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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STATISTICAL ANALYSIS PLAN

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

Statistical Analysis Plan Status: Version 1.0
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Study Product: VBM-FG2 discs

Sponsor Study No.: COV-VER-01-13
Covance Study No.: 8290036

Sponsor:
Altria Client Services, Inc.
PO Box 26583
Richmond, Virginia 23261-6583

Study Sites:

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Covance Clinical Research Unit, Evansville
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Sponsor Signatory:

[redacted]

1. STATISTICALANALYSIS PLAN APPROVAL SIGNATURES

By signing this page when the Statistical Analysis Plan (SAP) is considered final, the signatories agree to the statistical and phannacodynamic (PD) analyses to be performed for this study, and to the basic format of the tables, figures, and listings (TFLs). Once the SAP has been signed, programming of the TFLs based upon this document can proceed. Any modifications to the SAP and TFLs made after signing may result in a work-scope change.

Covance approval:

[redacted]

05 Nov 2013

Date (dd mmm yyyy)

Statistician

Sponsor approval:

[redacted]

or-/JOI/.2...0t-3

Date (dd mmm yyyy)

Lead Statistician

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3. ABBREVIATIONS

Abbreviations pe1tain to the SAP only (not the TFLs).

AE	Adverse event
ALCS	Altria Client Se1vices, Inc.
BMI	Body mass index
BOE	Biomarkers of exposure
CDARO	Clinical Data, Analysis, and Reporting Organization
CI	Confidence inte1val
CLIA-88	Clinical Laboratory Improvement Amendments of 1988
CO	Carbon monoxide
COHb	Carboxyhemoglobin
CPD	Cigarettes per day
CSR	Clinical study report
CV%	Coefficient of va1iation
ECG	Electrocardiogram
EOS	End of Study
FDA	Food and Dmg Administration
FTCD	Fagerstrom Test for Cigarette Dependence
ICF	Inf01med Consent F01m
ITT	Intent to treat
IVRS	Interactive voice response system
max	Maximum
MedDRA	Medical Dictiona1y for Regulatory Activities
mm	Minimum
N	Number of non-missing values
NE	Nicotine equivalent
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-l-butanol
PD	Pha1macodynamic
PEAE	Product-emergent adverse event
QTcB	QT inte1val c01Tected using Bazett' s fo1mula

QTcF	QT interval corrected using Fridericia's formula
SAP	Statistical Analysis Plan
SD	Standard deviation
S-PMA	S-phenylmercapturic acid
TFLs	Tables, figures, and listings

4. INTRODUCTION

This SAP has been developed after review of the clinical study protocol (dated 09 August 2013) and protocol amendment 1 (dated 20 August 2013).

This SAP desc1ibes the planned anal ysis of the data from this study. A detailed description of the planned TFLs to be presented in the clinical study rep01t (CS R) is provided in the accompanying TFL shell document.

The intent of this document is to provide guidance for the statistical analyses of the data. In general, the analyses are based on inf01mation from the protocol, unless they have been modified by agreement between Altiia Client Services, Inc. (ALCS) and Covance Clinical Data, Analysis, and Rep01tin g Or ganization (CDARO). A limited amount of inf01mation concerning this study (eg, objectives, study design) is given to help the reader's interpretation. This SAP must be finalized p1ior to the lock of the clinical database for this study. Due to the need for an interim analysis, the SAP must also be finalized before the conduct of the interim analysis. When the SAP and TFL shells are agreed upon and finalized, they will serve as the template for this study' s CSR.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. Some additional analyses have been added for exploratory purposes. If fmther analyses are required to supplement the planned analyses described in this SAP, they may be perf01med and will be identified in the CSR. Any substantial deviations from this SAP will be agreed upon between ALCS and Covance CDARO and identified in the CSR. Any Ininor deviations from the TFLs might not be documented in the CSR, but will be captured in a Running Note to SAP document.

5. PURPOSEAND STUDY OBJECTIVES

5.1 Purpose

The purpose of this study is to:

- Estimate the change in biomarkers of exposure (BOE) in adult smokers using VBM-FG2 versus adult smokers not using VBM-FG2.
- Dete1mine the appropriate cigarettes per day (CPD) repo1ting method for baseline measurements (for interactive voice response system [IVRS] Base line is defined as the average CPD recorded on Days 2 through 8).

5.2 Primary Objective

The prima1y objective of this study is to:

- Compare the differences in percent change in urina1y total 4-(methylniti·osainino)-1-(3-pyridyl)-1-butanol (NNAL) from Baseline to End of Study (EOS) between adult smokers

randomly assigned to Test Group *(ad libitum* VBM-FG2 use) and Control Group (no VBM-FG2).

