through Week 24 (EOS) or upon Early Termination will be recorded.

Stable doses 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 800 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 1/Week 12, Visit 2/Week 15, Visit 3/Week 18, Visit 4/Week 21, and Visit 5/Week 24, 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 continue to supply their own conventional cigarettes, at their own cost, for the duration of the study.

There will be no restrictions on cigarette brand at any time during the study.

6.0 VISIT 1 (WEEK 12 / DAY 84 ±3)

Visit 1 should be arranged in the morning to accommodate fasting blood sampling. Subjects should be reminded to maintain their product use during the morning of the study visit; abstinence is not required. Visit 1 of this study is the same as Visit 7 of the 12-week ALCS-RA-16-06-EV (CA20130) study. Study procedures scheduled at this visit should be performed only once (with the exception of rechecks).

6.1 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 ICF prior to any 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.

6.2 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 will be performed. Subjects who do not meet the inclusion/exclusion criteria required at Visit 1 (Week 12/Day 84 +/- 3) will not be enrolled in this study; data to be captured will include subject demographics and reason(s) for screen failure.

6.3 Review of Concomitant Medications

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

6.4 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.

6.5 Review of Adverse Events

All AEs occurring during this clinical trial after the subject has signed the ICF must be recorded in the electronic case report form (eCRF).

6.6 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.

6.7 Test e-Vapor Product Dispensation

Subjects randomized to a Test group will be given enough of their assigned test e-vapor product to last until they return to the study site at Visit 2 (Week 15) 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.).

6.8 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 1 - 5), 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 and 5). Subjects should be reminded to maintain their usual smoking/vaping behavior during the morning of the study visits; abstinence is not required.

6.9 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.

6.10 Changes in Your Health and Well-Being Questionnaire

Subjects will fill out the Changes in Your Health and Well-Being Questionnaire (Appendix 6A).

7.0 VISIT 2 (WEEK 15 / DAY 105 ±3)

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

7.1 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 Visit 1 (Week 12) will be performed.

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 Review of Concomitant Medications

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

7.4 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.

7.5 Physical Examination (Symptom-Driven)

A symptom-driven physical examination will be conducted.

7.6 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.

7.7 Review of Adverse Events

All AEs occurring during this clinical trial after the subject has signed the ICF must be recorded in the eCRF.

7.8 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.

7.9 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.

7.10 Test e-Vapor Product Dispensation

Subjects randomized to a Test group will be given enough of their assigned test e-vapor product to last until they return to the study site at Visit 3 (Week 18) 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.).

7.11 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, 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 and 5). Subjects should be reminded to maintain their usual smoking/vaping behavior during the morning of the study visits; abstinence is not required.

7.12 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 2 (Week 15) for collecting the first void urine sample in the morning of Visit 3 (Week 18), 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.

7.13 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.

7.14 Exhaled CO Measurement

Exhaled CO measurements will be performed by the clinic staff using the Micro+ basic™ Smokerlyzer® monitor (coVita). Subjects in the Control and Test groups are expected to have eCO measurements consistent with recent cigarette smoking or e-vapor use, respectively. Subjects in the Test groups with eCO measurements > 5 ppm will be counseled on the importance of study compliance. Subjects in the Test groups with eCO measurements > 8 ppm will be recorded as non-compliant at the Visit.

8.0 VISIT 3 (WEEK 18 / DAY 126 ±3)

Subjects should be reminded to maintain their usual smoking/vaping behavior during the day 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 Visit 1 (Week 12) will be performed.

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 Spirometry

All subjects will undergo spirometry tests (FEV_1, FVC, and FEV_1/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.

8.4 Review of Concomitant Medications

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

8.5 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.

8.6 Physical Examination (Symptom-Driven)

A symptom-driven physical examination will be conducted.

8.7 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.

8.8 Review of Adverse Events

All AEs occurring during this clinical trial after the subject has signed the ICF must be recorded in the eCRF.

8.9 QGEN and TQOLIT Questionnaires

Subjects will complete the QGEN and TQOLIT questionnaires (Appendix 1, Appendix 1A for Control Group, Appendix 1B for Test Groups).

8.10 Cough Questionnaire

Subjects will complete the Cough Questionnaire (Appendix 2).

8.11 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.

8.12 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.

8.13 Test e-Vapor Product Dispensation

Subjects randomized to a 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 (Week 21) 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.).

8.14 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, 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 and 5). Subjects should be reminded to maintain their usual smoking/vaping behavior during the morning of the study visits; abstinence is not required.

8.15 BOE and BOPH Urine Sample Collection

First Urine Void for BOEs and BOPHs

On the morning of Visit 3 (Week 18), 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).

8.16 BOPH and COHb Blood Sample Collection

Blood Collection for BOPH and COHb

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

8.17 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.

8.18 Exhaled CO Measurement

Exhaled CO measurements will be performed by the clinic staff using the Micro+ basic™ Smokerlyzer® monitor (coVita). Subjects in the Control and Test groups are expected to have eCO measurements consistent with recent cigarette smoking or e-vapor use, respectively. Subjects in the Test groups with eCO measurements > 5 ppm will be counseled on the importance of study compliance. Subjects in the Test groups with eCO measurements > 8 ppm will be recorded as non-compliant at the Visit.

9.0 VISIT 4 (WEEK 21 / DAY 147 ±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 Visit 1 (Week 12) 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 Review of Concomitant Medications

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

9.4 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.

9.5 Physical Examination (Symptom-Driven)

A symptom-driven physical examination will be conducted.

9.6 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.

9.7 Review of Adverse Events

All AEs occurring during this clinical trial after the subject has signed the ICF must be recorded in the eCRF.

9.8 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.

9.9 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.

9.10 Test e-Vapor Product Dispensation

Subjects randomized to a 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 (Week 24) 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.).

9.11 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, 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 and 5). Subjects should be reminded to maintain their usual smoking/vaping behavior during the morning of the study visits; abstinence is not required.

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 (Week 21) for collecting the first void urine sample in the morning of Visit 5 (Week 24), 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.

9.13 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.

9.14 Exhaled CO Measurement

Exhaled CO measurements will be performed by the clinic staff using the Micro+ basic™ Smokerlyzer® monitor (coVita). Subjects in the Control and Test groups are expected to have eCO measurements consistent with recent cigarette smoking or e-vapor use, respectively. Subjects in the Test groups with eCO measurements > 5 ppm will be counseled on the importance of study compliance. Subjects in the Test groups with eCO measurements > 8 ppm will be recorded as non-compliant at the Visit.

10.0 VISIT 5, END OF STUDY (WEEK 24 / DAY 168 ±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 Visit 1 (Week 12) 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 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 of the 12-week ALCS-RA-16-06-EV study will be used to calculate BMI).

10.4 Spirometry

All subjects will undergo spirometry tests (FEV_1, FVC, and FEV_1/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.

10.5 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.

10.6 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 11.2).

10.6.1 Clinical Chemistry

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

10.6.2 Hematology

Hematology will be performed, after at least 8 hours fasting, consisting of hemoglobin, hematocrit, RBC, WBC with differential, and platelet count.

10.6.3 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.

10.7 Review of Concomitant Medications

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

10.8 Physical Examination (Symptom-Driven)

A symptom-driven physical examination will be conducted.

10.9 12-Lead ECG

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

10.10 Urine Pregnancy Test

Female subjects will complete a urine pregnancy test.

10.11 Review of Adverse Events

All AEs occurring during this clinical trial after the subject has signed the ICF must be recorded in the eCRF.

10.12 QGEN and TQOLIT Questionnaires

Subjects will complete the QGEN and TQOLIT questionnaires (Appendix 1, Appendix 1A for Control Group, Appendix 1B for Test Groups).

10.13 Cough Questionnaire

Subjects will complete the Cough Questionnaire (Appendix 2).

10.14 mCEQ Questionnaire

Subjects will complete the appropriate mCEQ Questionnaire (Appendix 3A for Test groups, Appendix 3B for the Control group).

10.15 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 4).

10.16 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.

10.17 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.

10.18 Reminder Calls

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

10.19 BOE and BOPH Urine Sample Collection

First Urine Void for BOEs and BOPHs

On the morning of Visit 5 (Week 24), 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).

10.20 BOPH and COHb Blood Sample Collection

Blood Collection for BOPH and COHb

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

10.21 SMS System Use

The day prior to Visit 5 will be the final product use entry.

10.22 Exhaled CO Measurement

Exhaled CO measurements will be performed by the clinic staff using the Micro+ basic™ Smokerlyzer® monitor (coVita). Subjects in the Control and Test groups are expected to have eCO measurements consistent with recent cigarette smoking or e-vapor use, respectively. Subjects in the Test groups with eCO measurements > 5 ppm will be counseled on the importance of study compliance. Subjects in the Test groups with eCO measurements > 8 ppm will be recorded as non-compliant at the Visit.

10.23 Changes in Your Health and Well-Being Questionnaire

Subjects will fill out the Changes in Your Health and Well-Being Questionnaire (Appendix 6B).

10.24 End of Study Questionnaire

Subjects will fill out the End of Study Questionnaire Appendix 5A (Control group) and Appendix 5B (Test group).

10.25 Additional Consent for Post-Study Follow-up

Subjects who completed 24 weeks of product use, in both Test and Control groups, will be asked to provide additional consent (signed) for post-study follow-up contact at approximately 1, 2, 3, and 6 months after study discharge (Visit 5, Week 24) to determine their smoking status.

At each of these time points, subjects who consented will be contacted by phone and asked the following questions:

1. (For Test groups only) Have you continued to use e-vapor products?
2. Are you currently smoking cigarettes?
3. (If the answer to #2 is “yes”) How many cigarettes per day are you smoking?

Data collected during the post-study follow-up will be captured in source documents but will not be included in the Clinical Study Report.

11.0 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.[3, 4]

[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 must be recorded in the eCRF, including the date and time of onset and outcome of each event.

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.

11.1 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[4]).

[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).

11.2 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.

11.3 Pregnancy

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 enrolling into this study 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.

12.0 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.

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 5 (Week 24) should, if possible, be obtained. Subjects with AEs will be followed per Section 11.2.

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.

13.0 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 who 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 CRF. Subjects withdrawing or dismissed by the Investigator 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 will not be replaced.

14.0 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.

15.0 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)[5] and in accordance with SOPs which are written to meet applicable portions of Good Laboratory Practice regulations (21 CFR Part 58)[4].

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 aliquots above have been taken	HDPE

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 51 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.

15.1 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) NE (mg/g Cr)

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

15.2 BOE Blood (after overnight fasting, at least 8 hours):

1) COHb in whole blood (% sat)

15.3 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)

15.4 BOPHs Blood (after overnight fasting, at least 8 hours):

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

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

3) sICAM-1 in serum (ng/mL)

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

15.5 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.

16.0 STATISTICAL METHODS

16.1 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.

16.2 Sample Size Estimation

The 12-week ALCS-RA-16-06-EV study (CA20130) was 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)[6] for the Electronic Heating Cigarette Smoking System and sICAM values from another source[7] were used for the sample size calculation. A total of 450 subjects (300 in the Test groups and 150 in the Control group) were randomized.

In the current study, a total of up to 250 subjects (up to 100 in each of the Test groups and 50 in the Control group) who were compliant with the requirements of the 12-week ALCS-RA-16-06-EV study and continue to satisfy all inclusion/exclusion criteria of that study will be enrolled. The number of subjects is based on the anticipated number of protocol-compliant subjects in the Test groups rather than the power required to discriminate between Test and Control groups.

