A RANDOMIZED, CONTROLLED, OPEN-LABEL SHORT-TERM STUDY TO EVALUATE CHANGES IN EXPOSURE TO HARMFUL AND POTENTIALLY HARMFUL CONSTITUENTS IN ADULT SMOKERS WHO PARTIALLY OR COMPLETELY SWITCH TO VERVE® PRODUCTS (DISCS OR CHEWS) IN A CLINICAL SETTING

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25MAY2018

CLINICAL STUDY PROTOCOL

A RANDOMIZED, CONTROLLED, OPEN-LABEL SHORT-TERM STUDY TO EVALUATE CHANGES IN EXPOSURE TO HARMFUL AND POTENTIALLY HARMFUL CONSTITUENTS IN ADULT SMOKERS WHO PARTIALLY OR COMPLETELY SWITCH TO VERVE® PRODUCTS (DISCS OR CHEWS) IN A CLINICAL SETTING

Altria Client Services LLC Study No. ALCS-RDS-18-04-VRV
Celerion Project No. CA24563
Final Protocol Date: 30 March, 2018
Protocol Amendment 1: 25 May 2018

Sponsor:

Altria Client Services LLC
601 E. Jackson Street
Richmond, Virginia 23219, USA

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[redacted] 5-29-2018
(Signature) (Date)

A RANDOMIZED, CONTROLLED, OPEN-LABEL SHORT-TERM STUDY TO EVALUATE CHANGES IN EXPOSURE TO HARMFUL AND POTENTIALLY HARMFUL CONSTITUENTS IN ADULT SMOKERS WHO PARTIALLY OR COMPLETELY SWITCH TO VERVE® PRODUCTS (DISCS OR CHEWS) IN A CLINICAL SETTING

Altria Client Services LLC Study No. ALCS-RDS-18-04-VRV

Sponsor Contact: 

Celerion Project Manager: 

PROTOCOL SIGNATURE PAGE
Altria Client Services LLC Study No. ALCS-RDS-18-04-VRV

A RANDOMIZED, CONTROLLED, OPEN-LABEL SHORT-TERM STUDY TO EVALUATE CHANGES IN EXPOSURE TO HARMFUL AND POTENTIALLY HARMFUL CONSTITUENTS IN ADULT SMOKERS WHO PARTIALLY OR COMPLETELY SWITCH TO VERVE® PRODUCTS (DISCS OR CHEWS) IN A CLINICAL SETTING

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 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), IRBs (Title 21 CFR Part 56), the Basic Principles of the Declaration of Helsinki, and applicable legal and regulatory requirements.

Principal Investigator:	Printed Name: Site Name: Address: Phone: Fax: E-mail:	
	(Signature)	(Date)

SUMMARY OF AMENDMENT 1

Amendment 1 was generated to include the following changes to the Final Protocol dated 30 March, 2018:

1. The sample size calculations were modified to account for multiplicity adjustments between the continued cigarette smoking group and each of the two dual usage groups. Thus Section 11.2 Sample Size Estimation was updated as follows (changes are presented with new text in **bold** font and deleted text in ~~strikethrough~~ font):

   > "….Assuming a similar effect size for the new study as for the previous ALCS study (ToPP4ST_1011_07) between the continued cigarette smoking group and each of the two dual usage groups (≥50% CPD reduction with VERVE® DISCS or VERVE® CHEWS), a two-sided t test, 85% power, and ~~a 5%~~ **an α =0.025** Type I error rate~~,~~ **to account for the multiplicity adjustment for the two comparisons,** ~~30~~ **35** subjects are needed to complete for the continue cigarette smoking group and the dual usage groups. **We expect that the effect will be larger in the VERVE® only and smoking cessation groups, so 25 subjects are needed to complete these groups**."

   The sample size enrolled in each group of the study was thus increased as a result of modified sample size calculations and to account for possible dropouts. The number of subjects to be enrolled in Groups 1-3 was increased from 32 to 40 and from 24 to 30 in Groups 4-6. Therefore, the overall number of subjects to be enrolled into the study was increased from 168 to 210 subjects. Thus, the Study Outline (Design), Section 3.1 Design and Clinical Procedures, and Figure 1 Overall Study Design were updated to incorporate these changes.

2. Inclusion criterion 4.1.3 was updated to specify that subject's average daily consumption needs to be at least 10 but no more than 30 factory manufactured combustible cigarettes for 1 year prior to Screening rather than Check-in. Therefore , inclusion criterion 4.1.3 was updated as follows:

   > "4.1.3. Smoking history of an average of at least 10 but no more than 30 factory manufactured combustible cigarettes daily for at least 1 year prior to ~~Check-in~~ **Screening**…"

3. Urine cotinine test conducted during Screening will be reported as concentration values instead of qualitative test (≥ 500 ng/mL) that was previously listed in Section 5.6 Clinical laboratory Tests. Therefore, the urine cotinine test listed in 5.6.5 subsection was updated as follows:

   > "5.6.5. Urine cotinine; a positive **quantitative** ~~qualitative~~ test (≥ 500 ng/mL) will be required for participation in the study."

4. Section 7.8 Blood Sample Collection and Processing was updated to specify that subjects will abstain from product use for at least 15 minutes prior to the blood draw for COHb.

Typographical and formatting changes were made throughout the protocol.

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STUDY OUTLINE

A RANDOMIZED, CONTROLLED, OPEN-LABEL SHORT-TERM STUDY TO EVALUATE CHANGES IN EXPOSURE TO HARMFUL AND POTENTIALLY HARMFUL CONSTITUENTS IN ADULT SMOKERS WHO PARTIALLY OR COMPLETELY SWITCH TO VERVE® PRODUCTS (DISCS OR CHEWS) IN A CLINICAL SETTING

Study Purpose

The purpose of this study is to evaluate changes in exposure to selected harmful and potentially harmful constituents (HPHC) by measuring biomarkers in adult smokers who partially or completely switch from smoking to oral tobacco-derived nicotine (OTDN) products VERVE® Chews or VERVE® Discs use compared to those who continue exclusive smoking cigarettes or stop using all tobacco products.

Hypothesis:

Reducing daily cigarette consumption by at least 50% and using VERVE® products will result in a statistically significant reduction in 24-hour urinary total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) on Day 7 compared to continued cigarette smoking.

Objectives

The objectives of the study are:

Primary Objective:

To compare 24-hour urinary total NNAL in adult smokers who reduce cigarette consumption by at least 50% with supplementary (dual) usage of VERVE® Chews or VERVE® Discs to those who continue to smoke cigarettes for 7 days.

Secondary Objectives:

1. To compare biomarkers of exposure (total N-nitrosonornicotine [NNN], nicotine equivalents [NE], 2-aminonaphthalene [2-AN], 4-aminobiphenyl [4-ABP], 2-hydroxyethyl mercapturic acid [HEMA], 2-cyanoethylmercapturic acid [CEMA], S-phenyl mercapturic acid [S-PMA], 3-hydroxy-1-methylpropylmercapturic acid [3-HMPMA], 3-hydroxypropylmercapturic acid [3-HPMA], 2-hydroxypropylmercapturic acid [2-HPMA], N-acetyl-S-[2-carbamoylethyl] cysteine [AAMA], N-acetyl-S-[2-hydroxy-2-carbamoylethyl]cysteine [GAMA], 2-hydroxybutenylmercapturic acid [2-MHBMA], 2-OH-Fluorene [2-OHFle], 2-Naphthol,1-OH-Phenanthrene [1-OHPhe], urine mutagenicity, 1-hydroxypyrene [1-OHP], and carboxyhemoglobin [COHb]) in adult smokers who reduce cigarette consumption by at least 50% with supplementary (dual) usage of VERVE® Chews or VERVE® Discs to those who continue to smoke cigarettes for 5 and 7 days.
2. To compare 24-hour urinary total NNAL in adult smokers who reduce cigarette consumption by at least 50% with supplementary (dual) usage of VERVE® Chews or VERVE® Discs to those who continue to smoke cigarettes for 5 days.

3. To compare biomarkers of exposure (total NNAL, total NNN, NE, 2-AN, 4-ABP, HEMA, CEMA, S-PMA, 3-HMPMA, 3-HPMA, 2-HPMA, AAMA, GAMA, 2-MHBMA, 2-OHFle, 2-Naphthol, 1-OHPhe, urine mutagenicity, 1-OHP and COHb) in adult smokers who reduce cigarette consumption by at least 50% with supplementary (dual) usage of VERVE® Chews or VERVE® Discs to those who cease from all tobacco use for 5 and 7 days.
4. To compare biomarkers of exposure (total NNAL, total NNN, NE, 2-AN, 4-ABP, HEMA, CEMA, S-PMA, 3-HMPMA, 3-HPMA, 2-HPMA, AAMA, GAMA, 2-MHBMA, 2-OHFle, 2-Naphthol, 1-OHPhe, urine mutagenicity, 1-OHP and COHb) in adult smokers who completely switch to VERVE® Chews or VERVE® Discs to those who continue to smoke cigarettes for 5 and 7 days.
5. To compare biomarkers of exposure (total NNAL, total NNN, NE, 2-AN, 4-ABP, HEMA, CEMA, S-PMA, 3-HMPMA, 3-HPMA, 2-HPMA, AAMA, GAMA, 2-MHBMA, 2-OHFle, 2-Naphthol, 1-OHPhe, urine mutagenicity, 1-OHP and COHb) in adult smokers who completely switch to VERVE® usage to those who cease from all tobacco use for 5 and 7 days.
6. To compare subjective effects (Questionnaire of Smoking Urges – Brief [QSU-Brief] total score, responses to modified cigarette evaluation questionnaire [mCEQ] and the Use the Product Again questionnaire) among subjects who continue to smoke cigarettes, subjects with dual usage of VERVE® Chews or VERVE® Discs and cigarettes, subjects with complete switch to VERVE® Chews or VERVE® Discs, and subjects who cease from all tobacco use for 1, 5 and 7 days.
7. To characterize product use behaviors (such as: number of cigarettes per day, number of VERVE® use per day, average duration of each VERVE® use).

Design

This is an open label, randomized, 6 parallel-group clinical study evaluating changes in exposure to selected HPHC, subjective effects, and product use behavior in adult smokers who are randomly assigned to continue smoking, partially or completely switch to VERVE® Chews or VERVE® Discs products, or stop using any tobacco products for 7 days.

Subjects, who meet all inclusion criteria and none of the exclusion criteria, will check-in to the clinic on Day -3 at a time determined by the clinic. After check-in, subjects will engage in a brief product trial with each flavor of VERVE® Chews (two flavors: blue mint and green mint) and VERVE® Discs (two flavors: blue mint and green mint).This trial period will involve *ad libitum* use for 10 minutes each to allow subjects to become accustomed to using the products. The trial of each flavor of VERVE® Chews or VERVE® Discs product will be separated by approximately 30 minutes (from the start of each product trial). Subjects who are unwilling to use and/or cannot tolerate all four VERVE® products will not continue in the study.

Following completion of the VERVE® product trial on Day -3, subjects will continue to smoke their own brand (OB) cigarettes through 23:00 on Day -3 and from 7:00 to 23:00 on Days -2 and -1. Baseline cigarette consumption for each subject will be determined by the average

number of cigarettes smoked (cigarettes per day [CPD]) on Day -2 and Day -1 and will be used to calculate the CPD allowed for each subject, according to their assigned randomization group, for the remainder of the study. Other baseline study events will include 24-hour urine collections for biomarkers of exposure (total NNAL, total NNN, NE, 2-AN, 4-ABP, HEMA, CEMA, S-PMA, 3-HMPMA, 3-HPMA, 2-HPMA, AAMA, GAMA, 2-MHBMA, 2-OHFle, 2-Naphthol, 1-OHPhe, mutagenicity, and 1-OHP), blood sampling for COHb, and administration of the QSU-Brief and appropriate mCEQ questionnaire on Day -1.

On Day 1, subjects will be randomized into one of the following Groups:

- GROUP 1 (n = 40): Continue Smoking
  Subjects will be asked to continue smoking their OB cigarettes *ad libitum* for 7 days.
- GROUP 2 (n = 40): VERVE® Discs Dual Use
  Subjects will reduce their normal daily cigarette consumption by at least 50% of their baseline CPD and use at least 3 VERVE® Discs per day for 7 days.
- GROUP 3 (n = 40): VERVE® Chews Dual Use
  Subjects will reduce their normal daily cigarette consumption by at least 50% of their baseline CPD and use at least 3 VERVE® Chews per day for 7 days.
- GROUP 4 (n = 30): VERVE® Discs Exclusive Use
  Subjects will completely switch to exclusive use of VERVE® Discs, using at least 3 discs per day for 7 days.
- GROUP 5 (n = 30): VERVE® Chews Exclusive Use
  Subjects will completely switch to exclusive use of VERVE® Chews, using at least 3 chews per day for 7 days.
- GROUP 6 (n = 30): Tobacco Cessation
  Subjects will completely stop all tobacco product usage for 7 days.

Subjects will be randomized into each Group on Day 1 based on gender and CPD.

Subjects will begin using the assigned study products or completely stop using tobacco products on the morning of Day 1 and continue through discharge according to the randomization.

On each study day (Days 1 - 7), subjects in Group 1 will be allowed to smoke their OB cigarettes *ad libitum* (i.e., no restriction on the duration of use or the number of cigarettes per day) from 07:00 through 23:00. Subjects will be allowed to smoke upon request to the clinic staff but will only be allowed 1 cigarette at a time and will be instructed to return each cigarette butt upon completion.

On each study day (Days 1 - 7), subjects in Group 2 and Group 3 will smoke no more than 50% of their baseline CPD and will use the assigned VERVE® product *ad libitum* (i.e., no restrictions on the number of VERVE® products used at once, the number of VERVE® products used per day, or the duration of use) except for 3 specific VERVE® products use opportunities at approximately 11:00, 15:00, and 19:00 each day during which subjects will be asked to keep the assigned VERVE® product in their mouth for at least 10 minutes. Subjects will be allowed to

smoke upon request to the clinic staff but will only be allowed 1 cigarette at a time and will be instructed to return each cigarette butt upon completion. Subjects will be allowed to use the VERVE® product upon request and they will be instructed to return each used VERVE® product upon completion.

On each study day (Days 1 - 7), subjects in Group 4 and Group 5 will use the assigned VERVE® product *ad libitum* (i.e., no restrictions on the number of VERVE® products used at once, the number of VERVE® products used per day, or the duration of use) except for 3 specific VERVE® products use opportunities at approximately 11:00, 15:00, and 19:00 each day during which subjects will be asked to keep the assigned VERVE® product in their mouth for at least 10 minutes. Subjects will be allowed to use the VERVE® product upon request and they will be instructed to return each used VERVE® product upon completion.

On each study day (Days 1 - 7), subjects in Group 6 will completely stop tobacco usage and they will not be allowed to smoke or use VERVE® products.

All product use (CPD, VERVE® product per day (VPD), number of VERVE® products per use, and VERVE® product use duration, [i.e., time of VERVE® product placement in the subjects' mouth, and time it was removed from the subjects' mouth], as appropriate) will be determined to assess product use behavior.

Study events will include 24-hour urine collections for biomarkers of exposure (total NNAL, total NNN, NE, 2-AN, 4-ABP, HEMA, CEMA, S-PMA, 3-HMPMA, 3-HPMA, 2-HPMA, AAMA, GAMA, 2-MHBMA, 2-OHFle, 2-Naphthol, 1-OHPhe, mutagenicity, and 1-OHP) and blood sample collection for COHb assessment. Urine creatinine will be measured in each 24-hour collection and may be used to adjust the concentration values of urine biomarkers (further details will be included in the Statistical Analysis Plan [SAP]). Each 24-hour urine collection (Day-1, Day 5 and Day 7) will be from approximately (± 30 minutes) 07:00 on the scheduled day to approximately 07:00 the following day. The 24-hour urine collection begins on each scheduled day after the first morning void and any void prior to 07:00, and finishes the following morning with the last void collected at approximately 07:00 (including first morning void). Subjects will be specifically instructed to collect all urine voided, and any missed collection during the 24-hour interval will be documented as a deviation.

Subjects will also complete in the moment subjective effects questionnaires, which include:

- QSU-Brief (Appendix 2) – All subjects will complete the QSU-Brief on Days -1, 1, 5, and 7 in the morning at 07:00 (± 30 minutes) before product use, as appropriate, and at 21:30 (± 30 minutes).

- Modified Cigarette Evaluation Questionnaire (mCEQ-C or mCEQ-V; Appendix 3) – the appropriate mCEQ will be administered at 21:30 (± 30 minutes). All subjects will complete the mCEQ-C on Day -1. Subjects in Group 1 will also complete the mCEQ-C on Days 1, 5, and 7. Subjects in Groups 2 and 3 will complete both mCEQ-C and mCEQ-V on Days 1, 5, and 7.Subjects in Groups 4 and 5 will complete mCEQ-V on Days 1, 5, and 7.

- Use the Product Again questionnaire (Appendix 4) – Subjects in Groups 1 - 5 will complete the Use the Product Again questionnaire at 21:30 (± 30 minutes) on Day 7. Subjects in Group 1 will complete Use the Product Again questionnaire for cigarettes. Subjects in Groups 2 and 3 will complete both Use the Product Again questionnaire for cigarettes and VERVE® products. Subjects in Groups 4 and 5 will complete Use the Product Again questionnaire for VERVE® products.

Smoking will be limited to a designated area of the clinic. Subjects permitted to smoke (Groups 1, 2 and 3) will be housed separately from the subjects that exclusively use VERVE® products (Groups 4 and 5) and subjects who stop tobacco product use (Group 6). Study product use will not be permitted from 23:00 to 07:00 each day during the study. For study integrity, all smoked butts and all used VERVE® products will be collected throughout the study. Any illicit use of any tobacco- or nicotine-containing products or sharing of study products will be strictly prohibited and will be grounds for immediate termination from the study at the discretion of the Investigator.

Study Visits

- Screening within 28 days prior to Check-in (Day -3)
- Check-in and clinic confinement (Day -3 through Study Day 8)

Study Population and Sample Size

This study will enroll approximately 210 healthy adult male and female (no more than 60% of either gender) self-affirmed combustible cigarette smokers, 21 - 65 years of age, inclusive (determined at Screening), willing to abstain from smoking and use all four VERVE® products, and who fulfill all inclusion criteria and none of the exclusion criteria. Approximately 210 subjects will be enrolled to the study. All subjects must have an average daily consumption of at least 10 but no more than 30 factory manufactured combustible cigarettes for at least 12 months prior to Screening. Use of other types of tobacco- or nicotine-containing products will not be permitted within 1 week prior to Check-in.

Subjects will not be forced to smoke or use any tobacco product at any time during the study.

Subjects withdrawn from the study may be replaced at the discretion of the Sponsor.

Study Products

Product A: Subject's OB Cigarette (Reference Product)

Product B: Oral tobacco-derived nicotine chews marketed as VERVE® Discs Blue Mint (~1.5 mg nicotine/piece) (Test Product)

Product C: Oral tobacco-derived nicotine chews marketed as VERVE® Discs Green Mint (~1.5 mg nicotine/piece) (Test Product)

Product D: Oral tobacco-derived nicotine chews marketed as VERVE® Chews Blue Mint (~1.5 mg nicotine/piece) (Test Product)

Product E: Oral tobacco-derived nicotine chews marketed as VERVE® Chews Green Mint

(~1.5 mg nicotine/piece) (Test Product)

Outcome Variables

Primary

The primary outcome variable is:

- 24-hour total urinary NNAL (mg/24 hours) excreted on Day 7.

Secondary

The secondary outcome variables are:

- 24-hour urinary total total NNN, NE, 2-AN, 4-ABP, HEMA, CEMA, S-PMA, 3-HMPMA, 3-HPMA, 2-HPMA, AAMA, GAMA, 2-MHBMA, 2-OHFle, 2-Naphthol, 1-OHPhe, mutagenicity, and 1-OHP excreted on Day 5 and Day 7.
- 24-hour urinary total NNAL excreted on Day 5.
- COHb on Day 5 and Day 7.
- QSU-Brief responses and factor scores on Day 1, Day 5, and Day 7.
- Responses to the appropriate mCEQ on Day 1, Day 5, and Day 7.
- Responses to the Use the Product Again questionaire on Day 7.
- Product use behavior daily from Day 1 to Day 7 (i.e., CPD, VPD, number of VERVE® products per use, and the mean duration of each VERVE® product use).

Statistical Methods

SAS software (version 9.3 or higher, Cary, North Carolina) will be used for all data presentation and summarization including summary tables, graphs, and data listings. Statistical methods will be discussed in detail in the SAP.

Statistical Analysis and Data Summarization

All data will be listed by subject number, group, and study day (and time point as necessary), and summarized by group (total and by product flavor for VERVE® groups) and study day (and time point as necessary). 24-hour urinary and COHb biomarker data will be listed and summarized. Absolute and percent change from baseline values will be listed and summarized as appropriate. Descriptive statistics (number of observations [n], arithmetic mean [mean], median, standard deviation [SD], minimum, and maximum) will be used for continuous data variables and frequency counts (n and percentage) for categorical data variables as described in the SAP. Figures will be used to display the data graphically.

Demographics, smoking history, baseline daily cigarette use (Day -2 and Day -1), and baseline Fagerström Test for Cigarette Dependence (FTCD) scores will be summarized overall, and by group with descriptive statistics for continuous variables and frequency counts and percentage for categorical variables.

Urinary Biomarkers and Subjective Effects Questionnaire

Linear mixed models for analysis of covariance (ANCOVA) will be used to compare the Day 5 and Day 7 biomarker values and subjective effects questionnaire scores between groups as described in the study objectives. In the statistical models, the outcome variable will be included as a dependent variable; group, and gender will be included as fixed effects; and baseline values/scores will be included as covariates. The SAS procedure Proc Mixed will be used. The least-squares means (LSM) difference and 95% confidence interval for the LSM difference between the Test and Reference Groups will be provided.

Product Use Behavior

The number of each product used per day and the duration of each VERVE® product used during each product use period will be listed and summarized by study product using descriptive statistics, as appropriate.

Safety Data

Clinical safety evaluations will be performed to ensure that the subjects meet the requirements of the study and to monitor subject safety. Screening safety evaluations will include a physical examination, a 12-lead electrocardiogram (ECG), a clinical laboratory assessment (clinical chemistry, hematology, urinalysis, and serology), vital signs measurements, a urine drug screen, an alcohol breath test, a serum pregnancy test (females only), and follicle-stimulating hormone (FSH; postmenopausal females only) tests. On-study safety evaluations will include a symptom-driven physical examination, vital signs measurements, urine drug screen, alcohol breath test, and urine pregnancy test (females only). End-of-Study (or early termination) safety evaluations will include a symptom-driven physical examination, and vital signs measurements.

Adverse events (AEs) spontaneously reported by the subjects in all groups or observed by the site staff will be monitored from the time of the first product use (VERVE® product trial on Day -3) until the End-of-Study (or early termination). Events captured between Screening and the first study product use (VERVE® product trial on Day -3) will be documented as baseline signs and symptoms (in medical history) and not AEs. Any concomitant medications taken from 30 days prior to Screening through the End-of-Study (or early termination) will also be recorded.

AE data will be coded (to the lowest level term) 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 body system, preferred term, and study product. Frequency counts of AEs will also be summarized by severity and relationship to study product.

SUMMARY OF EVENTS

	Screening	Check-in	Baseline		Study Days								End-of-Study or Early Termination
STUDY EVENT Day	Within 28 days prior to Check-in	-3	-2	-1	1	2	3	4	5	6	7	8	
Informed Consent	X												
Verified Clinical Trials Check	X												
VERVE® Product Trial		X [1]											
Check-in Procedures		X											
Confinement		X	X	X	X	X	X	X	X	X	X	X	
Discharge from clinic													X
Medical History and Demographics	X												
Review of Inclusion/Exclusion Criteria	X	X			X [2]								
Tobacco/Nicotine Product Use History	X												
Pregnancy/FSH Test (females)	X [3]	X [4]											
Physical Examination	X	X [5]											X [5]
Vital Signs	X	X											X
Body Weight, Height, and BMI	X												
12-Lead ECG	X												
HIV, HbsAg, and HCV Serology	X												
Clinical Chemistry, Hematology, and Urinalysis	X												X
Urine Cotinine Screen	X												
Urine Drug Screen and Breath Alcohol Test	X	X											
Review of Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X
FTCD	X												
Ad Libitum Use of OB Cigarettes	X	X	X [6]	X [6]									

	Screening	**Check-in**	**Baseline**		**Study Days**								**End-of-Study or Early Termination**
STUDY EVENT Day	Within 28 days prior to Check-in	-3	-2	-1	1	2	3	4	5	6	7	8	
Randomization					X [7]								
Product Use or Abstinence					X [8]	X [8]	X [8]	X [8]	X [8]	X [8]	X [8]		
CPD and/or VPD Documentation		X	X	X	X [9]	X [9]	X [9]	X [9]	X [9]	X [9]	X [9]		
Blood for COHb Assessment				X [10]					X [10]		X [10]		
24-hour Urine Collection [11]				X					X		X		
QSU-Brief Questionnaire				X [12]	X [12]				X [12]		X [12]		
mCEQ Questionnaire				X [13]	X [13]				X [13]		X [13]		
Use Product Again Questionnaire											X [14]		
Meals [15]		X	X	X	X	X	X	X	X	X	X	X	
Review of AEs		X	X	X	X	X	X	X	X	X	X	X	X
Tobacco Cessation Information	X												X

EXPLANATION OF SUPERSCRIPTS

[1] Brief product trial of each flavor of VERVE® Chews (two flavors [blue mint and green mint]) and VERVE® Discs (two flavors [blue mint and green mint]) (i.e., *ad libitum* use for 10 minutes each). Trial of each flavor of VERVE® Chews or VERVE® Discs product will be separated by approximately 30 minutes (from the start of each product trial).

[2] Prior to randomization

[3] Serum pregnancy (all females) and FSH (to confirm postmenopausal females).

[4] Urine pregnancy test only.

[5] Symptom-driven physical examination.

[6] Following completion of the VERVE® product trial on Day -3, subjects will continue to smoke their own brand (OB) cigarettes through 23:00 on Day -3 and from 07:00 to 23:00 on Days -2 and -1. Baseline cigarette consumption for each subject will be determined by the average number of cigarettes smoked (CPD) on Day -2 and Day -1 and will be used to calculate the CPD allowed for each subject.

[7] After completion of 24-hour urine collection and prior to product use.

[8] Subjects will use the assigned products or be abstinent, as per randomization. All subjects (except Group 6) will use the assigned study product ad libitum (except during meals and study procedures, as appropriate) from 07:00 through 23:00. Subjects in Group 2 and Group 3 will smoke no more than 50% of their baseline CPD and will use assigned VERVE® product ad libitum except for 3 specific VERVE® product use opportunities at 11:00, 15:00, and 19:00 each day during which subjects will be asked to keep VERVE® product in their mouth for at least 10 minutes. Subjects in Group 4 and Group 5 will only use the assigned VERVE® product ad libitum except for 3 specific VERVE® product use opportunities at 11:00, 15:00, and 19:00 each day during which subjects will be asked to keep assigned VERVE® product in their mouth for at least

10 minutes. Subjects will abstain from any product use from the start of the subjective effects questionnaires administration scheduled for 21:30 (±30 minutes) until the COHb sample has been collected on Days -1, 5, and 7.

[9] Product use will be documented for Groups 1, 2, 3, 4, and 5 only. All product use (CPD, VPD, number of VERVE® product per use, and VERVE® products use duration, [i.e., time of VERVE® product placement in the subjects' mouth, and time it was removed from the subjects' mouth], as appropriate) will be determined to assess product use behavior.

[10] The blood sample for COHb will be collected 15 minutes to 45 minutes following the start of subject's in the moment subjective questionnaires (QSU-Brief, mCEQ, and Use Product Again, as appropriate) at 21:30 (±30 minutes). Subjects will abstain from product use, as appropriate, for at least 15 minutes prior to blood draw for COHb.

[11] Each 24-hour urine collection will be from approximately (± 30 minutes) 07:00 to approximately 07:00 on the following day (e.g., from 07:00 on Day -1 to 07:00 on Day 1). Aliquots for analysis of biomarkers of exposure and bio-banking will be taken from each complete pooled 24-hour urine collection.

[12] All subjects will complete the QSU-Brief on Days -1, 1, 5, and 7 in the morning at 07:00 (± 30 minutes) before product use, as appropriate, and at 21:30 (± 30 minutes).

[13] Subjects in Groups 1-5 will complete the appropriate mCEQ at 21:30 (±30 minutes). All subjects will complete mCEQ-C on Day-1. Subjects in Group 1 will also complete the mCEQ-C on Days 1, 5, and 7. Subjects in Groups 2 and 3 will complete both mCEQ-C and mCEQ-V on Days 1, 5, and 7.Subjects in Groups 4 and 5 will complete mCEQ-V on Days 1, 5, and 7.

[14] Subjects in Groups 1-5 will complete the Use the Product Again questionnaire at 21:30 (±30 minutes). Subjects in Group 1 will complete Use the Product Again questionnaire for cigarettes. Subjects in Groups 2 and 3 will complete both Use the Product Again questionnaire for cigarettes and VERVE® products. Subjects in Groups 4 and 5 will complete Use the Product Again questionnaire for VERVE® products.

[15] Standard meals and snacks will be served at appropriate times as determined by the clinic during confinement. The meal menu for Days -2, 4 and 6 will be the same and the meal menu for Days -1, 5 and 7 will be the same.

ABBREVIATIONS AND DEFINITIONS

1-OHP	1-Hydroxypyrene
AE	Adverse event
ALCS	Altria Client Services, LLC
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BLQ	Below the limit of quantitation
BMI	Body mass index
°C	Degrees Celsius
CDMS	Clinical Data Management System
CFR	Code of Federal Regulations
cm	Centimeter
COHb	Carboxyhemoglobin
CPD	Cigarette(s) per day
CV	Coefficient of variation
DMP	Data Management Plan
ECG	Electrocardiogram
eCRF	Electronic case report form
eSPO	Electronic subject reported outcomes
°F	Degrees Fahrenheit
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
FSPTCA	Family Smoking Prevention and Tobacco Control Act
FTCD	Fagerström Test for Cigarette Dependence
g	Gram
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HDPE	High-density polyethylene
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonisation
ID	Identification
IRB	Institutional Review Board
IWRS	Interactive Web Response System
kg	Kilogram(s)
LC	Liquid chromatography
LOQ	Limit of quantitation
LSM	Least-squares means
µg	Microgram
m^2	Square meter(s)
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
MITT	Modified intent to treat
mL	Milliliter(s)
MS	Mass spectrometry
n	Number, sample size, number of observations
NE	Nicotine equivalent(s)
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
NNN	N-nitrosonornicotine
OB	Own Brand
OTDN	Oral Tobacco-Derived Nicotine
PP	Per-protocol

QA	Quality Assurance
QSU-Brief	Questionnaire of Smoking Urges – Brief
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SEM	Standard error of the mean
SHM	Sample Handling Manual
US	United States
VPD	VERVE® product(s) per day
WBC	White blood cell
WHO	World Health Organization

1 INTRODUCTION AND STUDY RATIONALE

1.1 Background

Innovative and novel tobacco-derived nicotine oral products offer reduced risk alternatives to adult consumers of combustible tobacco products. There is overwhelming scientific evidence regarding a risk continuum in the range of tobacco products available currently in the market. According to this body of evidence, combustible tobacco products such as combustible cigarettes are the most risky and non-combustible tobacco products present relatively lower risks. [1]

1.1.1 Background for VERVE® Discs

VERVE® Discs are chewable OTDN nicotine products which are currently available in the commercial market. VERVE® Discs are packaged in tubes. Each tube contains 16 pieces of the product. VERVE® Discs are non-dissolvable OTDN products with two flavors, Blue Mint and Green Mint, with each piece of the product containing approximately 1.5 mg of tobacco-derived nicotine that meets specifications recognized by the US Pharmacopeia.

1.1.1.1 Product Safety Information for VERVE® Discs

Pharmacokinetic Studies

Two clinical studies have been conducted with a prototype form of the OTDN product and two have been conducted with a marketed version of the product.

The first study (CEL-SOL-01-11) included two prototype OTDN products (11-Solid-OOE-45 [1 mg nicotine] and 11-Solid- OOE-46 [2 mg nicotine]). This randomized, single-blind, 2-period crossover study included 9 female and 9 male healthy adult cigarette smokers with a mean age of 37.1 years. The purpose of this study was to characterize the nicotine plasma PK profile from single, 30-minute uses of the products separated by a 24 hour washout. Subjects were instructed to chew the product as desired during the 30-minute product use period. Four (4) subjects (22%) experienced 4 mild AEs with use of the 1 mg product and five subjects (28%) reported 7 mild AEs with use of the 2 mg product. The most common AEs were throat irritation (4 subjects) and dyspepsia (2 subjects).

The second study (COV-VER-01-13) was a randomized, controlled, open-label, parallel group, multicenter, 5-week pilot study to determine changes in biomarkers of exposure in adult smokers allowed *ad libitum* use of VBM-FG2 (a prototype VERVE® Discs product) relative to adult smokers who were not allowed use of VBM-FG2. This study was conducted in 154 adult smokers who were considered to be in overall good health. Subjects were randomized (based on gender, daily cigarette consumption [≤ 20 and > 20 CPD], and quit attempts [any quit attempts/no quit attempts]) to Test (allowed VBM-FG2 use) or Control (not allowed VBM-FG2 use) treatment in a 3:2 ratio (92 subjects randomized to Test: 62 subjects randomized to Control). Twenty-five (25) subjects (27.2%) in the Test group experienced 39 mild AEs and 2 moderate AEs compared to 7 subjects

(11.3%) in the Control group who experienced 17 mild AEs. The most common AEs in the Test group were mild cough (6 subjects) and mild oropharyngeal pain (4 subjects).

Two studies (ALCS-RA-16-19-VRV and ALCS-RA-16-26-VRV) were completed using the same marketed versions of the VERVE® Discs as will be used in the current study. The purpose of these studies was to characterize the nicotine plasma PK profile and subjective measures associated with use of VERVE® Discs Blue Mint and Green Mint compared to OB cigarettes and Nicorette® Fresh Mint™ nicotine polacrilex gum (2 mg). Both were randomized, single-blind, 4-period crossover studies, and prior to Check-in for clinical conduct, subjects participated in a 5-day at-home product trial period with 16 pieces of each VERVE® Disc product. On each in-clinic study day, subjects used the assigned product under controlled conditions (smoked a single cigarette with 10 inhalations taken at approximately 30-second intervals, used one piece of the VERVE® product for 30 minutes, or "chewed and parked" one piece of nicotine gum for 30 minutes according to the product's instructions for use).

ALCS-RA-16-19-VRV included 14 female and 16 male healthy adult cigarette smokers in the product trial period and 11 females and 14 males in the in-clinic period. During the product trial period, 5 of 30 subjects experienced a total of seven mild AEs (two episodes of headache and one episode each of salivary hypersecretion, back pain, anxiety, irritability, and rash). The PI considered only the salivary hypersecretion to be possibly related to the VERVE® products. During in-clinic period, four subjects experienced five mild AEs (two episodes of headache and one episode each of tinnitus, dizziness, and hot flush) with use of the Blue Mint product and two subjects experienced two mild AEs (musculoskeletal discomfort and pruritis) with use of the Green Mint product. None of the AEs experienced during the in-clinic period were considered to be related to the VERVE® products by the PI.

ALCS-RA-16-26-VRV included 10 female and 29 male healthy adult cigarette smokers in the product trial period and 9 females and 19 males were included in the in-clinic period. During the product trial period, 4 of 39 subjects experienced four mild AEs (two episodes of dyspepsia and one episode each of dizziness and sinus congestion) and two moderate AEs (gingival swelling and toothache). The PI considered one episode of dyspepsia and dizziness to be possibly related to the VERVE® products. During in-clinic period, three subjects experienced four mild AEs (constipation, chills, back pain, and rhinorrhea) with use of the Blue Mint product and two subjects experienced four mild AEs (two episodes of vessel puncture site haemorrhage and one episode each of, vessel puncture site haematoma and vessel puncture site pain) with use of the Green Mint product. None of the AEs experienced during the in-clinic period were considered to be related to the VERVE® products by the PI.

Consumer Response Center Data

Altria Client Services LLC (ALCS) has continuously monitored consumer calls to the Consumer Response Center (CRC) regarding VERVE® Discs products. As of December 31, 2017, consumers reported via the Consumer Response Center three adverse events related to the use of the Blue Mint VERVE® Discs product ("choking" [1] and "tooth damage" [2]) and one related to the use of the Harvest Blend VERVE® Discs product for "headache" (over 145,000 tubes distributed for sale with 16 pieces per tube).

ALCS has also conducted an assessment of the ingredients and components of the specific test products. Based on these assessments, the test products are considered toxicologically acceptable and deemed suitable for human consumption, and it is anticipated that the products in this study will be well-tolerated.

1.1.2 Background for VERVE® Chews

VERVE® Chews are OTDN products which are currently available in the commercial market. The non-dissolvable OTDN chewable products are packaged in tubes. Each tube contains 12 pieces of the product. The non-dissolvable OTDN products are available in two flavors, Blue Mint and Green Mint, with each piece of the product containing approximately 1.5 mg of tobacco-derived nicotine that meets specifications recognized by the US Pharmacopeia.

1.1.3 Product Safety Information for VERVE® Chews

Pharmacokinetic Studies

One study (ALCS-RA-16-23-VRV) has been completed using the same marketed versions of the VERVE® Chews as will be used in the current study. The purpose of the previous study was to characterize the nicotine plasma PK profile and subjective measures associated with use of VERVE® Chews Blue Mint and Green Mint compared to a single OB cigarettes and 30 minutes of use of Nicorette® Fresh Mint™ nicotine polacrilex gum (2 mg). This was a randomized, single-blind, 4-period crossover study, and prior to Check-in for clinical conduct, subjects participated in a 5-day at-home product trial period with 12 pieces of each VERVE® Chews product. On each study day, subjects used the assigned product under controlled conditions (smoked a single cigarette with 10 inhalations taken at approximately 30-second intervals, used one piece of VERVE® product for 30 minutes, or "chewed and parked" one piece of nicotine gum for 30 minutes according to the product's instructions for use). Ten female and 20 male healthy adult cigarette smokers participated in the product trial period and 10 females and 18 males participated in the in-clinic period. During the product trial period, 2 of 30 subjects experienced a total of three mild AEs (constipation, headache, and vessel puncture site pain). None were considered to be related to the VERVE® products by the PI. During the in-clinic period, two subjects experienced two mild AEs (vessel puncture site pain and epistaxis) with use of the Blue Mint product and two subjects reported four mild AEs (two episodes of headache and two

episodes of rash) with use of the Green Mint product. Only one episode of headache was considered to be possibly related to use of the VERVE® products.

Consumer Response Center Data

ALCS has continuously monitored consumer calls to the CRC regarding the non-dissolvable OTDN products since the market launch in May 2015. As of December 31, 2017, there have been no Adverse Events reported in the CRC Datamart for the non-dissolvable OTDN products (over 19,000 tubes distributed for sale).

ALCS has also conducted an assessment of the ingredients and components of the specific test products. Based on these assessments, the test products are considered toxicologically acceptable and deemed suitable for human consumption, and it is anticipated that the products in this study will be well-tolerated.

1.1.4 Product Safety Information

The study products are subject's OB cigarettes, VERVE® Discs, and VERVE® Chews products. Subjects will be informed of the four US Surgeon General's warnings required for cigarettes and FDA warning required for VERVE® Discs and VERVE® Chews.

Cigarettes have the following warnings**:**

SURGEON GENERAL'S WARNING: Smoking Causes Lung Cancer, Heart Disease, Emphysema, and May Complicate Pregnancy.

SURGEON GENERAL'S WARNING: Quitting Smoking Now Greatly Reduces Serious Risks to Your Health.

SURGEON GENERAL'S WARNING: Smoking By Pregnant Women May Result in Fetal Injury, Premature Birth, and Low Birth Weight.

SURGEON GENERAL'S WARNING: Cigarette Smoke Contains Carbon Monoxide.

VERVE® Discs and Chews have the following warning:

"WARNING: This product contains nicotine. Nicotine is an addictive chemical."

Additional health information for VERVE® Discs and Chews found on the U.S. Smokeless Tobacco Company website: "This Product contains nicotine, which is addictive. Nicotine can harm your baby if you are pregnant or nursing. Nicotine can increase your heart rate, blood pressure and aggravate diabetes. Nicotine can cause dizziness, nausea and stomach pain."

VERVE® Chews has the following additional allergen health information:

"PHENYLKETONURICS: CONTAINS PHENYLALANINE."

1.2 Purpose of This Study

The purpose of this study is to evaluate changes in exposure to selected HPHC by measuring biomarkers in adult smokers who partially or completely switch to OTDN VERVE® Chews or VERVE® Discs compared to those who continue smoking cigarettes or stop using all tobacco products.

1.3 Hypothesis

Reducing daily cigarette consumption by at least 50% and using VERVE® products for 7 days will result in a statistically significant reduction in 24-hour urinary total NNAL on Day 7 compared to continued cigarette smoking.

2 STUDY OBJECTIVES

The objectives of the study are:

Primary Objective:

To compare 24-hour urinary total NNAL in adult smokers who reduce cigarette consumption by at least 50% with supplementary (dual) usage of VERVE® Chews or VERVE® Discs to those who continue to smoke cigarettes for 7 days.

Secondary Objectives:

1. To compare biomarkers of exposure (total NNN, NE, 2-AN, 4-ABP, HEMA, CEMA, S-PMA, 3-HMPMA, 3-HPMA, 2-HPMA, AAMA, GAMA, 2-MHBMA, 2-OHFle, 2-Naphthol, 1-OHPhe, urine mutagenicity, 1-OHP and COHb) in adult smokers who reduce cigarette consumption by at least 50% with supplementary (dual) usage of VERVE® Chews or VERVE® Discs to those who continue to smoke cigarettes for 5 and 7 days
2. To compare 24-hour urinary total NNAL in adult smokers who reduce cigarette consumption by at least 50% with supplementary (dual) usage of VERVE® Chews or VERVE® Discs to those who continue to smoke cigarettes for 5 days
3. To compare biomarkers of exposure (total NNAL, total NNN, NE, 2-AN, 4-ABP, HEMA, CEMA, S-PMA, 3-HMPMA, 3-HPMA, 2-HPMA, AAMA, GAMA, 2-MHBMA, 2-OHFle, 2-Naphthol, 1-OHPhe, urine mutagenicity, 1-OHP and COHb) in adult smokers who reduce cigarette consumption by at least 50% with supplementary (dual) usage of VERVE® Chews or VERVE® Discs to those who cease from all tobacco use for 5 and 7 days.
4. To compare biomarkers of exposure (total NNAL, total NNN, NE, 2-AN, 4-ABP, HEMA, CEMA, S-PMA, 3-HMPMA, 3-HPMA, 2-HPMA, AAMA, GAMA, 2-MHBMA, 2-OHFle, 2-Naphthol, 1-OHPhe, urine mutagenicity, 1-OHP and COHb) in adult smokers who completely switch to VERVE® Chews or VERVE® Discs to those who continue to smoke cigarettes for 5 and 7 days.
5. To compare biomarkers of exposure (total NNAL, total NNN, NE, 2-AN, 4-ABP, HEMA, CEMA, S-PMA, 3-HMPMA, 3-HPMA, 2-HPMA, AAMA, GAMA,

2-MHBMA, 2-OHFle, 2-Naphthol, 1-OHPhe, urine mutagenicity, 1-OHP and COHb) in adult smokers who completely switch to VERVE® usage to those who cease from all tobacco use for 5 and 7 days.

6. To compare subjective effects (Questionnaire of Smoking Urges – Brief [QSU-Brief] total score, responses to modified cigarette evaluation questionnaire [mCEQ] and the Use the Product Again questionnaire) among subjects who continue to smoke cigarettes, subjects with dual usage of VERVE® Chews or VERVE® Discs and cigarettes, subjects with complete switch to VERVE® Chews or VERVE® Discs, and subjects who cease from all tobacco use for 1, 5 and 7 days.
7. To characterize product use behaviors (such as: number of cigarettes per day, number of VERVE® use per day, average duration of each VERVE® use).

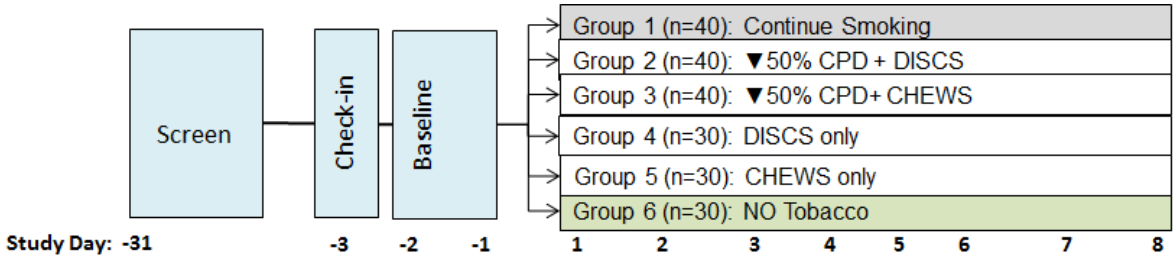
3 SUMMARY OF STUDY DESIGN

3.1 Design and Clinical Procedures

This is an open label, randomized, 6 parallel-group clinical study evaluating changes in exposure to selected HPHC, subjective effects, and product use behavior in adult smokers who are randomly assigned to continue smoking, partially or completely switch to VERVE® Chews or VERVE® Discs products, or stop using any tobacco products for 7 days.

The overall design of the study is shown in Figure 1.

Figure 1: Overall Study Design



Study Products:

Product A: Subject's OB Cigarette (Reference Product)

Product B: Oral tobacco-derived nicotine chews marketed as VERVE® Discs Blue Mint (~1.5 mg nicotine/piece) (Test Product)

Product C: Oral tobacco-derived nicotine chews marketed as VERVE® Discs Green Mint (~1.5 mg nicotine/piece) (Test Product)

Product D: Oral tobacco-derived nicotine chews marketed as VERVE® Chews Blue Mint (~1.5 mg nicotine/piece) (Test Product)

Product E: Oral tobacco-derived nicotine chews marketed as VERVE® Chews Green Mint (~1.5 mg nicotine/piece) (Test Product)

This study will enroll healthy adult male and female (no more than 60% of either gender) self-affirmed combustible cigarette smokers, 21 - 65 years of age, inclusive (determined at Screening), willing to abstain from smoking and use all four VERVE® products, and who fulfill all inclusion criteria and none of the exclusion criteria. Approximately 210 subjects will be enrolled to the study. All subjects must have an average daily consumption of at least 10 but no more than 30 factory manufactured combustible cigarettes for at least 12 months prior to Screening. Use of other types of tobacco- or nicotine-containing products will not be permitted within 1 week prior to Check-in.

Subjects will not be forced to smoke or use any tobacco product at any time during the study.

Subjects, who meet all inclusion criteria and none of the exclusion criteria, will check-in to the clinic on Day -3 at a time determined by the clinic. After check-in, subjects will engage in a brief product trial with each flavor of VERVE® Chews (two flavors: blue mint and green mint) and VERVE® Discs (two flavors: blue mint and green mint). This trial period will involve *ad libitum* use for 10 minutes each to allow subjects to become accustomed to using the products. The trial of each flavor of VERVE® Chews or VERVE® Discs product will be separated by approximately 30 minutes (from the start of each product trial). Subjects who are unwilling to use and/or cannot tolerate all four VERVE® products will not continue in the study.

Following completion of the VERVE® product trial on Day -3, subjects will continue to smoke their OB cigarettes through 23:00 on Day -3 and from 07:00 to 23:00 on Days -2 and -1. Baseline cigarette consumption for each subject will be determined by the average number of cigarettes smoked (CPD) on Day -2 and Day -1 and will be used to calculate the CPD allowed for each subject in Group 2 or Group 3, according to their assigned randomization group, for the remainder of the study. Other baseline study events will include 24-hour urine collections for biomarkers of exposure (total NNAL, total NNN, NE, 2-AN, 4-ABP, HEMA, CEMA, S-PMA, 3-HMPMA, 3-HPMA, 2-HPMA, AAMA, GAMA, 2-MHBMA, 2-OHFle, 2-Naphthol, 1-OHPhe, mutagenicity, and 1-OHP), blood sampling for COHb, and administration of the QSU-Brief and the appropriate mCEQ questionnaire on Day -1.

On Day 1, subjects will be randomized into one of the following Groups:

- GROUP 1 (n = 40): Continue Smoking

  Subjects will be asked to continue smoking their OB cigarettes *ad libitum* for 7 days.

- GROUP 2 (n = 40): VERVE® Discs Dual Use

  Subjects will reduce their normal daily cigarette consumption by at least 50% of their baseline CPD and use at least 3 VERVE® Discs per day for 7 days.

- GROUP 3 (n = 40): VERVE® Chews Dual Use

  Subjects will reduce their normal daily cigarette consumption by at least 50% of their baseline CPD and use at least 3 VERVE® Chews per day for 7 days.

- GROUP 4 (n = 30): VERVE® Discs Exclusive Use
  Subjects will completely switch to exclusive use of VERVE® Discs, using at least 3 discs per day for 7 days.

- GROUP 5 (n = 30): VERVE® Chews Exclusive Use
  Subjects will completely switch to exclusive use of VERVE® Chews, using at least 3 chews per day for 7 days.

- GROUP 6 (n = 30): Tobacco Cessation
  Subjects will completely stop all tobacco product usage for 7 days.

Subjects will be randomized into each Group on Day 1 based on gender and CPD.