5.3 Secondary Objectives

The seco ndaiy objectives of this study are to:

- Compare the difference in BOE (minary total NNAL, nicotine metabolites, S- phenylmercaptmic acid [S-PMA], blood carboxyhemoglobin [COHb], and exhaled carbon monoxide [CO]) and CPD between two methods for dete1mining CPD during the Baseline Period:
    - Recall of average daily CPD for prior week using Past 7 Day Cigarettes Use Questionnaire (Day I).
    - Daily CPD tracking using an IVRS (7 day average of values recorded on Days 2 through 8).
- Compare the differences in percent change in urina1y nicotine equivalent (NE), S-PMA, blood COHb, exhaled CO, and CPD from Base line to EOS 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 EOS between Test Group and Control Group over 4 weeks.
- Characterize subgroups based on change in CPD from Baseline to EOS (no change, <50% reduction, 2:50% reduction, 100% reduction, increase) within each study group.
- Characterize subgroups based on change in total NNAL from Baseline to EOS (no change, reduction, increase) within each study group.
- Compare changes in the Fagerstrom Test for Cigarette Dependence (FTCD) from Baseline (Day 8) to EOS within and between each study group.
- Compare changes on the Quit Attempts and Quitting Intentions from Baseline (Day I) to EOS within and between each study group.

6. STUDY DESIGN

This is a randomized, controlled, open-label, parallel group, multi-center, 5-week pilot study to dete1mine changes in BOE in adult smokers allowed *ad libitum* use ofVBM-FG2 relative to adult smokers who are not allowed use ofVBM-FG2. The data collected from this study will be used to estimate the variability of differences in the percent change from Baseline to the EOS in urina1y total NNAL between Test and Control Groups; these findings will be used to estimate the sample size for a future pivotal study. This study will be conducted in approximately 150 adult

smokers who are considered to be in overall good health. Subjects will be randomized (based on gender, daily cigarette consumption [<20 and 2::20], and quit attempts [any quit attempts/no quit attempts]) to Test (allowed VBM-FG2 use) or Control (not allowed VBM-FG2 use) product 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.

Screening	**Baseline Period***		**Product Use Periodt**			
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	Day29± 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 libitmn 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.
t Product Use Period = after the daily IVRS call on Day 8 through the daily IVRS call on Day 36.

Note: Subjects in both groups are allowed to smoke their regular brand cigarettes during the entire study period

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 EOS). All subjects will be inf01med that they are allowed to smoke their own cigarettes or to quit smoking during the study.

Screening (Visit I) will occur within 28 days of Day 1 (Day -28 to Day -I). An fuf01med Consent F01m (ICF) must be signed prior to conducting any study related procedures. Potential subjects will undergo an initial evaluation (vital signs, mine 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 and electrocardiogram [ECG]). Laboratory values will be evaluated by a local laboratory.

Subjects will return to the study site on the evening of Day I for Visit 2. A physical examination will be conducted and subjects who satisfy all the inclusion criteria and exclusion criteria will be eligible for emollment in the study. Once a subject is emolled in the study (Day I), 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 while at the study site, to indicate their CPD over the previous week. Dmi ng the Baseline Peli od (Days 1 to 8) subjects will rep01t CPD daily through an IVRS.

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 dist1ibution 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.

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 instrncted to report all adverse events (AEs) and changes in concomitant medications and if necessa1y , to return to the study site for fmt her evaluation. During the EOS visit (Day 36 or Early Ten nination), additional assessments will be perf01med to confo m the health and well-being of the subject.

7. STUDY PRODUCT

The VBM-FG2 discs are oral, non-dissolvable products containing tobacco-derived nicotine (approximately1.5 mg/disc) that may provide an opportunity for adult cigarette smokers to move down the continuum of risk. These discs are a tobacco-derived nicotine product designed to appeal to adult cigarette smokers who are interested in tobacco product alternatives to cigarettes. These discs are designed to be spit-free and chewable.

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

The groups will be presented in the TFLs as follows:

Study Group	**Abbreviation**
Subjects allowed *ad libitum* use of VBM-FG2	Test
Subjects not allowed use of VBM-FG2	Control

8. SAMPLE SIZE JUSTIFICATION

This pilot study is being conducted with an objective to collect data on the variability of the prima1youtcome 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 plinciples for pilot studies.

9. SAMPLE COLLECTION AND ENDPOINTS

Urine BOE (with the exception of creatinine) will be analyzed using validated analytical methods with appropriate quality controls according to the Food & Dmg Administration (FDA) Guidance for Industiy: Bioanalytical Method Validation (May 2001) and in accordance with FDA Good Laborato1y Practice regulations (Title 21 CFR Pait 58).[12] Uline creatinine and blood COHb will be analyzed at a Clinical Laborat01y Improvement Amendments (CLIA)-88 certified clinical laborat01y. Biomarke rs of exposure will include:

Urine:

- Nicotine
- 5 metabolites of Nicotine
    - