A Randomized, Controlled, Parallel Group Pilot Clinical Study to Determine Changes in Biomarkers of Exposure (BOE) in Adult Smokers Allowed ad libitum VBM-FG2 Disc Use Relative to Adult Smokers Not Allowed VBM-FG2 Disc Use

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Altria
Altria Client Services

Protocol Number: **COV-VER-01-13**

Protocol Name: **A Randomized, Controlled, Parallel Group Pilot Clinical Study to Determine Changes in Biomarkers of Exposure (BOE) in Adult Smokers Allowed *ad libitum* VBM-FG2 Disc Use Relative to Adult Smokers Not Allowed VBM-FG2 Disc Use**

PILOT AMBULATORY VBM-FG2 EXPOSURE (PAVE) STUDY

Issue Date: 09 August 2013

Sponsor:

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SPONSOR AGREEMENT

I have read the following protocol and agree to the conduct of the study as described herein:

[redacted]

8/9/13
Date

Altria Client Services, Inc
Health and Behavioral Sciences

INVESTIGATOR AGREEMENT

I have read the following protocol and agree to conduct the study as described herein:

[redacted] 12 Aug 2013

Covance Daytona Clinical Research Unit Date

INVESTIGATOR AGREEMENT

I have read the following protocol and agree to conduct the study as described herein:

[redacted]

13 AUG 2013
Date

Covance Evansville Clinical Research Unit

INVESTIGATOR AGREEMENT

I have read the following protocol and agree to conduct the study as described herein:

[redacted]

09 AUG 2013
Date

Covance Dallas Clinical Research Unit

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SYNOPSIS

ALCS Protocol Number:
COV-VER-01-13

Abbreviated Protocol Title:
PILOT AMBULATORY VBM-FG2 EXPOSURE (PAVE) STUDY

Long Protocol Title:
A Randomized, Controlled, Parallel Group Pilot Clinical Study to Determine Changes in Biomarkers of Exposure (BOE) in Adult Smokers Allowed *ad libitum* VBM-FG2 Disc Use Relative to Adult Smokers not Allowed VBM-FG2 Disc Use.

Study Sites: 3

Study Objectives:
The primary objective of this study is to:

- Compare the differences in percent change in urinary total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) from Baseline to End of Study between adult smokers randomly assigned to Test Group (*ad libitum* VBM-FG2 use) and Control Group (no VBM-FG2).

The secondary objectives of this study are to:

- Compare the difference in biomarkers of exposure (BOE; urinary total NNAL, nicotine metabolites, S-phenylmercapturic acid [S-PMA], blood carboxyhemoglobin [COHb] and exhaled carbon monoxide [CO]) and cigarettes per day (CPD) between two methods for determining CPD during the Baseline Period:
    - Recall of average daily CPD for prior week using Past 7 Day Cigarettes Use Questionnaire (Day 1).
    - Daily CPD tracking using an interactive voice response system (IVRS; 7 day average of values recorded on Days 2 through 8).
- Compare the differences in percent change in urinary nicotine equivalent [NE], S-PMA, blood COHb, exhaled CO, and CPD from Baseline to End of Study between adult smokers randomly assigned to Test Group (*ad libitum* VBM-FG2 use) and Control Group (no VBM-FG2).
- Compare the changes in all BOE and CPD from Baseline to End of Study between Test Group and Control Group over 4 weeks.
- Characterize subgroups based on change in CPD from Baseline to End of Study (no change, <50% reduction, ≥50% reduction, 100% reduction, increase) within each study group.
- Characterize subgroups based on change in total NNAL from Baseline to the End of Study (no change, reduction, increase) in each study group.
- Compare changes in the Fagerström Test for Cigarette Dependence from Baseline (Day 8) to End of Study within and between each study group.
- Compare changes on the Quit Attempts and Quitting Intentions from Baseline (Day 1) to End of Study within and between each study group.

The Baseline Period is from Day 1 to Day 8. *Statistically, "Baseline" will be defined as a single time point at the end of the Baseline Period (except where noted). The last study visit will be defined as End of Study.*

Study Design/Visit Schedule:
This is a randomized, controlled, open-label, parallel group, multi-center, 5-week pilot study to determine changes in BOE in adult smokers allowed *ad libitum* use of VBM-FG2 (Test Group) relative to adult smokers who are not allowed used of VBM-FG2 (Control Group). This study will be conducted in approximately 150 adult smokers randomized in a 3:2 ratio (Test: Control) with no more than a 60:40 distribution of either males or females to either group.

Screening (Day -28 to Day -1):

1. Visit 1/Screening (Day -28 to Day -1)
2. VBM-FG2 product trial

Baseline Period (Day 1 to Day 8):

3. Visit 2 (Day 1)
4. Visit 3 (Day 8 ± 1 day) - randomization

Electronic IVRS conducted daily (Days 1 to 8)

Product Use Period (Day 8 – Day 36):

5. Visit 4 (Day 15 ± 1 day)
6. Visit 5 (Day 22 ± 1 day)
7. Visit 6 (Day 29 ± 1 day)
8. Visit 7/End of Study (Day 36 ± 1 day)

Electronic IVRS conducted daily (Days 8 to 36)

Number of Subjects per Group:
Approximately 150 subjects will be randomized (based on gender, daily cigarette consumption [≤20 and >20], and quit attempts [any quit attempt/ no quit attempts]) in a 3:2 ratio (not more than 60:40 distribution of either male or female) to the Test:Control Group.

Group 1 (Test)

- Adult smokers provided VBM-FG2 discs for *ad libitum* use (n = 90)

Group 2 (Control)

- Adult smokers not provided VBM-FG2 discs (n = 60)

Subject Population:
The study population will consist of approximately 150 adult (21 to 65 years of age, inclusive) cigarette smokers across 3 study sites.

Study Duration:
The expected duration of the study, from first subject, first visit through last subject, last visit will be approximately 3 months. The expected study duration for each individual subject is approximately 5 weeks (potentially 9 weeks from Screening to end of Study).

Statistics:
The purpose of this Pilot Study is to collect data to estimate the variability of the primary outcome, which will be used to estimate the sample size for a future pivotal study. The sample size for this study is believed to be appropriate based on statistical principles for pilot studies.

Primary Outcome Measures

- Differences in the percent change from Baseline to End of Study in urinary total NNAL between the Test and Control Groups

Secondary Outcome Measures

- Differences in all BOE during the Baseline Period between Day 1 (weekly recall) versus Day 8 (daily tracking using IVRS).

- Differences in CPD during the Baseline Period between once weekly recall (Days 1 and 8) versus daily tracking (average of recordings on Days 2 through 8).
- Differences in the percent change from Baseline to End of Study in the other BOE (urinary NE, S-PMA, blood COHb, exhaled CO) and CPD between the Test and Control Groups.
- Differences from Baseline to End of Study in all BOE and CPD between the Test and Control Groups.
- Proportion of subjects in subgroups based on cigarette consumption change from Baseline to End of Study (no change, <50% reduction, ≥50% reduction, 100% reduction, increase) within and between the Test and Control Groups.
- Proportion of subjects in subgroups based on total NNAL change from Baseline to End of Study (no change, reduction, increase) within each group.
- Changes from Baseline (Day 8) to End of Study in Fagerström Test for Cigarette Dependence, within and between the Test and Control Groups.
- Changes from Baseline (Day 1) to End of Study on the Quit Attempts and Quitting Intentions, within and between the Test and Control Groups.

Statistically, "Baseline" will be defined as a single time point at the end of the Baseline Period unless otherwise noted. The last study visit will be defined as End of Study.

Statistical methods

Descriptive statistics
Descriptive statistics will be used to characterize the data during the Baseline Period and over time. All summaries of categorical data will present frequency counts and proportions. All summaries of continuous data will present the number of non-missing values, mean, median, standard deviation, minimum, maximum, coefficient of variation, and 95% confidence interval.

Primary outcome measure analyses
A linear mixed model for repeated measures analysis of variance will be used for the analyses of the primary outcome measure. The terms of the model will be outlined in the statistical analysis plan. SAS procedure Proc Mixed will be used for the statistical computing.

Secondary outcome measure analyses
A linear mixed model for repeated measures analysis of variance will be used for the analyses of the secondary outcome measures. The model will include terms for study group (or tracking method for cigarette consumption), study visit and subject. SAS procedure Proc Mixed will be used for the statistical computing.

For correlations, a linear regression analysis will be conducted to examine the relationships between levels of biomarkers (dependent variable) with either the weekly cigarette counts (independent variable) or the daily cigarette counts. The coefficients of determination will be compared.

The Mantel-Haenszel Chi-Square Test will be used to test the frequency differences of product use categories between the 2 groups.

Interim Analysis:

An interim data analysis will be conducted after the first 50 (approximately 30 Test Group and 20 Control Group) subjects have completed the study. The purpose of the analysis is to obtain timely information for the planning of a proposed pivotal study.

1 INTRODUCTION

1.1 Background

The harm caused by tobacco use is primarily attributable to cigarette smoking. Despite the known health consequences, millions of adults are likely to continue smoking. Discouraging initiation and promoting cessation are and should remain core strategies to reduce tobacco-related harm; however, it is unlikely that they will eliminate tobacco use altogether. Transitioning adult smokers from cigarettes to demonstrably less hazardous non-combustible tobacco products could positively impact smoking cessation (number of years smoked) and number of cigarettes per day (CPD).

Altria Client Services (ALCS) is committed to the development of less harmful tobacco product alternatives for adult cigarette smokers. There is overwhelming scientific evidence regarding a risk continuum in the range of tobacco products currently available on the market. According to this body of evidence, cigarettes are the most risky tobacco product and smokeless tobacco products present relatively lower risks[1]. Making available lower risk tobacco products for those adult smokers that do not quit smoking, can complement strategies that have been proven to reduce harm from cigarette smoking (i.e., smoking cessation and discouraging initiation).

1.1.1 Product information

Altria Client Services has developed a new tobacco product; VBM-FG2. VBM-FG2 discs are oral, non-dissolvable products containing tobacco-derived nicotine that may provide an opportunity for adult cigarette smokers to move down the continuum of risk. VBM-FG2 discs are a tobacco-derived nicotine product designed to appeal to adult cigarette smokers who are interested in tobacco product alternatives to cigarettes. VBM-FG2 discs are designed to be spit-free and chewable.

The product consists of a polymer matrix, which is embedded with a cellulose fiber that meets or exceeds the monograph requirements for Powered Cellulose as published in the Food Chemicals Codex, 4th Edition. The matrix also contains flavors that are generally recognized as safe.

The polymer being used meets the requirements of the FDA-modified ISO 10933, Part 1 "Biological Evaluation of Medical Devices" tests for materials in contact with human tissue with a contact time of 30 days or less. The nicotine is pharmaceutical grade, derived from tobacco obtained from a facility that operates under FDA's Good Manufacturing Practice regulations for pharmaceutical active ingredients. The level of nicotine in a VBM-FG2 disc is approximately 1.5 mg. The amount of nicotine in a VBM-FG2 disc is lower than the range of nicotine typically found in pouched smokeless tobacco products currently on the market.

1.1.2 Previous human studies

A previous version of VBM-FG2 (VBM-FEXP) has been sold in a lead market in the Commonwealth of Virginia since June, 2012. This product is very similar to the product being tested, it contains 1.5 mg tobacco-derived nicotine and has similar ingredients

except that the VBM-FG2 has a softer texture. Before introduction of VBM-FEXP to the market a pharmacokinetic (PK) study was conducted with 2 prototype products (11-SOLID-OOE-45 and 11-SOLID-OOE-46 containing 1 and 2 mg tobacco derived nicotine, respectively) in December 2011. The purpose of this study was to characterize the nicotine plasma PK profile from a single use of the prototypes. This randomized, single-blind, 2-period crossover PK study (study number: CEL-SOL-01-11) was conducted in 18 (M/F = 9/9) healthy adult smokers following single use of the 2 prototypes. Subjects were allowed to use 1 of the 2 prototype oral tobacco products by chewing them and moving them around in the mouth, as desired, for 30 minutes on Day 1 and crossed over to the other test product on Day 2 of the study. Blood samples for plasma nicotine concentration were drawn on Days 1 and 2 at 5 minutes prior to and 2, 4, 8, 12, 16, 20, 30, 45, 60, 90, 120, 240, 480, and 720 minutes following placement of the test product in the mouth.

The geometric mean baseline-adjusted maximum observed concentration values for nicotine were 1.40 and 2.51 ng/mL for 11-SOLID-OOE-45 and 11-SOLID-OOE-46, respectively, and the geometric mean area under the concentration-time curve from Hour 0 to the last measurable concentration values for nicotine were 5.69 and 9.73 ng·hr/mL for 11-SOLID-OOE-45 and 11-SOLID-OOE-46, respectively. Maximum nicotine plasma concentrations were reached by approximately 0.65 hours while mean half-life was between 3 and 4 hours, regardless of the dose administered or gender.

Six (33%) subjects experienced a total of 11 mild adverse events (AEs) over the course of the study. The most common AE was throat irritation (4 subjects), followed by dyspepsia (2 subjects) and nausea (2 subject). Based on the results of this study it was determined that single administrations of the VBB-FG2 disc prototypes yielded rate and extent of nicotine absorption that were linear and approximately dose proportional for the 2 mg prototype compared to the 1 mg prototype. Single administrations of non-dissolvable VBM-FEXP prototypes containing 1 and 2 mg tobacco-derived nicotine was well tolerated in this group of healthy male and female adult smokers.

In addition to this study, ALCS has conducted several consumer research studies of varying durations of exposure. Of particular note was an extended home use test over a period of 12-weeks among adult smokers, ages 21 to 54 years, to understand tobacco product use behavior. The products were well tolerated by the participants in this 12-week study (n = 284).

Furthermore, ALCS continuously monitors consumer calls to the Consumer Response Center (CRC). As of June 27, 2013, since the launch of the previous version of VBM-FG2, the CRC has received 2 calls considered to be potential AEs. In one call, the consumer reported “Almost swallowed product,” and in the second call the consumer reported breaking a molar tooth while chewing on Verve® discs for the first time. Overall, based on the information presented, it is anticipated that VBM-FG2 will be well tolerated in this study.

The participants will be made aware of the possible risks associated with the use of the product. VBM-FG2 packages will have the following warning: “This product contains

tobacco-derived nicotine. Nicotine 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."

1.2 Rationale

The current study will serve as a pilot study for a larger study with a similar design. The purpose of this pilot study is to estimate changes in biomarkers of exposure (BOE) in adult cigarette smokers using VBM-FG2 discs relative to adult smokers who continue smoking and do not receive VBM-FG2 discs. Results of this study will be used to estimate the sample size for a proposed pivotal study. Results of this study will also be used to determine the optimal method by which to measure product use behavior; daily product use tracking via interactive voice response system (IVRS) or weekly product use recall.

2 PURPOSE AND STUDY OBJECTIVES

2.1 Purpose

The purpose of this study is to 1) estimate the change in BOE in adult smokers using VBM-FG2 versus adult smokers not using VBM-FG2, and 2) determine the appropriate CPD reporting method for baseline measurements (for IVRS Baseline is defined as the average CPD recorded on Days 2 through 8)

2.2 Primary Objective

The primary objective of this study is to:

- Compare the differences in percent change in urinary total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) from Baseline to End of Study between adult smokers randomly assigned to Test Group (*ad libitum* VBM-FG2 use) and Control Group (no VBM-FG2).

2.3 Secondary Objectives

The secondary objectives of this study are to:

- Compare the difference in BOE (urinary total NNAL, nicotine metabolites, S-phenylmercapturic acid [S-PMA], blood carboxyhemoglobin [COHb], and exhaled carbon monoxide [CO]) and CPD between two methods for determining CPD during the Baseline Period:
    - Recall of average daily CPD for prior week using Past 7 Day Cigarettes Use Questionnaire (Day 1).
    - Daily CPD tracking using an IVRS (7 day average of values recorded on Days 2 through 8).

- Compare the differences in percent change in urinary nicotine equivalent (NE), S-PMA, blood COHb, exhaled CO, and CPD from Baseline to End of Study between adult smokers randomly assigned to Test Group (*ad libitum* VBM-FG2 use) and Control Group (no VBM-FG2).

- Compare the changes in all BOE and CPD from Baseline to End of Study between Test Group and Control Group over 4 weeks.

- Characterize subgroups based on change in CPD from Baseline to End of Study (no change, <50% reduction, ≥50% reduction, 100% reduction, increase) within each study group.

- Characterize subgroups based on change in total NNAL from Baseline to End of Study (no change, reduction, increase) within each study group.

- Compare changes in the Fagerström Test for Cigarette Dependence from Baseline (Day 8) to End of Study within and between each study group

- Compare changes on the Quit Attempts and Quitting Intentions from Baseline (Day 1) to End of Study within and between each study group.

3 STUDY DESIGN AND EVALUATION

3.1 Study Design

This is a randomized, controlled, open-label, parallel group, multi-center, 5-week pilot study to determine changes in BOE in adult smokers allowed *ad libitum* use of VBM-FG2 relative to adult smokers who are not allowed use of VBM-FG2. This study will be conducted in approximately 150 adult smokers who are considered to be in over all good health. Subjects will be randomized (based on gender, daily cigarette consumption [<20 and ≥20], 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 (90 subjects randomized to Test: 60 subjects randomized to Control) with no more than a 60:40 distribution of either males or females to either group.

Figure A: Study Design

Screening	**Baseline Period***		**Product Use Period†**			
Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Day -28 to Day -1	Day 1	Day 8±1	Day 15±1	Day 22±1	Day 29±1	Day 36±1
Subject evaluated against inclusion and exclusion criteria for study eligibility	Baseline CPD data gathered using recall of previous week and daily IVRS call.		Randomization in a 3:2 ratio (Test:Control) • Test = *ad libitum* VBM-FG2 • Control = no VBM-FG2			
	↑ **Enrollment**		↑ **Randomization**			

*Baseline Period = after the daily IVRS call on Day 1 through the daily IVRS call on Day 8.
†Product Use Period = after the daily IVRS call on Day 8 through the daily IVRS call on Day 36.

3.1.1 Duration of Study

Expected duration of the study, from first subject first visit through last subject last visit is approximately 3 months. Expected duration for each subject is expected to be up to approximately 5 weeks (potentially 9 weeks from Screening to End of Study). All subjects will be informed that they are allowed to smoke their own cigarettes or to quit smoking during the study.

3.1.2 Screening

Screening (Visit 1) will occur within 28 days of Day 1 (Day -28 to Day -1). An Informed Consent Form (ICF) must be signed prior to conducting any study related procedures. Potential subjects will undergo an initial evaluation (vital signs, urine pregnancy test [females only], and questionnaires) to determine initial eligibility.

If the Subject passes the initial evaluation, then he/she will be provided with a sample of VBM-FG2 and asked to use the product as they like for 15 minutes. Subjects will then complete a Potential Purchase Interest Questionnaire. If they indicate that they "definitely would buy" or "probably would buy" the product on the questionnaire, then the subject will undergo the rest of the screening procedures (clinical labs, electrocardiogram [ECG]). Laboratory values will be evaluated by a local laboratory.

Additional details related to Screening are located in Section 6 (Study Procedures and Observations).

3.1.3 Baseline Period

Subjects will return to the study site on the evening (between approximately 16:00 and 19:00) of Day 1 for Visit 2. A physical examination will be conducted and subjects who

satisfy all the inclusion criteria and exclusion criteria will be eligible for enrollment in the study.

Once a subject is enrolled in the study (Day 1), if they choose to no longer participate, they will be considered a drop-out/early termination subject.

During the Baseline Period, at Visits 2 and 3 (Days 1 and 8), blood and urine samples will be collected for analysis of BOE. Subjects will also complete the Past 7 Day Cigarettes Use Questionnaire (Appendix 5) while at the study site, to indicate their CPD over the previous week.

During the Baseline Period (Days 1 to 8) subjects will report CPD daily through an IVRS conducted each day between 16:00 and 19:00.

At Visit 3, approximately 150 subjects will be randomized to either the Test or Control Group in a 3:2 ratio (with not more than a 60:40 distribution of either males or females to either group). VBM-FG2 will be dispensed to subjects randomized to the Test Group for *ad libitum* use beginning after the Day 8 IVRS.

Additional details related to these visits are located in Section 6 (Study Procedures and Observations).

3.1.4 Product Use Period

The Product Use Period will begin following the Day 8 ± 1 IVRS and will continue through Day 36 ± 1. Subjects in the Test group will be provided VBM-FG2 for *ad libitum* use. Subjects in both Test and Control Groups will continue daily tobacco use tracking via an IVRS and return to the study site once a week during the 4 week Product Use Period for Visits 4 through 7, Days 15, 22, 29, and 36, respectively.

These weekly visits will include collection of urine and blood samples for BOE measurements, dispensing VBM-FG2 supplies (Test Group Only - Days 8, 15, 22, 29) and return of VBM-FG2 supplies and collection of empty product packaging (Test Group Only - Days 15, 22, 29, 36) as appropriate.

Subjects will be instructed to report to the Investigator all AEs and changes in concomitant medications and if necessary, to return to the study site for further evaluation.

During the End of Study visit (Day 36 or Early Termination), additional assessments will be performed to confirm the health and well-being of the subject.

Additional details related to these visits are located in Section 6 (Study Procedures and Observations).

3.2 Study Population

Adult cigarette smokers from 21 to 65 years of age, inclusive, will be evaluated for possible participation in the study. Approximately150 subjects will be randomized across

3 study sites. Upon written approval from ALCS, study sites may enroll additional subjects. Subjects must satisfy all inclusion and exclusion criteria to be enrolled in the study.

4 SUBJECT SELECTION AND DISCONTINUATION

4.1 Inclusion

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

1) sign an Institutional Review Board (IRB)-approved ICF for the study.
2) be between the ages of 21 and 65 years, inclusive, at the time of Screening.
3) consumed a minimum of 10 manufactured CPD daily during the last 12 months.
4) indicate that he/she smokes cigarettes "every day" at Screening and on Day 1
5) be able to fully comprehend the English language.
6) have an active phone number and must have daily access to a touchtone phone between 1600 and 1900 hours.
7) be interested in alternative tobacco products to cigarettes at Screening.
8) indicate that they "definitely would buy" or "probably would buy" on the VBM-FG2 *Potential Purchase Interest Questionnaire*.
9) be in generally good health.
10) if female, have a negative urine dipstick pregnancy test.
11) if female heterosexually active and of childbearing potential (i.e., not surgically sterile or two years naturally postmenopausal), agree to use a medically accepted method of contraception from Screening through the End of Study.

    Surgically sterile includes bilateral tubal ligation, essure, hysterectomy, or bilateral oophorectomy at least 6 months prior to enrollment. Naturally postmenopausal is defined as women having 2 years without menses (confirmed by follicle stimulating hormone levels).

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

12) have clinical laboratory tests within the appropriate reference range or which are clinically acceptable to the Investigator.

13) have a negative ethanol, amphetamines, opiates, cannabinoids, and cocaine urine drug screen.

14) test negative for human immunodeficiency (HIV), hepatitis B (hepatitis B surface antigen [HBsAg]), and Hepatitis C (anti-hepatitis C virus antibody [anti-HCV]).

15) be willing and able to comply with the requirements of the study.

4.2 Exclusion

A subject who meets any of the following exclusion criteria will not be enrolled in the study. Subject must not:

1) be pregnant, nursing, or planning to become pregnant during the study period.

2) indicate that he/she intends to quit smoking within the next 30 days (at Screening or on Day 1).

3) have uncontrolled hypertension, history of coronary heart disease or other significant heart conditions, and/or other significant medical conditions that might interfere with study procedures.

4) have used prescription anti-diabetic medication and/or insulin therapy within 12 months of Day 1.

5) have a history of drug or alcohol abuse within the 24 months prior to Screening.

6) have participated in a clinical study for an investigational drug, device, or biologic within 30 days prior to enrollment (Day 1).

7) be a current user of nicotine replacement therapy (indicate every day or some days on Subject Screener/Tobacco History Questionnaire).

8) be a current or former employee of the tobacco industry or a first-degree relative (e.g., parent, sibling, child) of a current or former employee of the tobacco industry.

9) have been involved in the development of the study design/conduct or be a first-degree relative (e.g., parent, sibling, child) of someone involved in the development of the study design/conduct.

10) be a current employee or personnel involved with the study at the study site.

11) be currently participating in the study at a different study site (i.e., each subject can only be in the study population once).

4.3 Subject Discontinuation

Investigators are urged to enroll only those eligible subjects who are likely to complete the entire study and who are willing to comply with the protocol-specified procedures. It is the right and duty of the Investigator to interrupt the test product of any subject whose health or well-being may be threatened by continuation in this study, or who may be experiencing unmanageable factors that may interfere with the study procedures and/or the interpretation of study results. Such subjects will be withdrawn from the study.

4.3.1 Subject Discontinuation Criteria

Subject participation in the study may be prematurely discontinued for any of the following reasons:

- Withdrawal of informed consent (subject's decision and right to withdraw at any time for any reason);
- Any clinical AE, laboratory abnormality, or intercurrent illness, which in the opinion of the Investigator, indicates that continued participation in the study is not in the best interest of the subject;
- Failure to comply with protocol requirements;
- Subjects who become prisoners or become incarcerated;
- Termination of the study by ALCS;
- Subjects who are lost to follow-up;

4.3.2 Procedures for Discontinuation

If a subject discontinues participation in the study, the reason for withdrawal or discontinuation will be documented in the case report form (CRF) and source documents. End of Study/Early Termination will be performed (see section 6.2.5). If a subject chooses to withdraw from the study because of an AE, the principal specific event and any related test results must be captured in the source documents and CRF on both the End of Study CRF and the Adverse Event CRF. Subjects who discontinue participation in the study due to an AE experienced during study conduct will, at minimum, be followed until resolution, stabilization, or the subject is lost to follow-up.

If a subject is lost to follow-up, a reasonable effort is required to contact the subject and perform the End of Study procedures. A reasonable effort is considered, at minimum, 3 phone attempts followed by a certified letter to the subject's last known address requesting their return to the study site for a safety evaluation and return of any test product.

4.3.3 Replacement of Subjects

Subjects who discontinue early may be replaced at the discretion of the Sponsor.

5 STUDY CONDUCT

5.1 Ethics

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

The study will be conducted in compliance with the protocol. No deviation(s) from the protocol will be implemented without the prior review and approval of the IRB except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation (if applicable to IRB policies) will be reported to the IRB as soon as possible. The protocol, any amendments, and the subject ICF will receive IRB approval prior to initiation of the study.

5.2 Randomization and Administration

5.2.1 Study Group Assignment (Randomization)

Each site will be assigned a unique two-digit (e.g. 01, 02, etc.) site number.
At each site, each subject will be assigned a unique sequential enrollment number consisting of "E" + a sequential number beginning with 001 (e.g. E001, E002, E003, E004) at enrollment on Day 1. This enrollment number in combination with the site number will remain with the subject until they are randomized on Day 8.

On Day 8 subjects will be randomized (based on gender, daily cigarette consumption [≤20 and >20], and quit attempts [any quit attempt/ no quit attempts]) to either the Test or Control Group in a 3:2 ratio (not more than 60:40 distribution of either male or female), according to a randomization schedule. Each subject will be assigned a randomization number based on this randomization schedule. This randomization number will be used for identification throughout the study and will not be used for any other subject at the study site. Further details on the randomization will be available in the Randomization Specification Plan prepared by Covance and approved by ALCS.

Because this is an open label study, product use assignments will not be blinded.

5.2.2 Test Product Administration

Subjects in the Test Group will be provided VBM-FG2 discs and told to use them *ad libitum* throughout the study.

5.3 Blinding/Unblinding

Not applicable. This study is open label.

5.4 Prohibited Medications During the Study

Use of prescription anti-diabetic medication and/or insulin therapy within 12 months of Day 1 and throughout the course of the study is prohibited. Investigational drugs not yet approved for their intended use by FDA are prohibited for 30 days prior to Screening and throughout the course of the study.

6 STUDY PROCEDURES AND OBSERVATIONS

6.1 Time and Events Schedule

	Screening		Baseline Period		Product Use Period			
	Visit 1		Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	EOS/ET Visit 7
Procedure	**Day -28 to -1**		**Day 1**	**Day 8±1**	**Day 15±1**	**Day 22±1**	**Day 29±1**	**Day 36± 1**
Obtain Informed Consent	X							
Review Inclusion/Exclusion Criteria	X							
Subject Screener/Tobacco History	X							
Identification of Brand of Cigarettes[1]	X		X	X	X	X	X	X
Photocopy Cigarette Pack	X							
Medical History/Demographics	X							
Height	X							
Weight, BMI	X							X
Vital Signs[2]	X		X	X	X	X	X	X
Pregnancy Test[3]	X		X	X	X	X	X	X
Concomitant Medications	X		X	X	X	X	X	X
Smoking Cessation Counseling	X							X
Product Trial	X							
Potential Purchase Interest Questionnaire	X							X
ECG[4]		X						X
Clinical Labs (Chemistry)[5]		X						X
Clinical Labs (Hematology)[6]		X						X
Clinical Labs (Urinalysis)[7]		X						X
HIV, HBsAg, anti-HCV		X						
Urine Drug Screen		X						
Fagerström Test for Cigarette Dependence			X	X				X
Past 7 Days Cigarette Use Questionnaire			X	X				
Other Tobacco Product Use Questionnaire[8]			X	X	X	X	X	X
Physical Examination			X					X
Quit Attempts and Quitting Intentions Questionnaire – Day 1			X					
Adverse Events[9]			X	X	X	X	X	X

Procedure	Screening Visit 1 Day -28 to -1		Baseline Period Visit 2 Day 1	Visit 3 Day 8±1	Product Use Period Visit 4 Day 15±1	Visit 5 Day 22±1	Visit 6 Day 29±1	EOS/ET Visit 7 Day 36± 1
BOE Analytical Labs (Urine)[10]			X	X	X	X	X	X
BOE Analytical Labs (Blood) [11]			X	X	X	X	X	X
BOE (Exhaled CO) [12]			X	X	X	X	X	X
Collection of Banked Urine Sample				X				X
Collection of Banked Blood Sample				X				X
IVRS Product Use Entry[13]			X	X	X	X	X	X
Dispense VBM-FG2				X	X	X	X	
Collect Used/Unused VBM-FG2 packages					X	X	X	X
Quit Attempts and Quitting Intentions Questionnaire – End of Study								X

Anti-HCV = anti-hepatitis C virus antibody; BMI = body mass index; BOE = biomarker of exposure; ECG = electrocardiogram; EOS = End of Study; ET = Early Termination; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; IVRS = Interactive voice Response System

1 If a subject's most commonly used brand of cigarettes has changed, a photocopy will be made of the new preferred brand cigarette pack
2 Respiratory rate, pulse rate, blood pressure, and oral temperature; vital sign measurements will be taken with subjects in the sitting position after at least 10 minutes of rest and at least 15 minutes after the last cigarette smoked
3 A urine dipstick pregnancy test will be performed at Screening for all females. All additional tests pregnancy test will be conducted via serum.
4 12-lead ECG (10 electrodes)
5 Comprehensive/Complete Metabolic Panel
6 Complete Blood Count (CBC) with differential
7 Visual examination, chemical examination, microscopic examination
8 Other Tobacco Product Use Questionnaire captures the use of tobacco products other than cigarettes and VBM-FG2.
9 All AEs occurring after signing of the ICF should be captured in the source and CRF.
10 **Urine:** nicotine and its 5 metabolites (Cotinine, trans-3 '-Hydroxycotinine, trans-3 '- Hydroxycotinine-O-glucuronide, Nicotine-N-glucuronide, and Cotinine-N-glucuronide), total NNAL, *S*-phenyl mercapturic acid, and creatinine
11 **Blood:** carboxy-hemoglobin (COHb)
12 **Respiratory:** exhaled CO
13 Daily tobacco product use will be entered into an IVRS between 16:00 and 19:00 (Day 1 through End of Study)

6.2 Procedures by Visit

The Investigator is responsible for adherence to the protocol. Prompt and complete reporting of all pertinent data is essential. In order to minimize variability of evaluations, it is preferred that the same individuals perform the same or similar evaluations for all subjects within a site.

6.2.1 Visit 1: Screening (Day -28 to Day -1)

6.2.1.1 Screening Part 1

All potential subjects

- Explain study and obtain signature of informed consent
- Review inclusion/exclusion criteria
- Subject Screener/Tobacco History
- Identification of preferred brand of cigarettes
- Photocopy cigarette pack
- Medical history/demographics
- Height
- Weight, body mass index (BMI)
- Vital Signs
- Urine dipstick pregnancy test (female subjects only)
- Concomitant medications
- Product trial
- Potential Purchase Interest Questionnaire
- Smoking cessation counseling

6.2.1.2 Screening Part 2

Only subjects that pass Screening Part 1

- ECG
- Chemistry, hematology, urinalysis
- HIV, HBsAg, anti-HCV Screen
- Urine drug screen

6.2.2 Visit 2: (Day 1)

- Past 7 Day Cigarette Use Questionnaire
- Quit Attempts and Quitting Intentions Questionnaire – Day 1
- Other Tobacco or Nicotine Containing Product Use Questionnaire
- Fagerström Test for Cigarette Dependence
- Vital signs
- Identification of preferred brand of cigarettes
- Physical examination
- Concomitant medications
- AEs
- Serum pregnancy test (female subjects only)

- BOE samples (urine, blood, exhaled CO)
- IVRS product use daily tracking

6.2.3 Visit 3: Randomization (Day 8 ± 1)

- Fagerström Test for Cigarette Dependence
- Past 7 Day Cigarette Use Questionnaire
- Other Tobacco or Nicotine Containing Product Use Questionnaire
- Vital signs
- Identification of preferred brand of cigarettes
- Concomitant medications
- AEs
- Serum pregnancy test (female subjects only)
- BOE samples (urine, blood, exhaled CO)
- Collect banked urine, serum and plasma samples
- Randomization to a Product Use Group (Test or Control)
- Dispense VBM-FG2 (subjects in Test Group only)
- IVRS product use daily tracking continues

6.2.4 Visit 4: (Day 15 ± 1), Visit 5: (Day 22 ± 1), Visit 6: (Day 29 ± 1)

- Other Tobacco or Nicotine Containing Product Use Questionnaire
- Vital signs
- Identification of preferred brand of cigarettes
- Concomitant medications
- AEs
- Serum pregnancy test (female subjects only)
- BOE samples (urine, blood, exhaled CO)
- Collect used/unused VBM-FG2 packages
- Dispense VBM-FG2
- IVRS product use daily tracking continues

6.2.5 Visit 7: End of Study/Early Termination (Day 36 ± 1)

- Fagerström Test for Cigarette Dependence
- Other Tobacco or Nicotine Containing Product Use Questionnaire
- Potential Purchase Interest Questionnaire
- Quit Attempts and Quitting Intentions Questionnaire – End of Study
- Smoking cessation counseling
- Physical examination
- ECG
- Chemistry, hematology, urinalysis
- Vital Signs
- Identification of preferred brand of cigarettes
- Weight, BMI
- Concomitant medications

- AEs
- Serum pregnancy test (female subjects only)
- BOE samples (urine, blood, exhaled CO)
- Collect banked urine, serum and plasma samples
- Collect used/unused VBM-FG2 packages
- IVRS product use daily tracking completes

6.3 Details of Procedures

The Time and Events Schedule in Section 6.1 summarizes the study procedures to be performed at each visit. Details of the individual study procedures are described below.

6.3.1 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 his/her ICF.

6.3.2 Height, Weight, and Body Mass Index

Height (cm) and weight (kg) in indoor clothing with shoes off. Body mass index will be calculated as weight (kg)/height (m) squared.

6.3.3 Vital Signs

Vital signs (respiratory rate, pulse rate, blood pressure, oral temperature) should be taken in the sitting position after at least 10 minutes of rest and at least 15 minutes after the last cigarette smoked.

6.3.4 Identification of Preferred Brand of Cigarette

Study site staff will inquire as to a subject's most commonly used brand of cigarettes at each visit. If the subject's most commonly used brand changes a photocopy will be taken of the new pack.

6.3.5 Photocopy Cigarette Pack

Subjects will bring with them a pack of their most commonly used cigarettes. The pack will be color photocopied and the copy will be placed in the source documents.

6.3.6 Questionnaires

Self-administered questionnaires will be completed at various times throughout the study with a trained study coordinator present for assistance. The questionnaires to be used in this study are as follows and are located in the Appendices:

- Subject Screener/Tobacco History (history of tobacco use, quit intentions, etc.), Visit 1
- Potential Purchase Interest Questionnaire, Visit 1 and End of Study
- Fagerström Test for Cigarette Dependence, Visits 2, 3, and End of Study
- Past 7 Days Cigarette Use Questionnaire, Visits 2 and 3
- Other Tobacco Product Use Questionnaire, from Visit 2 through End of Study
- Quit Attempts and Quitting Intentions Questionnaire – Day 1, Visit 2
- Quit Attempts and Quitting Intentions Questionnaire – End of Study, End of Study

6.3.6.1 Product Trial and Potential Purchase Interest Questionnaire

Following ICF signature and preliminary check of subject's well being, vital signs and urine pregnancy test (female subjects only), each subject will be instructed that VBM-FG2 discs are a new kind of tobacco product designed to appeal to adult smokers interested in innovative types of spit-free tobacco product alternatives to cigarettes. Adult tobacco product consumers put the product in their mouth, chew on it, and should properly dispose of it when they are done. Subjects will then be provided a single VBM-FG2 disc and asked to place the disc in their mouth, chew on it as they like for up to 15 minutes, and then remove and discard the disc when done. After the subject has used the product, a Potential Purchase Interest Questionnaire will be administered. Only subjects who meet the non-invasive inclusion/exclusion criteria and indicate that they "definitely would buy" or "probably would buy" on the Questionnaire will be allowed to continue through the invasive inclusion/exclusion criteria (blood work).

6.3.7 Medical History/Demographics

A medical history will be obtained at Screening by the Investigator or qualified designee.

Medical history and demographic data, including name, sex, age (each subject must show proof of age with government-issued identification [e.g., driver's license] which will be photocopied as source documentation), race, tobacco use/history, and smoking history will be recorded for each subject.

6.3.8 Urine Dipstick Pregnancy Tests

A urine dipstick pregnancy test will be performed at Screening on all female subjects. This should be performed and results verified prior to the product trial.

6.3.9 Concomitant Medications

Except for medications listed as prohibited, all medications necessary for the health and well-being of the subject are permitted.

At Screening, concomitant medications need to be recorded in the subject's source documents and CRF. Subjects should be queried at each visit for additions, deletions, or modifications to existing concomitant medications. These changes need to be captured throughout the study.

6.3.10 Inclusion/Exclusion Criteria

The inclusion and exclusion criteria will be reviewed by the Investigator or qualified designee to ensure that the subject qualifies for the study.

6.3.11 Clinical Laboratory

All clinical laboratory tests will be conducted by the local laboratory facility accredited by the Centers for Medicare and Medicaid Services (Clinical Laboratory Improvement Amendments of 1988 [CLIA-88]). Values for the laboratory parameters are to be within the laboratory normal ranges. Subjects with Screening laboratory values outside the normal limits will be accepted into the study only after the Investigator or designee (a physician) has determined that the abnormal values are "not clinically significant".

Clinical chemistry (comprehensive metabolic panel), hematology (CBC with differential) and urinalysis will also be performed at Screening and End of Study. Comprehensive metabolic panel includes, at minimum:

- General function - glucose, calcium
- Proteins - albumin, total protein
- Electrolytes - sodium, potassium, CO_2, chloride,
- Kidney(s) – blood urea nitrogen, creatinine, uric acid
- Liver – alkaline phosphatase, alanine amino transferase, aspartate amino transferase, bilirubin

Complete blood count with differential will be performed at Screening and End of Study. Complete blood count with differential includes, at a minimum:

- White blood cells (WBC) – neutrophils, eosinophils, basophils, lymphocytes, monocytes
- Red blood cells (RBC) – RBC count, hemoglobin, hematocrit, RBC indices,
- Platelet count

Routine clinical urinalysis will be performed at Screening and End of Study/Early Termination. Urinalysis includes, at minimum, bilirubin, blood, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, and urobilinogen. Microscopic examination will be conducted if protein, leukocyte esterase, nitrite and/or blood are detected. Microscopic analysis will include RBC, WBC, casts, and bacteria.

6.3.12 Physical Examination

The Investigator (or qualified designee, which in this instance should be a physician, licensed physician's assistant, or nurse practitioner) will perform a physical examination on Day 1 and at End of Study. A general physical examination includes observations and questioning by the Investigator or his/her designee.

Note: Only Investigators licensed to conduct physical examinations are approved to perform physical examinations and must be listed on the Site Signature and Delegation of Duties Log.

6.3.13 ECG

A 12-lead ECG (10 electrodes) will be performed after at least 5 minutes of rest at Screening and End of Study.

6.3.14 Human Immunodeficiency Virus, Hepatitis B, and Hepatitis C Screen

Human immunodeficiency virus antibody, HbsAg, and anti-HCV screens will be performed at Screening.

6.3.15 Urine Drug Screens

Urine drug screens will be performed at Screening for ethanol, amphetamines, opiates, cannabinoids, and cocaine.

6.3.16 Serum Pregnancy Tests

A serum pregnancy test will be performed at all visits subsequent to Screening on all female subjects.

6.3.17 Adverse Events

Adverse events will be captured from ICF signing. Subjects should be queried at each visit for any additional AEs or modifications to existing events. These changes need to be captured throughout the study.

6.3.18 Analytical Laboratory (Biomarkers of Exposures)

Urine BOE (with the exception of creatinine) will be analyzed using validated analytical methods with appropriate quality controls according to the *FDA Guidance for Industry: Bioanalytical Method Validation* (May, 2001) and in accordance with FDA Good Laboratory Practice regulations (Title 21 CFR Part 58; Laboratory To Be Determined [TBD]). Urine creatinine and blood COHb will be analyzed at a CLIA-88 certified clinical laboratory (TBD). The specific information on the laboratories will be included in a Letter of Administrative Change.

Biomarkers of exposure will include:

Urine: nicotine and its 5 metabolites (Cotinine, trans-3 '-Hydroxycotinine, trans-3'-Hydroxycotinine-0-glucuronide, Nicotine-N-glucuronide, and Cotinine-N-glucuronide), total NNAL, urinary S-PMA, and creatinine.

Blood: COHb

Respiratory: exhaled CO

6.3.18.1 Urine Sample Collection for Biomarker Analysis

A urine sample will be collected at Visits 2 through 7. Urine will be collected upon arrival at the study site. Participants will be instructed to not void their bladders for

approximately 2 hours before the study visit. The total volumes for each urine void will be recorded.

Briefly, aliquots (in the order of priority) will be prepared according to Table A for each subject. All aliquots will be prepared and then stored at -20°C or lower until analyzed or shipped. The additional back-up sample may be used for potential re-assays of BOEs and will be stored until the Clinical Study Report is finalized.

Table A: Samples for Analysis of Urinary Biomarkers of Exposure

Urine Biomarkers	Number of Aliquots	Aliquot volume (mL)	Total Volume for Parameter (mL)	Container Type
Total NNAL	2	10	20	HDPE
Nicotine Equivalents	2	5	10	HDPE
S-PMA	2	5	10	HDPE
Creatinine	2	5	10	HDPE
Additional Back-up Sample	1	50	50	HDPE
Banked Sample	1	50	50	HDPE

6.3.18.2 Blood Sample Collection for Biomarker Analysis

Blood sample collections for analytical labs will be collected at Visits 2 through 7. Blood samples should be collected after urine collection following vital sign measurements. Subject visits should be scheduled such that blood samples can be collected as late in the day as possible and preferably at the same or similar time with each visit.

A 4-mL blood sample for COHb analysis will be drawn in sodium heparin (green top) vacutainer tubes. Immediately following collection, the blood samples will be gently inverted and refrigerated. The whole blood samples will be properly labeled and delivered to the laboratory. An additional 2 (5 mL) samples of blood (1 for serum and 1 for EDTA/plasma) will be collected at Visit 3 and again at End of Study for sample banking. Details on blood sample volumes for BOE analysis, clinical laboratory evaluations, and serology are noted in Table B.

Table B: Blood Sample Volumes

Parameter	Maximum Blood Volume Per Sample (mL)	Approximate Number of Blood Samples	Approximate Total Blood Volume
Hematology	4	2	8
Chemistry	8.5	2	17
HIV, HBsAg, anti-HCV	8.5	1	8.5
COHb	4	6	24
Sample Banking – Serum	5	2	10
Sample Banking – Plasma	5	2	10
Serum Pregnancy	8.5	6	51
	Total	Male	77.5
		Female	128.5

6.3.18.3 Sample Banking

Samples of urine and blood (serum and EDTA/plasma) will be collected at Visit 3 and End of Study, and stored for up to 1 year for possible future exploratory analysis (details of processing and storage are contained in a separate document). Each subject will give consent for the collection of samples for banking.

6.3.18.4 Exhaled CO Measurement

Exhaled CO measurement tests should occur immediately after blood collection. A standard exhaled CO Test will be performed with Micro+™ Smokerlyzer® CO monitors (or equivalent) following the manufacturer's instructions.

6.3.19 Interactive Voice Response System

Interactive Voice Response System is a tool which uses a telephone as a device to input information. It is an entirely automated and user-friendly system. To utilize the IVRS, a study subject will call into a pre-specified number and answer recorded questions using the number pad on a touch tone phone.

In this study an IVRS will be used between 16:00 and 19:00 on Days 1 to 36 to assess CPD. The IVRS assessment on Day 1 will serve as orientation to the system. Subjects will be instructed to call into the system and to answer a preset sequence of questions. During the Baseline Period, the same questions will be asked of every subject. Following randomization, beginning on Day 9, subjects assigned to the Control Group will continue to answer the same set of questions administered during the Baseline Period. Subjects randomized to the Test Group will be asked the same questions that were asked during the Baseline Period, as well as an additional 2 questions related to VBM-FG2 consumption.

6.3.20 Smoking Cessation Counseling

The Investigator or designee, at Screening and at the end of the Study or upon Early Termination, will advise all adult smokers that to reduce the health effects of smoking and using smokeless tobacco products, the best thing to do is to quit. The Investigator or designee will also offer all adult smokers the Quit Assist™ brochure and refer all adult smokers to the Quit Assist™ website, which contains citations to a number of third-party information sources, including websites, telephone resources, and other organizations with additional information.

7 CLINICAL SUPPLIES

7.1 Test Product

The test product consists of open-label, child resistant tubular packaged VBM-FG2 discs. The VBM-FG2 discs are mint-flavored, non-dissolving, discs that contain approximately 1.5 mg of nicotine. The amount of nicotine a subject actually receives depends on how he or she uses the product (e.g., how many discs are chewed, how hard they are chewed, and how long they are chewed or kept in the mouth).

7.2 Packaging and Labeling

The VBM-FG2 discs will be provided to subjects in a child resistant tubular container (16 discs within each tube).

The label has black letters on a white background. Stating:

Tobacco Product

Consumer Test Product. Not for Sale.

Warning: This product contains tobacco-derived nicotine. Nicotine 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.

Distributed by Product Opinion Laboratory

Richmond VA 23261

The packaging also has a sticker indicating the product is VBM-FG2 and the date manufactured.

Prior to dispensing, the site will apply a label to disclose, at minimum, the protocol number and unique subject identifiers, date it was dispensed, and a statement to "keep out of reach of children".

7.3 Storage, Handling and Dispensing

Altria Client Services, Inc. will be responsible for assuring that the quality of the test product provided is adequate for the duration of the trial. Test products should be stored under room temperature [15 to 25°C (59 to 77°F)] conditions in a locked limited-access area.

The test product shall be dispensed in accordance with the protocol. Test product must be dispensed only from IRB-approved protocol-specific study sites. The product must only be dispensed by the Investigator or designee documented on the Site Signature and Delegation of Duties Log.

Subjects in the Test Group will initially receive 7 tubes of VBM-FG2 at Visit 3. Subjects will be asked to bring back all product packages (empty, partially used, unopened) and unused product at each subsequent study visit. Study sites will perform accountability on the returned product and tailor future dispensation numbers based on product use. If a subject has used more than 6 of the 7 tubes received, an additional 3 tubes will be dispensed for the next week. At subsequent visits, additional tubes will be dispensed in the same manner (for example; if 9 of the 10 tubes are used, 13 tubes will be given. This will continue to a maximum of 16 tubes in 1 week; otherwise subjects will receive the same amount (7 unopened tubes per week). Unused tubes will be re-dispensed to the same subject.

Only unused tubes with the tamper evident seal intact should be dispensed to the subject.

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

The subjects will be instructed to store the containers in a cool dry place and not to leave the container(s) in extreme conditions (e.g. in a car parked in the heat/cold, freezer, etc).

7.4 Test Product Records at Study Sites

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

- Amount received/placed in storage area
- Amount dispensed to and returned by each subject, including unique subject identifiers
- Non-study disposition (e.g., lost, wasted, broken)
- Amount returned to Sponsor
- Amount destroyed at study site, if applicable
- 10 tubes of VBM-FG2 will be retained by each study site until final Clinical Study Report is issued

7.5 Return and Destruction of Test Product

7.5.1 Return

Upon completion or termination of the study, all unused and/or partially used test product must be returned to Altria Client Services, Inc. or designee, if not authorized by ALCS to be destroyed at the study site.

All test products returned to Altria Client Services, Inc. or designee must be accompanied by the appropriate documentation and be clearly identified by protocol number and site number on outermost shipping container. Returned supplies should be in the original containers (e.g., tubes that have clinical labels attached). Empty containers should not be returned to Altria Client Services, Inc. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures and provided that appropriate records of disposal are kept. The responsible ALCS Contact (or designee) should arrange the return of unused test product(s).

7.5.2 Destruction

If written authorization to destroy test product has been issued by Altria Client Services, Inc. to a study site, it is the Investigator's responsibility to ensure that arrangements have been made for the disposal, according to applicable regulations, guidelines, and institutional procedures. Appropriate records of disposal must be documented. The

unused test products can only be destroyed after being inspected and reconciled by the responsible ALCS Contact (or designee).

8 ADVERSE EVENT REPORTING IN CLINICAL TRIALS

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.[2,3]
>
> [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 after the subject has signed the ICF document must be recorded in the CRF, including the date and time of onset and outcome of each event. Events captured between Screening (Visit 1) and Visit 2 occurring prior to study product usage will be documented as baseline signs and symptoms and not AEs, unless "likely" or "definitely" associated with product trial use in Screening Part 1.

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

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

The Investigator will review each event and rate each reported sign or symptom on a 3-point severity scale. The following definitions for **rating severity**[2] 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[4,5] (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 "certainly/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 to the Sponsor within 24 hours of the site's learning of the SAE or, at the latest, on the following workday. The Sponsor's representative to contact about this study is:

Jianmin Liu, M.D.
Clinical Quality Assurance Manager
Altria Client Services Inc.
601 E. Jackson Street
Richmond, Virginia 23119
Phone: (804) 335-2441
Cellular: (804) 852-4156
Fax: (804) 335-2300

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 to a final outcome regardless of whether the subject is still participating in the study. Final outcome may be classified as resolved, improved, unchanged, worse, fatal, or unknown (lost to follow-up). Where appropriate, medical tests and examinations will be performed to document the outcome of the AE.