Subjects will begin using the assigned study products or completely stop using tobacco products on the morning of Day 1 and continue through discharge according to the randomization.

On each study day (Days 1 - 7), subjects in Group 1 will be allowed to smoke their OB cigarettes *ad libitum* (i.e., no restriction on the duration of use or the number of cigarettes per day) from 07:00 through 23:00. Subjects will be allowed to smoke upon request to the clinic staff but will only be allowed 1 cigarette at a time and will be instructed to return each cigarette butt upon completion.

On each study day (Days 1 - 7), subjects in Group 2 and Group 3 will smoke no more than 50% of their baseline CPD and will use the assigned VERVE® product *ad libitum* (i.e., no restrictions on the number of VERVE® products used at once, the number of VERVE® products used per day, or the duration of use) except for 3 specific VERVE® products use opportunities at approximately 11:00, 15:00, and 19:00 each day during which subjects will be asked to keep the assigned VERVE® product in their mouth for at least 10 minutes. Subjects will be allowed to smoke upon request to the clinic staff but will only be allowed 1 cigarette at a time and will be instructed to return each cigarette butt upon completion. Subjects will be allowed to use the VERVE® product upon request and they will be instructed to return each used VERVE® product upon completion.

On each study day (Days 1 - 7), subjects in Group 4 and Group 5 will use the assigned VERVE® product *ad libitum* (i.e., no restrictions on the number of VERVE® products used at once, the number of VERVE® products used per day, or the duration of use) except for 3 specific VERVE® products use opportunities at approximately 11:00, 15:00, and 19:00 each day during which subjects will be asked to keep the assigned VERVE® product in their mouth for at least 10 minutes. Subjects will be allowed to use the VERVE® product upon request and they will be instructed to return each used VERVE® product upon completion.

On each study day (Days 1 - 7), subjects in Group 6 will completely stop cigarette use and they will not be allowed to smoke or use VERVE® products.

All product use (CPD, VPD, number of VERVE® product per use, and VERVE® product use duration, [i.e., time of VERVE® product placement in the subjects' mouth, and time it was removed from the subjects' mouth], as appropriate) will be determined to assess product use behavior.

Study events will include 24-hour urine collections for biomarkers of exposure (total NNAL, total NNN, NE, 2-AN, 4-ABP, HEMA, CEMA, S-PMA, 3-HMPMA, 3-HPMA, 2-HPMA, AAMA, GAMA, 2-MHBMA, 2-OHFle, 2-Naphthol, 1-OHPhe, mutagenicity, and 1-OHP) and blood sample collection for COHb assessment. Urine creatinine will be measured in each 24-hour collection and may be used to adjust the concentration values of urine biomarkers (further details will be included in the SAP). Each 24-hour urine collection (Day -1. Day 5 and Day 7) will be from approximately (± 30 minutes) 07:00 on the scheduled day to approximately 07:00 the following day. The 24-hour urine collection begins on each scheduled day after the first morning void and any void prior to 07:00, and finishes the following morning with the last void collected at approximately 07:00 (including first morning void). Subjects will be specifically instructed to collect all urine voided, and any missed collection during the 24-hour interval will be documented as a deviation.

Subjects will also complete in the moment subjective effects questionnaires, which include:

- QSU-Brief (Appendix 2) - All subjects will complete the QSU-Brief on Days -1, 1, 5, and 7 in the morning at 07:00 (± 30 minutes) before product use, as appropriate, and at 21:30 (± 30 minutes).
- Modified Cigarette Evaluation Questionnaire (mCEQ; Appendix 3) – the appropriate mCEQ will be administered at 21:30 (± 30 minutes). All subjects will complete the mCEQ-C on Day -1. Subjects in Group 1 will also complete the mCEQ-C on Days 1, 5, and 7. Subjects in Groups 2 and 3 will complete both mCEQ-C and mCEQ-V on Days 1, 5, and 7.Subjects in Groups 4 and 5 will complete mCEQ-V on Days 1, 5, and 7.
- Use the Product Again questionnaire (Appendix 4) – Subjects in Groups 1 - 5 will complete the Use the Product Again questionnaire at 21:30 (± 30 minutes) on Day 7. Subjects in Group 1 will complete Use the Product Again questionnaire for cigarettes. Subjects in Groups 2 and 3 will complete both Use the Product Again questionnaire for cigarettes and VERVE® products. Subjects in Groups 4 and 5 will complete Use the Product Again questionnaire for VERVE® products.

Smoking will be limited to a designated area of the clinic. Subjects permitted to smoke (Groups 1, 2 and 3) will be housed separately from the subjects that exclusively use VERVE® products (Groups 4 and 5) and subjects who stop tobacco product use (Group 6). Study product use will not be permitted from

23:00 to 07:00 each day during the study. For study integrity, all smoked butts and all used VERVE® products will be collected throughout the study. Any illicit use of any tobacco- or nicotine-containing products or sharing of study products will be strictly prohibited and will be grounds for immediate termination from the study at the discretion of the Investigator.

3.2 Clinical Safety Evaluations

Clinical safety evaluations will be performed to ensure that the subjects meet the requirements of the study and to monitor subject safety. These will include physical examinations, vital signs, ECG, clinical laboratory tests (clinical chemistry, hematology, urinalysis, and serology), urine drug screens, breath alcohol tests, and pregnancy tests (females only) at designated time points during the study. AEs will be monitored and recorded from the time of the first product use (VERVE® product trial at Check-in) through the End-of-Study (or Early Termination).

For all scheduled clinical laboratory tests, approximately 30 mL of blood will be collected from each subject.

4 SUBJECT SELECTION

The following inclusion and exclusion criteria must be satisfied.

4.1 Inclusion Criteria

4.1.1. Voluntary consent to participate in this study documented on the signed informed consent form (ICF).

4.1.2. Healthy adult males and females 21 to 65 years of age, inclusive, at Screening.

4.1.3. Smoking history of an average of at least 10 but no more than 30 factory manufactured combustible cigarettes daily for at least 1 year prior to Screening. Brief periods (i.e., up to 7 consecutive days) of non-smoking during the 3 months prior to Screening (e.g., due to illness or participation in a study where smoking was prohibited) will be permitted.

4.1.4. Positive urine cotinine (≥ 500 ng/mL) at Screening.

4.1.5. Female subjects who are heterosexually active and of childbearing potential (e.g., neither surgically sterile at least 6 months prior to Check-in nor postmenopausal with amenorrhea for at least 1 year prior to Check-in with FSH levels consistent with postmenopausal status) must have been using one of the following forms of contraception for the time period indicated and agree to continue using it through completion of the study:

- hormonal (e.g., oral, vaginal ring, transdermal patch, implant, injection) consistently for at least 3 months prior to Check-in,

- double barrier (i.e., condom with spermicide or diaphragm with spermicide) consistently for at least 4 weeks prior to Check-in,
- intrauterine device for at least 4 months prior to Check-in,
- exclusive partner who has been vasectomized for at least 6 months (inclusive) prior to Check-in.

Female subjects of childbearing potential who are not currently engaging in heterosexual intercourse must agree to use one of the above methods of birth control through completion of study, in the event that they have heterosexual intercourse during the course of the study.

4.1.6. Female subjects who are of non-childbearing potential must have undergone one of the following sterilization procedures at least 6 months prior to Check-in:

- hysteroscopic sterilization (including Essure® or similar nonsurgical sterilization procedures);
- bilateral tubal ligation or bilateral salpingectomy;
- hysterectomy;
- bilateral oophorectomy;

Or be postmenopausal with amenorrhea for at least 1 year prior to Check-in and have FSH levels consistent with postmenopausal status.

4.1.7. Willing to comply with the requirements of the study.

4.1.8. Willing to use all four VERVE® test products after products trial at Check-in.

4.1.9. Willing and able to abstain from cigarettes from Day 1 through the End of the study.

4.2 Exclusion Criteria

Subjects will be excluded from the study if there is evidence of any of the following criteria at Screening, Check-in, or prior to randomization, as appropriate.

4.2.1. Use of any type of tobacco- or nicotine-containing products other than manufactured cigarettes (e.g., e-vapor products, roll-your-own cigarettes, bidis, snuff, nicotine inhaler, pipe, cigar, chewing tobacco, nicotine patch, nicotine spray, nicotine lozenge, or nicotine gum) in the 7 days prior to Check-in

4.2.2. Self-reported puffers (i.e., adult smokers who draw smoke from the cigarette into the mouth and throat but do not inhale).

4.2.3. Planning to quit smoking in the next 30 days (from Screening visit).

4.2.4. History or presence of clinically significant gastrointestinal, renal, hepatic, neurologic, hematologic, endocrine, oncologic, urologic, existing respiratory diseases, immunologic, psychiatric, lymphatic, or cardiovascular disease, or any other condition that, in the opinion of the Investigator, would jeopardize the safety of the subject or impact the validity of the study results.

4.2.5. Clinically significant abnormal findings on the vital signs, physical examination, medical history, ECG, or clinical laboratory results, in the opinion of the Investigator.

4.2.6. Positive test for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV) at Screening.

4.2.7. History or presence of any type of malignant tumors.

4.2.8. Current evidence or any history of congestive heart failure.

4.2.9. Diabetes mellitus (fasting glucose ≥ 126 mg/L [7 mmol/L]) that is not controlled by diet/exercise alone, in the opinion of the Investigator.

4.2.10. An acute illness (e.g., upper respiratory infection, viral infection) requiring treatment with prescribed medicines within 2 weeks prior to Check-in.

4.2.11. Dentition that prevents subjects from chewing VERVE® products.

4.2.12. Allergic to or cannot tolerate mint flavoring agents or phenylalanine.

4.2.13. Any planned surgery from the time of Screening through the End-of-Study.

4.2.14. History of drug or alcohol abuse within 24 months prior to Check-in.

4.2.15. Fever (i.e., body temperature > 100.5°F) at Screening or Check-in. One recheck may be performed at the Investigator's discretion.

4.2.16. Body mass index (BMI) greater than 40.0 kg/m^2 or less than 18.0 kg/m^2 at Screening.

4.2.17. Systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 90 mmHg at Screening or Check-in, measured after being seated for at least 10 minutes. One recheck may be performed at the Investigator's discretion.

4.2.18. Clinically significant ECG abnormalities, in the opinion of the Investigator.

4.2.19. Estimated creatinine clearance (by Cockcroft-Gault equation) < 80 mL/minute at Screening.

4.2.20. Serum alanine aminotransferase (ALT) ≥ 1.5 times the upper limit of normal and/or aspartate aminotransferase (AST) ≥ 1.5 times the upper limit of normal at Screening.

4.2.21. Positive screen for alcohol (breath) or any of the following drugs of abuse (urine), regardless of the reason of use: amphetamines,

methamphetamines, opiates, cannabinoids, or cocaine at Screening or Check-in.

4.2.22. Female subjects who are pregnant (positive serum pregnancy test at Screening or urine pregnancy test at Check-in), lactating, or intend to become pregnant from Screening through the End-of-Study.

4.2.23. Use of prescription or over-the-counter bronchodilator medication (e.g., inhaled or oral ß-agonists) within 12 months prior to Check-in.

4.2.24. Use of medications or foods known or are suspected to interact with cytochrome P450 2A6 (including, but not limited to, amiodarone, amlodipine, amobarbital, buprenorphine, clofibrate, clotrimazole, desipramine, disulfiram, entacapone, fenofibrate, isoniazid, grapefruit, ketoconazole, letrozole, methimazole, methoxsalen, metyrapone, miconazole, modafinil, orphenadrine, pentobarbital, phenobarbital, pilocarpine, primidone, propoxyphene, quinidine, rifampicin, rifampin, secobarbital, selegiline, sulconazole, tioconazole, tranylcypromine) within 14 days or 5 half-lives of the drug, whichever is longer, prior to Check-in or during the study.

4.2.25. Use of antibiotic treatment within 2 weeks prior to Check-in.

4.2.26. Plasma donation within 7 days prior to Check-in.

4.2.27. Donation of blood or blood products (with the exception of plasma as noted above), had significant blood loss, or received whole blood or a blood product transfusion within 56 days prior to Check-in.

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

4.2.29. Participation in two or more ALCS studies within the past 12-month period prior to Check-in.

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

4.2.31. Subject or a first-degree relative (i.e., parent, sibling, child, spouse/partner) is a current employee of the study site.

4.3 Restrictions

4.3.1. No tobacco- or nicotine-containing product use from Day 1 until the End-of-Study except per protocol except at the designated time when only the study products or subjects' OB cigarettes are allowed.