16.3 Criteria for Evaluation

16.3.1 Primary Endpoints

The primary endpoints are the following biomarkers measured at Baseline (Day 1 of the 12-week ALCS-RA-16-06-EV study) and Week 24 (EOS):

- 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)
- sICAM-1 in serum (ng/mL)
- Total NNAL in urine with creatinine adjusted (ng/g Cr)
- COHb in whole blood (% sat)

16.3.2 Secondary Endpoints

The secondary endpoints are:

1) FEV_1 (% predicted), FCV, and FEV_1/FVC measured at Screening (Visit 2 of the 12-week ALCS-RA-16-06-EV study), Week 18, and Week 24 (EOS)
2) Levels of selected biomarkers (same as the primary endpoints) and the following additional biomarkers measured at Baseline, Week 18, and Week 24 (EOS):
    a) Creatinine-adjusted NNN in urine (ng/g Cr) and eCO
3) The average daily cigarettes smoked and Test Product use reported by subjects from Baseline through Week 24 (EOS)
    a) Test Products used per day, as determined by the number of new cartridges used and the average number of puffs taken (1 – 20 or >20), to be documented through text message
    b) The number of cigarettes smoked per day will be documented by the subjects through text message

16.3.3 Exploratory Endpoints

The exploratory endpoints are:

1) Assess changes in BOPHs and BOEs (same as in the primary objective) measured at Baseline, Week 18, and Week 24 (EOS) between the subgroups that used different flavored Test e-vapor products

2) NE (nicotine, cotinine, trans-3'-hydroxycotinine, trans-3'-hydroxycotinine-O-glucuronide, nicotine-N-glucuronide, and cotinine-N-glucuronide) in urine with creatinine adjustment (mg/g Cr) measured at Baseline, Week 18, and Week 24 (EOS)

3) Responses (Score) to the QGEN and TQOLIT questionnaires and the Cough Questionnaire recorded at Baseline, Week 18, and Week 24 (EOS)

4) Reponses to Reasons for Use and Not-use of Test Product (Week 24 [EOS]) and mCEQ questionnaires (Baseline and Week 24) (Test group only)

16.3.4 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

16.4 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 after Week 12.

The clinical safety population (CSP) will consist of all subjects who record at least one use of study products (i.e., conventional cigarettes or test e-vapor products) after Week 12.

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 2 - 5, 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.

16.4.1 Demographics and Baseline Characteristics

Demographics and 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, and 95% confidence interval, as appropriate) for continuous variables (e.g., BMI) and frequency counts for categorical variables (e.g., gender).

16.4.2 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.

16.4.2.1 Primary Endpoint Analyses

A linear MMRM analysis will be used for comparing each Test group to the Control group in the mean absolute change from Baseline to Week 24 (EOS) for 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 covariate and subject is the random effect factor. The unstructured covariance structure will be used for modeling covariance. The least-squares 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 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 PP population will also be conducted.

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 raw values (creatinine-adjusted raw values for urine variables) and absolute change from baseline values.

16.4.2.2 Secondary Endpoint Analyses

- Changes in FEV_1, FVC, and FEV_1/FVC ratios from Baseline to Week 18 and to Week 24 (EOS) in the Test and Control groups.

- The MMRM as used for the primary endpoints will be used to test the differences in the mean absolute change from Baseline to Week 18 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 the average number of e-vapor cartridge used per day by group from Week 12 through Week 18 and from Week 19 through Week 24 (EOS). Frequency tables will also be used to summarize the number and percent of subjects with a reduction, no change, or increase in cigarette or e-vapor cartridge use from Baseline to Week 24 (EOS) 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.

16.4.2.3 Exploratory Endpoints Analyses

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

- changes in BOPHs and BOEs from Baseline to Week 24 (EOS) between the subgroups that used different flavored Test e-vapor products

- changes in urine NE from Baseline to Week 18 and Week 24 (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 Week 24 (EOS) in the Test and Control groups

16.5 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, no imputation will be used. Details about missing data imputation for the primary endpoints will be provided in the statistical analysis plan.