8.4 Pregnancy

Pregnancy occurring in a female study subject during the study will be documented in a note to file and as a protocol deviation in the clinical conduct study report to the IRB. Pregnancy itself is not a SAE. The Investigator or designee will discontinue the pregnant subject from the study and will advise her to seek prenatal care and counseling from her primary care provider. If the pregnant subject smokes, the Investigator will offer her a Quit Assist™ brochure and refer her to the Quit Assist™ website, which contains citations 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.

The site clinical 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 site clinical 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.

9 Data Management

Every effort will be made to ensure that data management practices adhere to international ethical and scientific quality standard of clinical data management procedures. The sponsor will select and contract with a contract research organization (CRO) to maintain the database for this investigation.

9.1 Database Design and Creation

An appropriate database will be designed and created within a validated Clinical Data Management System (CDMS). This database will be designed to store the data as recorded on the CRFs and will ensure a one-to-one mapping between the CRFs and the electronic copy stored in the system.

9.2 Data Coding

Upon completion of CRF data entry by the CRO, a secondary, in-house clinical review will be conducted. Adverse event coding will be undertaken using Medical Dictionary for Regulatory Activities. This version of the dictionary will remain the same throughout the trial.

9.3 Data Entry and Verification

The data recorded on the CRFs will be entered via independent, double data entry into the CDMS.

9.4 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 the vendor responsible for the analysis of these study data.

9.5 Data Validation

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

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

9.6 Database Lock

On completion of the trial, after data entry is complete and the data has been pronounced clean, the database will be locked and final write access will be removed.

A data management plan will be created to describe the details of the data management.

10 STATISTICS

10.1 Sample Size Determination

This pilot study is being conducted with the objective to collect data on the variability of the primary outcome measure, which will be used to estimate the sample size for a future pivotal study. The sample size for this study is believed to be appropriate based on statistical principles for pilot studies.

10.2 Criteria for Evaluation

10.2.1 Primary Outcome Measure (Endpoints)

The primary outcome measure is:

- Differences in the percent change from Baseline to the End of Study in urinary total NNAL between Test and Control Groups.

10.2.2 Secondary Outcome Measures (Endpoints)

The secondary outcome measures are:

- Differences in all BOE during the Baseline Period between Day 1 (weekly recall) versus Day 8 (daily tracking using IVRS).

- Difference in CPD during the Baseline Period between once weekly recall (Days 1 and 8) versus daily tracking (average of recordings on Days 2 through 8).
- Differences in the percent change from Baseline to End of Study in BOE (urinary NE , S-PMA, blood COHb, exhaled CO) and CPD between the Test and Control Groups.
- Differences from Baseline to End of Study in all BOE and CPD between the Test and Control Groups.
- Proportion of subjects in subgroups based on cigarette consumption change from Baseline to End of Study (no change, <50% reduction, ≥50% reduction, 100% reduction, increase) within and between the Test and Control Groups.
- Proportion of subjects in subgroups based on total NNAL change from Baseline to End of Study (no change, reduction, increase) within each group.
- Changes from Baseline (Day 8) to End of Study in Fagerström Test for Cigarette Dependence, within and between the Test and Control Groups.
- Changes from Baseline (Day 1) to End of Study on the Quit Attempts and Quitting Intentions, within and between the Test and Control Groups.

10.2.3 Safety Outcome Measures (Endpoints)

Safety analyses will be conducted on the safety population. Safety analyses will include summaries and analysis of AEs as well as summaries of vital signs and laboratory test results.

See Section 8 for details of procedures for assessment and reporting of AEs.

10.3 Data Set Descriptions

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

Per-protocol (PP) population is defined as a subset of the ITT population which is comprised of subjects who completed the study without any major protocol violations.

10.4 Data Set Analyses

Both the ITT and the PP populations will be used in the statistical analyses.

Gender, average daily cigarette consumption (≤20 and >20) and quit attempts may affect the primary outcome of the study and they will be considered in the randomization. A randomization plan will be developed to balance these factors between the product use groups. Other factors such as study site, socio-economic status, etc., will be adjusted in statistical analyses. The details of the plan will be provided in the statistical analysis plan.

Deviations from the approved statistical analysis plan will be reported in the final study report.

10.4.1 Demographics and Baseline Characteristics

Demographic baseline characteristics will be summarized by product use group with descriptive statistics (the number of non-missing values, mean, median, standard deviation [SD], minimum, maximum, CV, 95% confidence interval [CI]) for continuous variables (e.g., BMI) and frequency counts for categorical variables (e.g., gender). Fisher's exact test will be used to test for the differences in categorical variables between the two study groups and t test, to test for the differences in continuous variables.

10.4.2 Endpoint Analyses

All descriptive and inferential statistical analyses will be performed using SAS software version 9.3.

10.4.2.1 Primary Endpoint Analyses

A linear mixed model for repeated measures analysis of variance will be used for the analyses of the primary outcome measure. Terms of the model will be defined in the statistical analysis plan. SAS procedure Proc Mixed will be used for the statistical computing.

10.4.2.2 Secondary Endpoint Analyses

For the secondary outcome measures with a difference over time, a linear mixed model for repeated measures analysis of variance will be used for the analysis of the secondary outcome measure. The model will include terms for study group and/or cigarette tracking method, study time, and subject. SAS procedure Proc Mixed will be used for the statistical computing.

For correlations, a linear regression analysis will be conducted to examine the relationships between levels of biomarkers (dependent variable) with either the weekly cigarette counts (independent variable) or the daily cigarette counts. The coefficients of determination will be compared.

For proportion of subjects, The Mantel-Haenszel Chi-Square Test will be used to test the frequency differences between the two groups.

10.4.3 Safety Data Analyses

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 group using frequency counts.

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 will be described in the text of the final report.

10.4.4 Interim Analyses

An interim data analysis will be conducted after the first 50 subjects (approximately 30 Test Group and 20 Control Group subjects) have completed the study. The analysis will be based on data from the 50 subjects up to the completion time point.

The purpose of the analysis is to obtain timely information for the planning of a proposed pivotal study. Descriptive statistics (n, mean, median, SD, range, 95% CI) will be provided by study group for subject demographics, the primary endpoint variable, and the secondary endpoint variables that are continuous in scale. Frequency distribution (number and proportion) will be provided for the safety variables and the secondary endpoint variables that are categorical.

10.5 Accounting for Missing, Unused, and Spurious Data

No imputations will be made for missing safety data.

11 QUALITY ASSURANCE

11.1 Compliance with Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, ALCS or designee. The Investigator should not implement any deviation or change to the protocol without prior review and documented approval from the IRB of an Amendment, except where necessary to eliminate an immediate hazard(s) to study subjects. Any significant deviation must be documented.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB approval, as soon as possible the deviation or change will be submitted to:

- IRB for review and approval;
- ALCS;
- Regulatory Authority(ies), if required.

Documentation of approval signed by the chairperson or designee of the IRB(s) must be sent to ALCS.

If an Amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s) for review and approval; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the Amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

11.2 Monitoring for Protocol Compliance

Altria Client Services, or designee, must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On-site they will review study records in comparison with source documents, discuss the conduct of the study with the Investigator, and verify that the facilities remain acceptable.

In addition, ALCS internal auditors and government inspectors may evaluate the study and must be allowed access to CRFs, source documents and other study files. Altria Client Services audit reports will be kept confidential.

Additional information regarding protocol specific monitoring procedures is maintained by ALCS, external to the protocol.

THE INVESTIGATOR MUST NOTIFY ALCS PROMPTLY OF ANY INSPECTIONS SCHEDULED BY REGULATORY AUTHORITIES, ALLOW ALCS TO BE PRESENT AND PROMPTLY FORWARD COPIES OF INPECTION REPORTS TO ALCS.

12 ETHICAL AND LEGAL CONSIDERATIONS

12.1 Institutional Review Board

Before study initiation, the Investigator must have written and dated approval from the IRB for the protocol, ICF, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to subjects. The IRB approval should be obtained in writing, clearly identifying the trial, the documents reviewed, and the date of the review.

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

The Investigator or Sponsor should also provide the IRB with a copy of any product labeling, reports, updates and other information according to regulatory requirements or Institution procedures.

12.2 Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate.

12.2.1 Informed Consent Procedures

Preparation of the consent form must include all elements required by ICH, GCP and applicable regulatory requirements, and must adhere to the ethical principles that have their origin in the Declaration of Helsinki. The consent form must also include a

statement that ALCS and regulatory authorities have direct access to subject records. Prior to the beginning of the study, the Investigator must have the IRB's written approval of the written ICF and any other information to be provided to the subjects.

The Investigator must provide the subject with a copy of the consent form and written information about the study in the language in which the subject is most proficient. The language must be non-technical and easily understood. The investigator should allow time necessary for subject to inquire about the details of the study, then informed consent must be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The subject should receive a copy of the signed informed consent and any other written information provided to study subjects prior to subject's participation in the trial.

12.2.2 Update of Informed Consent

The informed consent and any other information provided to subjects, should be revised whenever important new information becomes available that is relevant to the subject's consent, and should receive IRB approval prior to use. The Investigator, or a person designated by the Investigator should fully inform the subject of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

12.3 Confidentiality

12.3.1 Confidentiality of Data

By signing this protocol the Investigator affirms to ALCS that information furnished to the Investigator by ALCS will be maintained in confidence and such information will be divulged to the Institutional Review Board, Ethical Review Committee, or similar or expert committee, affiliated institution, and employees only under appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the Investigator.

12.3.2 Confidentiality of Subject Records

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s). By signing this protocol the Investigator agrees that ALCS (or Sponsor representative), IRB, or Regulatory Agency representatives may consult and/or copy study documents in order to verify CRF data. By signing the consent form, the subject agrees to this process. If study documents will be photocopied during this process of verification, the subject will be identified by unique code; full name and other personal identifiers will be masked.[6]

12.3.3 Confidentiality of Investigator Information

By signing this protocol the Investigator recognizes that certain personal identifying information (e.g., name, hospital or clinic address, curriculum vitae) may be made part of

a regulatory submission and may be transmitted (either in hard copy or electronically) to ALCS for internal study management purposes or as required by individual regulatory agencies. Additionally, the Investigator's name, hospital/clinic address/phone number may be included when reporting certain SAEs to other investigators and stored in managed regulatory-controlled databases.

13 ADMINISTRATIVE

13.1 Records and Reports

An Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the test product or entered as a control in the investigation. Data reported on the CRF that are derived from source documents, must be consistent with the source documents or the discrepancies must be explained.

The CRF must be completed legibly in ink. Subjects are to be identified by initials, date of birth, and subject number, if applicable. All requested information must be entered on the CRF in the spaces provided. If an item is not available or is not applicable, it must be documented as such; do not leave a space blank.

The Investigator will maintain a Site Signature and Delegation of Duties Log to document signatures and initials of all persons authorized to make entries and/or corrections on the CRFs. A correction must be made by striking through the incorrect entry with a single line and entering the correct information adjacent to the incorrect entry. The correction must be initialed and dated by the person making the correction and must not obscure the original entry. The source documents may further provide an explanation for the change, if necessary.

The completed CRF must be promptly reviewed, signed and dated by a qualified investigator or sub-investigator. The Investigator must retain a copy of the CRFs including records of the changes and corrections.

13.2 Records Retention

The Investigator must maintain copies of all documents and records related to the conduct of the trial (such as test product disposition records, copies of CRFs (or electronic files), and source documents, etc.) for the maximum period required by applicable regulations and guidelines, or Institution procedures, or for the period specified by ALCS, whichever is longer. At a minimum, trial records must be retained for at least 2 years after the last approval/authorization of a marketing application or at least 5 years have elapsed since the formal discontinuation of clinical development of the test product.

If the Investigator wishes to relocate the records or is unable to retain them for the specified retention period, ALCS must be contacted and notified in writing.

If the Investigator withdraws from the study (e.g., relocation, retirement) the records shall be transferred to a mutually agreed upon designee (e.g., another investigator, IRB). Altria Client Services must be notified in writing of any such transfer.

All trial documents shall be made available if required by relevant health authorities. The Investigator must contact ALCS prior to destroying any records associated with the study.

13.3 Sponsor

The sponsor of this study is:

Altria Client Services, Inc.
P.O. Box 26583
Richmond, VA 23261-6583

13.4 Investigators, Study Sites, and Institutional Review Boards

Only investigators qualified by training and experience to perform a clinical investigation with a test product are selected. Altria Client Services or designee will contact and select all principal investigators (legally responsible party[ies] at each study site), who, in turn, will select their staff.

A list of active Investigator names, sub-investigator names, Institution names/addresses and reviewing IRBs names/addresses is maintained by ALCS, external to the protocol.

13.5 Central Organizations and/or Vendors

A list of names and addresses of organizations and/or vendors involved in subject management and associated testing and analysis where it affects the validity of the investigation is maintained by ALCS, external to the protocol.

14 GLOSSARY OF TERMS AND LIST OF ABBREVIATIONS

14.1 List of Abbreviations

Term	Definition
AE	Adverse event
ALCS	Altria Client Services
anti-HCV	Anti-hepatitis C virus antibodies
BMI	Body mass index
BOE	Biomarkers of exposure
°C	Degrees Celsius
CBC	Complete blood count
CDMS	Clinical Data Management System
CFR	Code of Federal Regulations
CI	Confidence interval
CLIA-88	Clinical Laboratory Improvement Amendments of 1988
CO	Carbon monoxide
COHb	Carboxyhemoglobin
CPD	Cigarettes per day
CRC	Consumer Response Center
CRF	Case report form
CRO	Contract research organization
ECG	Electrocardiogram
°F	Degrees Fahrenheit
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
ITT	Intent to treat
IVRS	Interactive voice response system
kg	Kilogram(s)
m	Meter(s)
mg	Milligram(s)
mL	Milliliter(s)
NE	nicotine equivalent
ng	Nanogram(s)
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
PAVE	Pilot Ambulatory VBM-FG2 exposure
PK	pharmacokinetic(s)

PP	Per protocol
RBC	Red blood count
SAE	Serious adverse event
SAP	Statistical analysis plan
S-PMA	S-phenylmercapturic acid
TBD	To be determined
US	United States
WBC	White blood cell

15 REFERENCES

1. Hatsukami DK, Joseph AM, Lesage M, et al. Developing the Science Base for Reducing Tobacco Harm. Nicotine Tob Res. 2007; Suppl 4:S537-553.
2. ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (E2A). *Federal Register*. Vol. 60, March 1, 1995, p. 11284.
3. ICH Guideline for Good Clinical Practice: Consolidated Guidance (E6). *Federal Register*. Vol. 62, May 9, 1997, p. 25692.
4. 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.
5. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *Lancet* 2000;356:1255-1259.
6. U.S. Department of Health and Human Services. HIPAA Privacy Rule. Information for Researchers. De-identifying Protected Health Information Under the Privacy Rule. Available online at http://privacyruleandresearch.nih.gov/pr_08.asp#8a. Last accessed August 30, 2011.

Appendix 1 Investigator Obligations

Each clinical investigator is responsible for conducting the study in accordance with the protocol, all applicable laws, regulations, and the ICH Consolidated Guideline: GCP.

A. Institutional Review Board (IRB) Review/Approval

It is the Investigator's responsibility to ensure that all aspects of the ethics review are conducted in accordance with the current Declaration of Helsinki as described in the ICH GCP guidelines, and/or in accordance with local laws, whichever provides the greatest level of protection for the study subjects. The protocol and any information supplied to the subject to obtain informed consent, including written informed consent forms (ICF), subject recruitment procedures (e.g., advertisements) and written information (e.g., information leaflets), must be reviewed and approved by a qualified IRB prior to enrolling subjects in the study. Prior to study initiation, ALCS must receive documentation of the IRB approval, which specifically identifies the study/protocol and a list of the committee members.

Amendments to the protocol and revisions to the ICF must also be submitted to and, if required, approved by the IRB.

At intervals required by the IRB, but not less than annually, the Investigator must submit to the IRB a progress report with a request for re-evaluation and re-approval of the study. A copy of the progress report and re-approval of the study must be sent to ALCS.

When ALCS provides the Investigator with an Expedited Safety Report, the Investigator must promptly forward a copy to the IRB according to local regulatory requirements or institution procedures.

After completion or termination of the study, Investigators should follow any applicable institutional policies and procedures for notifying the IRB of the study's completion. This submission and approval or acknowledgement should be sent to ALCS for submission in the trial master file.

As part of the record retention requirements for the study, the Investigator must maintain documentation of all submission, correspondence, and approvals to and from the IRB.

B. Informed Consent

Informed consent must be obtained from each subject prior to entering the study, and must meet the requirements of the Declaration of Helsinki as defined by the ICH GCP guidelines and/or conform to local laws, whichever provides the greatest level of protection. Each subject must be provided, in an understandable manner, written and verbal information that describes the nature and duration of the study. Additionally, the subject must be allowed adequate time to consider the potential risks and benefits

associated with his/her participation in the study. The informed consent must also contain language that allows ALCS (or designated representative), regulatory authorities, and the IRB direct access to the subject's source documents for the purpose of review and copying.

The consent form must be signed and dated by the study subject. In situations where study subjects are not legally competent to provide consent (e.g., a minor or mentally incapacitated subject) written consent must be obtained from an authorized guardian or representation. The ICF must also be signed and dated by the individual obtaining the informed consent.

The Investigator, as part of the study documentation, must retain the signed and dated ICF and must provide a copy to each subject or authorized representative.

C. Data Reporting and Case Report Forms (CRFs)

Data reflecting the subject's participation in the study and experiences with the test product must be reported by the Investigator to ALCS. These data must be recorded on CRFs or other media approved by ALCS. For rules regarding completion and correction of CRFs, see the CRF instructions that accompany the CRFs. Case report forms must be signed and dated by the Investigator and must be submitted in a timely manner to ALCS.

D. Record Retention

The Investigator must ensure that all records pertaining to the conduct of the clinical study, including signed CRFs, ICFs, test product accountability records, source documents, and other study documentation are adequately stored for the required time period to allow for retrieve and reconstruction of the study. This documentation must be retained for the most conservative time period below:

- 2 years following approval/authorization of the last marketing application that the data was used to support; or
- 5 years after formal discontinuation of the clinical development program; or
- a record retention period mandated by any national and/or local laws, regulations, and customs;
- or as specified by ALCS.

The Investigator must not destroy any records associated with the study without receiving approval from ALCS. The Investigator must notify ALCS in the event of accidental loss or destruction of any study records. If the Investigator leaves the institution where the study was conducted, ALCS must be contacted to arrange alternative record storage options.

Study documentation includes all CRFs; Safety reports received from ALCS; Serious Adverse Experience Reports sent to ALCS; data correction forms; source documents; monitoring logs; sponsor-investigator correspondence; protocols and amendments; clinical supplies receipts; dispensing and final disposition records; IRB correspondence

and approvals; signed consent forms; and Statement of Investigator forms/Investigator Agreements.

Source documents include all original records or observation, results, and activities necessary to reconstruct and evaluate the study. Source documents include, but are not limited to, laboratory reports, electrocardiogram tracings, X-ray films, ultrasound photographs, subject diaries, subject progress notes, hospital charts, appointment books, radiology reports or pharmacy records, and any other records or reports of procedures performed during the study. Source documents also may include copies of the CRF or sponsor supplied worksheets when original information is recorded directly onto these forms.

Whenever possible, an original recording of an observation must be retained as the source document. However, a photocopy of a record is acceptable provided it is legible and is a verified copy of the original document.

E. Deviation from the protocol

The Investigator must not deviate from the protocol without prior written approval from ALCS and as required, the IRB. In medical emergencies, the Investigator should use medical judgment and remove the subject from immediate hazard. Altria Client Services and the IRB must be notified regarding the type of emergency and course of action taken.

F. Investigational Product Accountability

The Investigator must maintain adequate and accurate records (including quantities and dates) for clinical supplies received from ALCS, dispensed during the study, and unused clinical supplies that were returned or destroyed. All clinical supplies must be accounted for at the termination of the study and a written explanation must be provided for discrepancies. All unused clinical supplies must be returned promptly to ALCS or, if authorized in writing by ALCS, properly destroyed at the study site (except for retained samples in the case of bioavailability/bioequivalence studies).

G. Study Monitoring

Each study will be monitored by qualified representatives of ALCS according to a predetermined monitoring plan. Monitoring visits provide ALCS with the opportunity to: evaluate the progress of the study; verify the accuracy and completeness of CRFs; assure that all protocol requirements, applicable laws and/or regulations and investigator obligations are being fulfilled; and resolve any inconsistencies in the study records. The Investigator must allow ALCS's representatives to periodically review, at mutually convenient times during the study and after the study has been completed, all CRFs and office, hospital, laboratory records supporting the participation of each subject in the study. Case report forms and supporting documentation of the study conduct must be kept up-to-date and available for each monitoring visit.

H. Sponsor Audits

At some point during the study, individuals from ALCS's Quality Assurance group or their authorized representative may visit the Investigator's site to conduct an audit of the study. The purpose of this visit will be to determine the Investigator's adherence to the protocol, applicable regulations, and ALCS's procedures, in addition to assessing the accuracy of the study data. Prior to initiating this audit, the Investigator will be contacted by ALCS to arrange a convenient time for this visit. The Investigator and staff are expected to cooperate with the auditors and allow access to all subject records supporting the CRFs and other study-related documents.

I. Inspection by Regulatory Authorities

At some point during or after the study, a regulatory authority may visit the Investigator to inspect the study. The Investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the CRFs and other study-related documents. The Investigator must immediately notify ALCS when contacted by any regulatory authority for purposes of conducting an inspection and allow ALCS to be present at the inspection.

J. Financial Disclosure by Clinical Investigators

All clinical investigators participating in clinical studies subject to FDA Regulation 21 CFR Part 54 – Financial Disclosure by Clinical Investigators are required prior to study initiation to submit a completed Financial Disclosure Form that sufficiently details any financial interests and arrangements that apply. For the purpose of this regulation, clinical investigator is defined as any investigator or subinvestigator who is directly involved in the treatment or evaluation of research subjects, including the spouse and any dependent child of each investigator or subinvestigator. These requirements apply to both US and foreign clinical investigators conducting covered clinical studies.

Any new investigators or subinvestigators added to the covered clinical study during its conduct must also submit a completed Financial Disclosure Form. The clinical investigators will also be reminded that they must report any changes in their financial information regarding significant equity interests and significant payments during the course of the study and for a period of 1 year after completion of their participation in the covered clinical study.

Appendix 2: Subject Screener / Tobacco History

Cigarettes:

1. Do you now smoke cigarettes every day, some days, or not at all?

   Every day
   Some days
   Not at all **(Skip to Question 7)**

2. Have you been smoking fairly regularly (i.e. on a routine basis) for more than 1 year?

   Yes _____ number of years
   No

3. On average, about how many cigarettes do you now smoke each day?

   _____cigarettes per day

4. During the past 12 months, how many times have you stopped smoking cigarettes for 24 hours or longer because you were trying to quit?

   _____ Number of times

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

   Yes
   No

6. Are you interested in tobacco product alternatives to cigarettes?

   Yes
   No

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

Tobacco Product	Check the box next to each tobacco product that you have EVER used, even once:	Of the tobacco products that you have ever used, check whether you NOW use the product		
		Every day	Some days	Not at all
Bidis or kreteks: Popular in other parts of the world. Bidis are small hand-rolled cigarettes. Kreteks are clove-flavored cigarettes.				
Electronic cigarettes: Often look like regular cigarettes but run on a battery. E-cigarette brands include NJOY, Blu, GreenSmoke and 21st Century.				
Premium cigars: Come in different sizes and shapes. Some examples of premium cigar brands are Macanudo, Arturo Fuente and Romeo y Julieta.				
Cigarillos: Generally narrower and shorter than premium cigars; they may come with plastic or wooden tips. Examples of cigarillo brands are Black & Mild, Swisher Sweets, and Dutch Masters.				
Large cigars: Not premium cigars; generally wider and longer than cigarillos. Phillies Blunt cigars is an example of a large cigar brand.				
Little cigars: Look similar to cigarettes, except they are brown and have a filter like a cigarette. Some examples of little filtered cigar brands are Winchester, Captain Black and Wrangler.				
Chewing tobacco: Coarsely shredded and sold in pocket-sized packs of loose tobacco leaves or in a "plug" or "twist" form. Brands include Red Man, Levi Garrett and Beech-nut.				
Snuff (dip): Finely ground form of tobacco that is usually sold in a tin. Brands include Grizzly, Copenhagen and Skoal.				
Snus: Spitless tobacco product that comes in small pouches and is usually sold in a tin. Camel Snus is an example of a snus brand.				
Dissolvable tobacco products: Designed to dissolve in the mouth. Examples include Camel Orbs, Strips, and Sticks. Others include Ariva and Stonewall.				
Hookah: Or "narghile" pipe, is a type of water pipe used to smoke tobacco.				
Pipe. A regular smoking pipe has a bowl for tobacco, stem and mouthpiece				

8. Please indicate with check marks the nicotine replacement product or products that (1) you have ever used, even once, and (2) now use every day, some days or not at all.

Nicotine Replacement Product	**Check the box next to each nicotine replacement product that you have <u>EVER</u> used, even once:**	**Of the nicotine replacement products that you have ever used, check whether you <u>NOW</u> use the product**		
		Every day	Some days	Not at all
Patch				
Gum				
Lozenge				
Nasal spray				
Inhaler				

Appendix 3: Potential Purchase Interest Questionnaire

1. Now that you have tried it, how likely would you be to buy VBM-FG2 if it was available in stores where you shop and priced at about $1.00 less than the price of premium cigarette brands for a package of 16 VBM-FG2 discs? Would you say that you…

A. Definitely would buy

B. Probably would buy

C. Might or might not buy

D. Probably would not buy

E. Definitely would not buy

Appendix 4: Fagerström Test for Cigarette Dependence[1]

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 movies, etc.)?

- ☐ Yes
- ☐ No

3. Which cigarette would you hate most to give up?

- ☐ The first one in the morning
- ☐ All others

4. How many cigarettes per day do you smoke?

- ☐ 10 or less
- ☐ 11 to 20
- ☐ 21 to 30
- ☐ 31 or more

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

[1]Fagerstrom, Determinants of tobacco use and renaming the FTND to the Fagerstrom Test for Cigarette Dependence, Nicotine Tob Res. 2012 Jan;14(1):75-8. doi: 10.1093/ntr/ntr137. Epub 2011 Oct 24.

Appendix 5: Past 7 Day Cigarettes Use Questionnaire

Cigarettes:

1. Do you now smoke cigarettes every day, some days, or not at all?

   Every day
   Some days
   Not at all **(skip final 2 questions)**

2. Now think about the past 7 days up to and including today. On how many of the past 7 days did you smoke cigarettes?

   _____Days

3. On average, on those days, how many cigarettes did you usually smoke each day?

   _____Cigarettes

Appendix 6: Other Tobacco or Nicotine Containing Product Use Questionnaire

Cigars, Cigarillos and/or Little Cigars:

1. Now think about the past 7 days up to and including today. During the past 7 days, did you smoke any type of cigars, cigarillos and/or little cigar every day, some days, or not at all?

   Every day **(Skip to question 3)**
   Some days
   Not at all **(Skip to question 4)**

2. On how many of the past 7 days did you smoke cigars, cigarillos, and/or little cigars?

   _____Days

3. On average, on those days, how many cigars, cigarillos, and/or little cigars did you usually smoke each day?

   _____cigars, cigarillos, and/or little cigars per day

Electronic Cigarettes (Often look like regular cigarettes but run on a battery.):

4. Now think about the past 7 days up to and including today. During the past 7 days, did you smoke and/or vape electronic cigarettes every day, some days, or not at all?

   Every day **(Skip to question 6)**
   Some days
   Not at all **(Skip to question 7)**

5. On how many of the past 7 days did you smoke and/or vape electronic cigarettes?

   _____Days

6. On average, on those days, how many electronic cigarettes cartomizers, refills, and/or disposables did you usually smoke and/or vape each day?

   _____cartomizers, refills, and/or disposables per day

Chewing Tobacco, Snuff, and/or Dip:

7. Now think about the past 7 days up to and including today. During the past 7 days, did you use any type of chewing tobacco, snuff and/or dip every day, some days, or not at all?

   Every day **(Skip to question 9)**
   Some days
   Not at all **(Skip to question 10)**

8. On how many of the past 7 days did you use chewing tobacco, snuff and/or dip?

   _____Days

9. On average, on those days, how many times did you usually use chewing tobacco, snuff, and/or dip each day?

   _____chewing tobacco, snuff, and/or dip per day

Snus (Spitless tobacco product that comes in small pouches and is usually sold in a tin.):

10. Now think about the past 7 days up to and including today. During the past 7 days, did you use snus every day, some days, or not at all?

    Every day **(Skip to question 12)**
    Some days
    Not at all **(Skip to question 13)**

11. On how many of the past 7 days did you use snus?

    _____Days

12. On average, on those days, how many times did you usually use snus each day?

    _____snus per day

Other Tobacco or Nicotine Containing Products: **(hookah, pipe, orbs, sticks, strips, nicotine patch, nicotine gum, nicotine lozenge, etc)**

****<u>Do not</u> include VBM-FG2 tobacco product disc information****

13. Now think about the past 7 days up to and including today. During the past 7 days, did you use at least one type of any other tobacco or nicotine containing product every day, some days, or not at all?

    Every day **(Skip to question 15)**
    Some days
    Not at all **(Skip final 2 questions)**

14. On how many of the past 7 days did you use any other tobacco or nicotine containing product?

    _____Days

15. On average, on those days, how many times did you usually use at least one type of any other tobacco or nicotine containing product each day?

    _____Other tobacco or nicotine containing products

Appendix 7: Quit Attempts and Quitting Intentions Questionnaire – Day 1

1. During the past 30 days have you stopped smoking cigarettes for 24 hours or longer because you were trying to quit?

   Yes
   No **(if no, skip to question 3)**

2. How many times during the past 30 days have you stopped smoking cigarettes for 24 hours or longer because you were trying to quit?

   ____Number of Times

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

   Yes
   No

Appendix 8: Quit Attempts and Quitting Intentions Questionnaire - End of Study

1. During the past 30 days have you stopped smoking cigarettes for 24 hours or longer because you were trying to quit?

   Yes
   No **(if no, skip to question 3)**

2. How many times during the past 30 days have you stopped smoking cigarettes for 24 hours or longer because you were trying to quit?

   ____Number of Times

3. Do you now smoke cigarettes every day, some days, or not at all?

   Every day
   Some days
   Not at all **(Skip final question)**

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

   Yes
   No