4.3.2. No foods or beverages containing alcohol for 48 hours prior to Screening, Check-in or during confinement.

4.3.3. No broiled or pan-fried meat, pre-cooked meats (*e.g.,* tuna, ham, corned beef, smoked lunchmeats), bacon, or sausage for 48 hours prior to Check-in or during confinement.

4.3.4. Caffeinated beverages (up to 1 cup per meal) may be served during confinement.

4.3.5. No strenuous exercise for 48 hours prior to Check-in or during confinement.

4.4 Medications

Any concomitant medications taken from 30 days prior to Screening through the End-of-Study (or upon early termination) will be recorded.

Prohibited medications are included in the exclusion criteria.

Stable doses (i.e., no dosage adjustments within 30 days prior to Screening) of prescription or over-the-counter medications required to treat an Investigator-approved disease or condition are permitted at the discretion of the Investigator. Hormonal contraceptives (e.g., oral, vaginal ring, transdermal patch, implant, injection) and hormonal replacement therapy are permitted. Occasional use of over-the-counter analgesics (e.g., acetaminophen, ibuprofen), antihistamines, and nasal decongestants are permitted as needed to treat AEs experienced by subjects at the discretion of the Investigator. Exceptions may be permitted at the discretion of the Investigator in consultation with the Sponsor, providing the medication in question would have no impact on the study. Any exceptions will be documented. Note that some decongestants might cause a positive urine drug screen result and therefore their use should be discouraged within 5 - 7 days of those tests.

5 SCREENING

The Investigator or his/her designee must perform the following procedures within 28 days prior to Day -3 (Check-in). Tobacco cessation information (details in Section 7.11) will also be provided during this time.

5.1 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 Screening/study procedures being performed. Written acknowledgment of the receipt of the full informed consent and the subject's freely tendered offer to participate will be obtained from each subject in the study and documented in the source documents. Each subject will receive a signed and dated copy of the ICF.

5.2 Medical History/Demographic Data/Record of Concomitant Medication

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

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

5.3 Review Inclusion/Exclusion Criteria

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

5.4 Tobacco/Nicotine Product Use History

Subjects will be required to report previous tobacco-product and nicotine-product use histories to satisfy the study inclusion and exclusion criteria. Smoking history must include usual number of cigarettes smoked per day and the number of years the subject has smoked.

The following characteristics of the OB cigarettes used will be documented: brand, brand style, flavor, and cigarette size. The average number of CPD (single number, not a range) will also be documented.

5.5 Physical Examination

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

5.5.2. Vital signs (respiratory rate, pulse rate, blood pressure, and body temperature) in the sitting position after at least 10 minutes of rest (with the exception of body temperature) and at least 15 minutes after the last cigarette smoked or VERVE® product used. One recheck of vital sign(s) may be performed at the Investigator's discretion.

5.5.3. General physical examination with observations and questioning by the Investigator or his/her designee.

5.5.4. 12-lead ECG in the supine position after at least 10 minutes of rest and at least 15 minutes after the last nicotine-containing product used. The QT interval corrected using the Bazett's formula will be recorded.

5.6 Clinical Laboratory Tests

All clinical laboratory tests will be conducted by a laboratory accredited by 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 or his/her designee. One recheck may be performed at the Investigator's discretion for all clinical laboratory tests except for the urine drug screen, breath alcohol test, and urine cotinine.

5.6.1. Hematology, consisting of hemoglobin, hematocrit, red blood cell (RBC), white blood cell (WBC) with differential, and platelet count.

5.6.2. Clinical chemistry (after fasting for at least 8 hours; fasting requirements may be waived in the case of rechecks, as appropriate), consisting of sodium, potassium, chloride, bicarbonate, ALT, AST, blood urea nitrogen, alkaline phosphatase, total bilirubin, glucose, creatinine (at Screening, creatinine clearance will be calculated using Cockcroft-Gault formula), total protein, uric acid, and albumin.

5.6.3. 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.

5.6.4. Serology test for HIV, HBsAg, and HCV.

5.6.5. Urine cotinine; a positive quantitative test (≥ 500 ng/mL) will be required for participation in the study.

5.6.6. Urine screen for amphetamines, methamphetamines, opiates, cannabinoids, and cocaine and breath test for alcohol. Subjects who test positive for alcohol and/or any of the drugs listed will be considered screen failures and will not complete the remaining screening assessments at this visit (with the exception of the Demographics and Tobacco/Nicotine Product Use History questionnaire).

5.6.7. Serum (at Screening) and Urine (at Check-in) pregnancy test for all females and serum FSH test for females reporting to be postmenopausal to confirm postmenopausal status.

5.7 Product Trial

Subjects will have the opportunity to try both VERVE® Discs and VERVE® Chews following completion of check-in procedures on Day -3. Subjects will engage in a brief product trial with each flavor of VERVE® Chews (two flavors

[blue mint and green mint]) and VERVE® Discs (two flavors [blue mint and green mint]) (i.e., *ad libitum* use for 10 minutes each) to get accustomed to using the products. Trial of each flavor of VERVE® Chews or VERVE® Discs product will be separated by approximately 30 minutes (from the start of each product trial). Subjects who are unwilling to use and/or cannot tolerate all four VERVE® products will not continue in the study.

5.8 Fagerström Test for Cigarette Dependence (FTCD)

Subjects will complete the FTCD questionnaire (Appendix 1).

6 MATERIALS

6.1 Study Products

Product A: Subject's OB Cigarette (Reference Product)

Product B: Oral tobacco-derived nicotine chews marketed as VERVE® Discs Blue Mint (~1.5 mg nicotine/piece) (Test Product)

Product C: Oral tobacco-derived nicotine chews marketed as VERVE® Discs Green Mint (~1.5 mg nicotine/piece) (Test Product)

Product D: Oral tobacco-derived nicotine chews marketed as VERVE® Chews Blue Mint (~1.5 mg nicotine/piece) (Test Product)

Product E: Oral tobacco-derived nicotine chews marketed as VERVE® Chews Green Mint (~1.5 mg nicotine/piece) (Test Product)

6.2 Study Materials Accountability, Storage, and Preparation

All study products will be provided by the Sponsor. The site staff will coordinate shipping of all study products from the Sponsor. The study staff will document the date each shipment was received and recorded in the inventory records. The study staff will document and reconcile the total number of study products shipped to the site, the total number of study products used during the study, and the total number of unused study products remaining at the end of clinical conduct.

The site pharmacy will retain and store 2 packages (16 discs per package) of each flavor VERVE® Discs product and 3 packs (12 pieces per pack) of each flavor VERVE® Chews products at the site until finalization of the final study report.

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

All subjects will be required to provide a sufficient supply of their OB combustible cigarettes to the study site for use from Check-in through Day 7 (10 days) in case they are randomized to continue smoking their OB cigarettes. This supply will be calculated from the number of CPD reported at Screening plus

an additional 20% rounded up to the next pack. For example, a subject reporting to smoke 15 cigarettes per day would bring nine packs (15 cigarettes per day x 10 days = 150 cigarettes + an additional 30 cigarettes = 180 cigarettes total [9 packs]). The clinical site will purchase additional cigarettes if subjects run out of cigarettes during the study.

Study products for dispensing to subjects will be prepared each day. Individual study product dispensing records will be maintained by the site pharmacy for each subject.

Individual study product dispensing records will be maintained by the site for each subject and must include the date and time that each cigarette and VERVE® product was dispensed and each cigarette butt and VERVE® product was returned by each subject (subjects will be requested to return cigarette butts and used VERVE® products as soon as product use is completed). Site staff will reconcile the logs against the returned cigarette butts and VERVE® products prior to discarding.

Unused VERVE® products will be destroyed by the site or returned to Sponsor at the direction of the Sponsor after a full accounting has been performed by the monitor. Unused OB cigarettes will be returned to the subjects at discharge or upon early withdrawal according to the site's standard practices. All returns or destruction of study products will be documented.

7 STUDY CONDUCT

Subjects meeting all inclusion criteria and none of the exclusion criteria will check-in to the study site on Day -3 to undergo the procedures described below.

7.1 Check-in Procedures (Day -3)

7.1.1. Brief written assessment (medical/medication questionnaire) to affirm that the inclusion and exclusion criteria/restrictions have not been violated since the Screening visit.

7.1.2. Symptom-driven physical examination.

7.1.3. Vital signs (respiratory rate, pulse rate, blood pressure, and body temperature) to be performed in the sitting position after at least 10 minutes of rest (with the exception of body temperature) and at least 15 minutes after the last cigarette smoked. One recheck of vital sign(s) may be performed at the Investigator's discretion.

7.1.4. Product trial of VERVE® Discs and Chews products

7.1.5. Documentation of subject's willingness to use the VERVE® products in the study and flavor preference.

7.1.6. *Ad libitum* use of OB cigarette and documentation of CPD.

7.1.7. Urine pregnancy test for females.

7.1.8. Urine sample for drugs of abuse (amphetamines, methamphetamines, opiates, cannabinoids, and cocaine) screen.

7.1.9. Breath alcohol test.

7.1.10. Review of concomitant medications.

7.1.11. Review of AEs

7.2 Subject Confinement

The subjects will be admitted to the study unit on Day -3 at a time designated by the clinic site and will remain in the clinic until completion of all study events on Study Day 8 or upon early termination.

7.3 Meal Schedule/Dietary Considerations

Standard meals and snacks will be served at appropriate times as determined by the clinic during confinement. Meals each day should be similar in caloric content. Meal times will be documented.

A standardized diet (*i.e.,* low mutagenicity) designed by a dietitian to minimize possible confounding influences for biomarkers assessed will be used. The following will not be permitted: broiled or pan-fried meat, pre-cooked meats (*e.g.,* tuna, ham, corned beef, smoked lunchmeats), bacon, and sausage. [2] These specially-designed meals will be served throughout the study according to a meal plan at the same approximate time throughout the study:

The same menu and approximate meal schedule will be administered uniformly to all subjects in all groups. The meal menu for Days -2, 4 and 6 will be the same and the meal menu for Days -1, 5 and 7 will be the same.

Consumption of alcoholic beverages will not be permitted during the study.

Water will be provided as desired during the study, and subjects will be encouraged to maintain their usual hydration habits.

7.4 Blinding

This will be an open-label study.

7.5 Subject Randomization

Subjects will be randomized into 6 groups (Groups 1 to 6) using an (Interactive Web Response System (IWRS). The randomization process may be completed on Day -1 as necessary to allow enough time to prepare the randomized products for use on Day 1.

Each subject will be assigned to a study group by the IWRS. Groups will be stratified by gender (male or female, no more than 60% of either gender) and CPD.

7.6 Study Product Use

No other use of tobacco- or nicotine-containing products will be allowed from Check-in through Discharge except as required by this protocol.

With certain exceptions (e.g., meals and other study events, specific VERVE® product use opportunities), all product use will be ad libitum upon request to the clinic staff from 07:00 to 23:00 each day. Only one cigarette will be dispensed for use at a time and subjects will be instructed to return all cigarette butts before being allowed to take OB cigarette. Subjects can receive one or more of the assigned VERVE® product for a single use episode at their request. Subjects will be instructed to return all used VERVE® product previously dispensed before being allowed to take additional VERVE® products. A partially smoked cigarette returned to the clinic staff will not be re-dispensed. Each VERVE® product may be used for as long as the subject desires, though during the specific VERVE® product use opportunities (product trial on Day -3 and 3 daily specific VERVE® products use opportunities at approximately 11:00, 15:00, and 19:00), subjects will be asked to use the product for at least 10 minutes.

On the evening of Days -1, 5, and 7, subjects will abstain from product use from the start of the subjective effects questionnaires administration until the COHb sample has been collected.

If a subject accidently disposes of a cigarette butt or used VERVE® product, a reasonable attempt should be made by the study staff to retrieve the cigarette butt or used VERVE® product, and the subject will be reminded that further such disposal may result in dismissal from the study.

All product use will take place in designated sections of the clinic. Subjects randomized to exclusive use of VERVE® products or cessation should not have access to any smoking area.

Day -3 to Day -1

All subjects will continue to smoke their OB cigarettes through 23:00 on Day -3 and from 7:00 to 23:00 on Days -2 and -1 according to their usual smoking behaviors.

Day 1 through Day 7

Subjects will begin using the assigned study products (OB cigarettes, dual use of OB cigarettes [≥50% CPD] and VERVE® Chews/ VERVE® Discs, and VERVE® Chews/ VERVE® Discs only) or completely stop using tobacco products from 07:00 on the morning of Day 1 according to the randomization.

Subjects randomized to continue smoking (Group 1) will continue to use their OB cigarettes for the duration of the study according to their usual smoking behaviors.