16.6 Subgroup Analysis

A subgroup analysis will be conducted for the Week 24 (EOS) change from Baseline in the primary biomarkers for covariates including gender, age class, race, and BMI that prove to be statistically significant in the MMRM model.

All subgroup analyses are exploratory in nature.

17.0 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).

17.1 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.

17.2 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.

17.3 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.

17.4 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.

17.5 Data Validation

After the data have been entered and verified, various edit checks (including manual review of listings) 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.

17.6 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.

18.0 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.

19.0 REPORTING FOR THE STUDY

19.1 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.

19.2 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.

20.0 GENERAL

20.1 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.[8] 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.

20.2 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)[9], and Institutional Review Boards (Title 21 CFR Part 56)[3].

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.

20.3 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.

20.4 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.

20.5 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.

20.6 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.

21.0 REFERENCES

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APPENDICES

Appendix 1: QGEN

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!

Appendix 1A: TQOLIT (Control Group)

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 <u>each</u> 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 1B: TQOLIT (Test Group)

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 vaping 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 vaping limit your usual physical activities?	O	O	O	O	O
Did you have difficulty doing work or other daily activities because of vaping?	O	O	O	O	O
Did vaping 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 vaping 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 vaping?	O	O	O	O	O
Did vaping make you worry about your health or future health problems?	O	O	O	O	O

Appendix 2: 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 3: mCEQ Questionnaires

Appendix 3A: 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 3B: 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 4: 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 5: End of Study Questionnaires

Appendix 5A: 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 5B: 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

Appendix 6: Changes in Your Health and Well-Being

Appendix 6A: Changes in Your Health and Well-Being

These questions are about your health and well-being now compared to when you enrolled in the study about 3 months ago.

1. **How much better or worse is your quality of life overall?**

Lot better now 1
Little better now.....2
About the same now.....3
Little worse now 4
Lot worse now.....5

2. **How much more or less limited are you in your everyday physical activities, such as walking, climbing stairs, carrying groceries, or participating in sports?**

Lot more limited now.....1
Little more limited now 2
About the same now.....3
Little less limited now.....4
Lot less limited now.....5

3. **How much more or less often do you have emotional problems, such as feeling anxious,depressed or irritable?**

Lot more often now.....1
Little more often now.....2
About the same now.....3
Little less often now.....4
Lot less often now.....5

4. **How much better or worse is your health in general?**

Much better now 1
Somewhat better now.....2
About the same now.....3
Somewhat worse now 4
Much worse now.....5

5. How much more or less confident are you about your health in the future?

Much more confident now 1
Somewhat more confident now 2
About the same now.....3
Somewhat less confident now.....4
Much less confident now 5

Appendix 6B: Changes in Your Health and Well-Being

These questions are about your health and well-being now compared to when you enrolled in the study about 6 months ago.

1. **How much better or worse is your quality of life overall?**

Lot better now 1
Little better now.....2
About the same now.....3
Little worse now 4
Lot worse now.....5

2. **How much more or less limited are you in your everyday physical activities, such as walking, climbing stairs, carrying groceries, or participating in sports?**

Lot more limited now.....1
Little more limited now 2
About the same now.....3
Little less limited now.....4
Lot less limited now.....5

3. **How much more or less often do you have emotional problems, such as feeling anxious,depressed or irritable?**

Lot more often now.....1
Little more often now.....2
About the same now.....3
Little less often now.....4
Lot less often now.....5

4. **How much better or worse is your health in general?**

Much better now 1
Somewhat better now.....2
About the same now.....3
Somewhat worse now 4
Much worse now.....5

5. How much more or less confident are you about your health in the future?

Much more confident now 1
Somewhat more confident now 2
About the same now.....3
Somewhat less confident now.....4
Much less confident now 5