Subjects randomized to a dual use group (Groups 2 and 3) will reduce their daily cigarette consumption by at least 50% (rounded to the nearest whole number) of that smoked during the baseline period. For example, subjects who smoked 20 CPD at baseline will be allowed to smoke up to 10 CPD during Days 1 through 7 and subjects who smoked 17 CPD at baseline will be allowed to smoke up to 8 CPD during Days 1 through 7. Subjects will use the assigned VERVE® product *ad libitum* except for 3 specific VERVE® product use opportunities at 11:00, 15:00, and 19:00 each day during which subjects will be asked to use the assigned VERVE® product for at least 10 minutes.

Subjects randomized to exclusive use of a VERVE® product only (Groups 4 and 5) will completely switch to use of the assigned VERVE® product during Days 1 through 7, using product *ad libitum* except for 3 specific VERVE® product use opportunities at 11:00, 15:00, and 19:00 each day during which subjects will be asked to use the assigned VERVE® product for at least 10 minutes.

7.7 Urine Collection and Processing

Prior to the first urine sample collection, each subject will be instructed as to urine collection methods.

All urine voided by each subject will be collected in 24-hour intervals from approximately 07:00 on Days -1, 5 and 7 through approximately 07:00 on Days 1, 6 and 8, respectively. The collection window start/finish time may be ± 30 minutes of 07:00, but subjects must void prior to being allowed to begin product use on Days -1, 5 and 7. Confirmation that subjects voided at some point in the morning prior to beginning product use will be documented. The actual start and stop times of each 24-hour interval will be documented.

Subjects will be instructed to make every attempt to void prior to the beginning and at the end of collection interval. The first morning void and all urine voided prior to the start of the collection interval at 07:00 will be discarded. The 24-hour collection may not start until the subject has passed at least his/her first morning void. All urine collected up to the stop time of the sample collection will be retained, including at least the first morning void on Days 1, 6 and 8.

Urine will be refrigerated at 2 - 8°C during the collection interval. Collections for each subject will be pooled periodically into one labeled container throughout the 24-hour interval and the total weight (g) will be measured and recorded at the end of the 24-hour interval. Any missed voids will be documented, including the reason for missing.

A detailed Sample Handling Manual (SHM) will be prepared providing specific instructions for preparation, storage, and shipment of urine samples. Brief descriptions are provided here.

Aliquots will be prepared according to the Sample Handling Manual (SHM) for the following analytes: total NNAL, total NNN, NE, 2-AN, 4-ABP, HEMA, CEMA, S-PMA, 3-HMPMA, 3-HPMA, 2-HPMA, AAMA, GAMA, 2-MHBMA, 2-OHFle, 2-Naphthol, 1-OHPhe, urine mutagenicity, 1-OHP, creatinine, and bio-banking.

All aliquots will be prepared within 60 minutes from removal of the pooled collection from the refrigerator and then stored at -20 ± 10°C until shipped for analysis or bio-banking.

Aliquots for bio-banking will be stored at a biorepository until they are shipped to a long-term storage facility chosen by the Sponsor. The samples for future evaluation will be stored indefinitely and may be used to measure various biomarkers associated with tobacco use. No genetic testing will be performed. All samples will be appropriately labeled.

7.8 Blood Sample Collection and Processing

A blood sample for COHb will be collected on Days -1, 5 and 7 between 15 minutes to 45 minutes following the start of subject's in the moment subjective questionnaires scheduled for at 21:30. Subjects will abstain from product use, as appropriate, for at least 15 minutes prior to blood draw for COHb.

Samples for COHb will be collected into two 4 mL sodium heparin vacutainers. Immediately following collection, the blood samples will be gently inverted to mix. The whole blood samples will be stored at 5°C (± 3°C) until shipped to Celerion Bioanalytical Services (Lincoln, Nebraska) for analysis. Additional instructions for blood sample collection, processing, and shipping will be provided separately.

For all schedules samples for COHb, approximately 8 mL of blood will be collected from each subject.

7.9 Subjective Effects Measurements

Subjects will also complete in the moment subjective effects questionnaires, which include:

- QSU-Brief (Appendix 2) – All subjects will complete the QSU-Brief onDays -1, 1, 5, and 7 in the morning at 07:00 (± 30 minutes) before product use, as appropriate, and at 21:30 (± 30 minutes).
- Modified Cigarette Evaluation Questionnaire (mCEQ-C or mCEQ-V; Appendix 3) – the appropriate mCEQ will be administered at 21:30 (± 30 minutes). All subjects will complete the mCEQ-C on Day -1. Subjects in Group 1 will also complete the mCEQ-C on Days 1, 5, and 7. Subjects in Groups 2 and 3 will complete both mCEQ-C and

mCEQ-V on Days 1, 5, and 7.Subjects in Groups 4 and 5 will complete mCEQ-V on Days 1, 5, and 7.

- Use the Product Again questionnaire (Appendix 4) – Subjects in Groups 1 - 5 will complete the Use the Product Again questionnaire at 21:30 (± 30 minutes) on Day 7. Subjects in Group 1 will complete Use the Product Again questionnaire for cigarettes. Subjects in Groups 2 and 3 will complete both Use the Product Again questionnaire for cigarettes and VERVE® products. Subjects in Groups 4 and 5 will complete Use the Product Again questionnaire for VERVE® products.

7.10 Safety Assessments

7.10.1. A symptom-driven physical examination will be conducted at Check-in and at the End-of-Study (or upon early termination) if any symptoms are present.

7.10.2. A brief written assessment (medical/medication history) of the subject to affirm that the eligibility criteria/restrictions have not been violated since Screening will be performed at Check-in.

7.10.3. Vital signs (respiratory rate, pulse rate, blood pressure, and body temperature) will be measured with subjects in the sitting position after at least 10 minutes of rest (with the exception of body temperature) and at least 15 minutes after the last cigarette smoked.

7.10.4. Review of concomitant medications.

7.10.5. The subjects will be instructed to inform the study physician and/or study staff of any AEs that may occur after the first study product use.

7.11 Tobacco Cessation Information

The Investigator or his/her designee, at Screening and at the End-of-Study or upon early termination, will advise all adult tobacco product users that to reduce the health effects of tobacco, the best thing to do is to quit. The Investigator or his/her designee will also refer all adult tobacco product users to the Quit Assist® website, which contains references to a number of third-party information sources, including websites, telephone resources, and other organizations with additional information.

8 ADVERSE EVENTS

8.1 Adverse Events

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

> Any unfavorable and unintended sign (including an abnormal laboratory finding[a]), symptom, or disease[b] temporally associated with the use of a study product, **whether or not** related to the study product. [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] This includes a newly developed, worsened preexisting, recurring intermittent or intercurrent illness, injury, or condition.

All AEs occurring during this clinical trial (from the subject's first study product use [VERVE® product trial] through discharge on Day 8 or Early Termination) must be recorded in the case report form, including the date and time of onset and outcome of each event. Events occurring between signing of the ICF and prior to the use of a study product will be documented as baseline signs and symptoms in the medical history and not AEs.

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.

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** [3] 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 [5, 6] (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 study 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 "definitely related" category may only be used when recurrence is observed.*

8.2 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. [3]

[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 a serious adverse study experience 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-related, must be reported by telephone and by fax or e-mail to the Sponsor and the medical monitor within 24 hours of the site's learning of the SAE or, at the latest, on the following workday.

The Investigator must also inform the IRB, in compliance with GCP reporting guidelines, **and the 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.

8.3 Adverse Event/Serious Adverse Event Follow-Up

Each AE including clinically significant laboratory abnormalities, whether serious or non-serious, will be followed until resolved, determined that follow-up is no longer required at the discretion of the Investigator, or lost to follow-up, 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.

8.4 Pregnancy

A positive pregnancy test prior to enrollment will be documented as a screen failure. Pregnancy occurring in a female study subject after randomization will be documented in a pregnancy form (provided separately) and as a protocol deviation to the IRB. Pregnancy itself is not an AE. The Investigator or designee will immediately discontinue the pregnant subject from the study and will advise her to seek prenatal care and counseling from her primary care provider. The Investigator will refer her to the Quit Assist® website, which contains references to a number of third-party information sources, including websites, telephone resources and other organizations with additional information. Advice given will be documented in the subject's source document.

All pregnancies must be reported by telephone and by fax or e-mail to the Sponsor and the medical monitor within 24 hours of the site's learning of the pregnancy or, at the latest, on the following workday.

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

9 REMOVAL OF SUBJECTS FROM STUDY, 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 he/she 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 randomized subject terminates early from the study and has used any study product provided by the Sponsor, all of the safety data normally required at the End-of-Study should be obtained, if possible. Subjects with AEs will be followed to a final outcome. Final outcome may be classified as resolved, improved, unchanged, worse, fatal, or unknown (lost to follow-up).

Subjects withdrawing from the study may be replaced at the discretion of the Sponsor. Subjects completing, withdrawing, or removed from this study cannot re-enter.

10 ANALYTICAL METHODOLOGY

10.1 Clinical Laboratory

Values for the clinical laboratory parameters will be determined by a laboratory facility accredited by the Centers for Medicare and Medicaid Services (CLIA-88) or at the clinic study site using CLIA-waived kits or procedures. Hematology, clinical chemistry, urinalysis, serology, urine drug screen, breath alcohol,

pregnancy, and FSH will be analyzed using standard clinical laboratory procedures.

10.2 Analytical Laboratories

Biomarkers (including urine creatinine) will be analyzed by a laboratory facility accredited by the Centers for Medicare and Medicaid Services (CLIA-88) or at the clinic study site using CLIA-waived kits or procedures using validated analytical methods with appropriate quality controls according to the *Food and Drug Administration (FDA) Guidance for Industry: Bioanalytical Method Validation* (May, 2001) [7] and in accordance with FDA Good Laboratory Practice regulations (Title 21 Code of Federal Regulations [CFR] Part 58).

11 STATISTICAL METHODS

11.1 General

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

SAS software (version 9.3 or higher, Cary, North Carolina) will be used for all data presentation and summarization including statistical analyses, summary tables, graphs, and data listings. Statistical methods will be discussed in detail in the SAP.

11.2 Sample Size Estimation

This study is designed to evaluate changes in exposure to selected HPHC when adult smokers partially or completely switch to oral tobacco-derived nicotine VERVE® Chews or VERVE® Discs compared to those who continue smoking cigarettes or stop using all tobacco products. Assuming a similar effect size for the new study as for the previous ALCS study (ToPP4ST_1011_07) between the continued cigarette smoking group and each of the two dual usage groups (≥50% CPD reduction with VERVE® DISCS or VERVE® CHEWS), a two-sided t test, 85% power and an α =0.025 Type I error rate to account for the multiplicity adjustment for the two comparisons, 35 subjects are needed to complete for the continue cigarette smoking group and the dual usage groups. We expect that the effect will be larger in the VERVE® only and smoking cessation groups, so 25 subjects are needed to complete in these groups.

11.3 Analysis Populations

Safety Analysis Dataset:

All subjects who used any study products (including subjects randomized to Group 6).

Modified Intent-to-Treat (MITT) Dataset:

All randomized subjects who have a valid baseline and post-baseline endpoint value (total NNAL). This population will be used for primary endpoints analysis.

Per-Protocol (PP) Dataset:

A subset of the MITT dataset and includes subjects who completed the study without major protocol deviations that are considered to impact data integrity (e.g., non-adherence to study group assignment).

If it is determined that a subject was pregnant during the study, all of the pregnant subject's data will be reported, but will be excluded from summarization and statistical analyses.

11.4 Data Summarization

All data will be listed by subject number, group, and study day (and time point as necessary), and summarized by group (total and by product type for VERVE® groups) and study day (and time point as necessary). 24-hour urine and COHb biomarker data will be listed and summarized. Absolute and percent change from baseline values will be listed and summarized as appropriate. Descriptive statistics (n, mean, median, SD, minimum, and maximum) will be used for continuous data variables and frequency counts (n and percentage) for categorical data variables as described in the SAP. Figures will be used to display the data graphically.

Demographics, smoking history, baseline daily cigarette use (Day -2 and Day -1), and baseline FTCD scores will be summarized overall, and by group with descriptive statistics for continuous variables and frequency counts and percentage for categorical variables.

Missing data will not be imputed.

11.5 Urine Biomarkers

The following variables will be determined for each urine biomarker.

- Measured concentration
- Total biomarker mass excreted per 24 hours (primary analysis variable)
- Total mass excreted per 24 hours absolute change from Baseline
- Total mass excreted per 24 hours percent change from Baseline

Urine biomarker concentration values reported as below the limit of quantitation (BLQ) will be set to one-half of the limit of quantitation prior to calculating the 24-hour mass excreted.

Calculation of Urine Nicotine Equivalents

NE will be calculated as the molar sum of nicotine and 5 major nicotine metabolites excreted in urine over 24 hours. Values of individual components reported as below the limit of quantitation will be set to one-half of the limit of quantitation prior use in the calculation below.

The concentration of each metabolite will first be adjusted by the 24-hour urine volume to obtain the total amount excreted in 24 hours, then divided by the

molecular weight of the metabolite to obtain the total amount of each in moles. The sum in moles will then be converted to mass of NE by multiplying by the molecular weight of nicotine.

Nicotine equivalents = (nicotine [mg]/162.23 [mg/mmol] + nicotine-gluc (mg/24 hours) [mg]/338.36 [mg/mmol] + cotinine [mg]/176.22 [mg/mmol] + cotinine-gluc [mg]/352.34 [mg/mmol] + trans-3'-hydroxycotinine [mg]/192.22 [mg/mmol] + trans-3'-hydroxycotinine-gluc [mg]/368.34 [mg/mmol]) x 162.23 [mg/mmol]

Creatinine Adjustments

Urine creatinine will be measured and, if needed, used to adjust the urine biomarker values as follows (further details will be included in the SAP):

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

11.6 Blood COHb

The following variables will be determined for blood COHb.

- Measured saturation (%) (primary analysis variable)
- Measured saturation (%) absolute change from Baseline
- Measured saturation (%) percent change from Baseline

Values reported as below the limit of quantitation (BLQ) will be set to one-half of the limit of quantitation for summarization and statistical analysis.

11.7 Subjective Effects

QSU-Brief

Descriptive statistics (n, mean, SD, CV%, minimum, median, and maximum) of the response.

The factor scores for the QSU-Brief will be calculated as follows.

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

The following variables will be determined for each factor score.

- Actual score (primary analysis variable)
- Absolute change from Baseline
- Percent change from Baseline

Modified Cigarette Evaluation Questionnaires

Responses on the 7-point scales for each mCEQ (mCEQ-V for days in which VERVE® products are used and mCEQ-C for days in which subject's OB

cigarettes are used) will be treated as continuous variables. Descriptive statistics (n, mean, SD, CV%, minimum, median, and maximum) of the response score will be provided by study product for the *ad libitum* product use episodes only.

Use Product Again Questionnaires

The maximum response score to the Use the Product Again questionnaire (Emax-upa) for each product will be summarized study product and group. A linear mixed model for analysis of variance will be performed on the Emax scores. The model will include group, study product, and day as fixed effects and subject nested as a random effect. The comparisons of interest will include the VERVE® products compared to subject's OB cigarette. Geometric LSM, 95% confidence intervals, and p-values will be provided for the study products in each response by group.

11.8 Product Use Behavior

The number of each product used per day (CPD and VPD, as appropriate) and the duration of each VERVE® product used during each product use period will be listed and summarized by study product using descriptive statistics, as appropriate.

11.9 Statistical Analysis

Linear mixed models for ANCOVA will be used to compare the Day 5 and Day 7 biomarker values and subjective effects questionnaire scores between groups as described in the study objectives. In the statistical models, the outcome variable will be included as a dependent variable; group, and gender will be included as fixed effects; and baseline values/scores will be included as covariates. The SAS Proc Mixed procedure will be used. The LSM difference and 95% confidence interval for the LSM difference between the Test and Reference Groups will be provided.

Normality and equal variance assumptions will be tested for biomarker variables. An appropriate data transformation will be used if parametric assumptions for the distribution of above-mentioned data are markedly violated.

The statistical significance level will be 5% for two-sided testing. Adjustments for multiple comparisons will not be made.

11.10 Safety Analysis

A by-subject AE data listing, including verbatim term, preferred term, study product, severity, and relationship to study product, will be provided.

The number of subjects experiencing AEs and the number of AEs will be summarized by study product using frequency counts.

Safety data, including laboratory evaluations and vital signs assessments will be summarized by time point of collection as appropriate.

Descriptive statistics will be calculated for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data.

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

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary.

12 DATA MANAGEMENT

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

12.1 Database Design and Creation

An appropriate database will be designed and created within a validated Clinical Data Management System (CDMS) which is compliant with 21 CFR Part 11. Electronic data capture will be used for this study and electronic case report form (eCRFs) will be developed according to the study protocol specifications. Clinical and analytical laboratory data will be collected external to the CDMS as external data files.

12.2 Data Coding

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

12.3 Data Entry and Verification

Data will be entered directly or transcribed from original sources into the eCRF by the Investigator or Investigator's staff. External 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. External data received from the IWRS and electronic Subject Reported Outcomes (eSRO) vendors (subject screening and randomization, study product and cigarette dispensing, and questionnaire data) will be integrated into the Clinical Data Interchange Standards Consortium study data tabulation model datasets.

12.4 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.

12.5 Data Validation

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

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

12.6 Database Lock

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

The Sponsor will be required to provide database lock approval.

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

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

13 MONITORING THE STUDY

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

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

monitor to ensure that any issues detected in the course of these monitoring visits are resolved.

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

The Investigator must notify the Sponsor (or designee) promptly of any inspections of the study or activities related to the study scheduled by regulatory authorities, allow the Sponsor (or designee) to be present, and promptly forward copies of inspection reports to the Sponsor (or designee).

14 REPORTING FOR THE STUDY

14.1 Case Report Forms

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

14.2 Study Report

A study report written consistent with ICH guidelines will be provided by Celerion to the Sponsor. The report 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.

At the time the draft study report is completed, Celerion's Quality Assurance (QA) unit will audit the report against the SAS data and the raw data. At the completion of the audit, a QA report will be issued internally allowing any findings to be addressed before report finalization.

15 GENERAL

15.1 Confidentiality

All study sites and vendors 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.

Neither the study site nor Celerion will supply to the Sponsor any subject names, initials, date of birth (except year), or other personal identifiers. [7] All such information appearing on any study document must be redacted before a copy of the document is supplied to the Sponsor. Study findings stored on a computer will be stored in accordance with applicable 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 applicable data protection laws.

15.2 Responsibility of the Investigator

The Investigator is responsible for ensuring that the clinical study is performed in accordance with GCP based on the current ICH Guideline for GCP, the corresponding sections of the US 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 other applicable legal and regulatory requirements.

The Investigator should ensure that all persons assisting with the study are qualified for the duties assigned, adequately informed and trained on the protocol and amendments to the protocol, the study 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.

15.3 Procedure for Amendments to Protocol

No deviations from this protocol will be permitted, except in a medical emergency. The Investigator and the Sponsor will discuss any amendment to this study. 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, if applicable, in writing by Advarra IRB d/b/a Chesapeake IRB.

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

15.4 Institutional Review Board

This protocol and ICFs will be reviewed and approved in writing by Chesapeake IRB prior to commencement of the study. The study will not be initiated without the approval from the IRB. Any amendments after protocol approval, if applicable, will be reviewed and approved by Advarra IRB d/b/a Chesapeake IRB prior to implementation. The IRB operations are in compliance with Title 21 CFR Part 56. Notice that the IRB approved protocol, ICF and any amendments to the protocol and ICF will be in the final study report.

15.5 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.

15.6 Study Record Retention

Investigator-specific essential documents and all primary data and copies thereof (e.g., eCRFs, laboratory records, data sheets, correspondence, photographs, computer records), 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 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 Celerion'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 data will be transferred to the Sponsor. Subject initials, serology results, date of birth (except year), and other personal identifiers [8] will be redacted from this data transfer file; any such information removed will be documented at the time of transfer.

16 REFERENCES

1. Hatsukami DK, Joseph AM, Lesage M, et al. Developing the Science Base for Reducing Tobacco Harm. Nicotine Tob Res 2007; Suppl 4:S537-53.
2. Smith CJ, McKarns SC, Davis RA, Livingston SD, Bombic BR, Avalos JT, Morgan WT, Doolittle DJ. Human urine mutagenicity study comparing cigarettes which burn or primarily heat tobacco. *Mutation Res* 1996; 361:1-9
3. ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (E2A). *Federal Register*. Vol. 60, March 1, 1995, p. 11284.
4. ICH Guideline for Good Clinical Practice: Consolidated Guidance (E6). *Federal Register*. Vol. 62, May 9, 1997, p. 25692.
5. Nebeker JR, Barach P, Samore MH. Clarifying Adverse Drug Events: A Clinician's Guide to Terminology, Documentation, and Reporting. *Ann Intern Med* 2004; 140:795-801.
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7. FDA Guidance for Industry. Bioanalytical Method Validation. 2001 May. http://www.fda.gov/downloads/Drugs/Guidances/ucm070107.pdf. Last accessed April 24, 2017.
8. U.S. Department of Health and Human Services. HIPAA Privacy Rule. Information for Researchers. De-identifying Protected Health Information Under the Privacy Rule. http://privacyruleandresearch.nih.gov/pr_08.asp#8a. Last accessed April 24, 2017.

17 APPENDICES

Appendix 1: Fagerström Test for Cigarette Dependence (FTCD)

Please answer each question below by checking (✓) your answer in the box (□).

1. How soon after you wake up do you smoke your first cigarette?
   - ☐ Within 5 minutes
   - ☐ 6 - 30 minutes
   - ☐ 31 - 60 minutes
   - ☐ After 60 minutes

2. Do you find it difficult to refrain from smoking in places where it is forbidden (e.g., in church, at the library, in the cinema, etc.)?
   - ☐ Yes
   - ☐ No

3. Which cigarette would you hate most to give up?
   - ☐ The first one in the morning
   - ☐ Any other

4. How many cigarettes per day do you smoke?
   - ☐ 31 or more
   - ☐ 21 - 30
   - ☐ 11 - 20
   - ☐ 10 or less

5. Do you smoke more frequently during the first hours after waking than during the rest of the day?
   - ☐ Yes
   - ☐ No

6. Do you smoke if you are so ill that you are in bed most of the day?
   - ☐ Yes
   - ☐ No

_____	_____	_____
Participant Signature	Date	Time

For Clinic Use Only:

Reviewed by (Initials): _____ Date (dd-mmm-yyyy): _____

Appendix 2: Questionnaire of Smoking Urges – Brief (QSU-Brief)

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

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

Cox LS, Tiffany ST, Christen AG. Evaluation of the brief questionnaire of smoking urges (QSU-Brief)in laboratory and clinical settings .Nicotine & Tobacco Research. 2001;3:7-16

Appendix 3: Modified Cigarette Evaluation Questionnaires

Cigarettes:

Please mark the number that best represents how smoking cigarettes made you feel (1- not at all, 2- very little, 3-a little, 4-moderately, 5-a lot, 6-quite a lot, 7-extremely)

Modified Cigarette Evaluation Questionnaire (mCEQ-C)

1. Was smoking cigarettes satisfying?
2. Did the cigarettes taste good?
3. Did you enjoy the sensations in your throat and chest?
4. Did smoking cigarettes calm you down?
5. Did smoking cigarettes make you feel more awake?
6. Did smoking cigarettes make you feel less irritable?
7. Did smoking cigarettes help you concentrate?
8. Did smoking cigarettes reduce your hunger for food?
9. Did smoking cigarettes make you dizzy?
10. Did smoking cigarettes make you nauseous?
11. Did smoking cigarettes immediately relieve your craving for a cigarette?
12. Did you enjoy smoking cigarettes?

VERVE® Products:

Please mark the number that best represents how using the VERVE® products made you feel (1- not at all, 2- very little, 3-a little, 4-moderately, 5-a lot, 6-quite a lot, 7-extremely)

Modified Cigarette Evaluation Questionnaire further modified for VERVE® products (mCEQ-V)

1. Was using the VERVE® product satisfying?
2. Did the VERVE® product taste good?
3. Did you enjoy the sensations in your throat and chest?
4. Did using the VERVE® product calm you down?
5. Did using the VERVE® product make you feel more awake?
6. Did using the VERVE® product make you feel less irritable?
7. Did using the VERVE® product help you concentrate?
8. Did using the VERVE® product reduce your hunger for food?
9. Did using the VERVE® product make you dizzy?
10. Did using the VERVE® product make you nauseous?
11. Did using the VERVE® product immediately relieve your craving for a cigarette?
12. Did you enjoy using the VERVE® product?

Appendix 4: Use the Product Again Questionnaire (Bipolar VAS)

(Item adapted from abuse-deterrent formulation drug trials "I would want to take this drug again")

Please respond to the following statement based on your experience with the <cigarette/VERVE®> product.

If given the opportunity, I would want to use the <cigarette/VERVE®> product again.

Definitely Would Not **Don't Care** **Definitely Would**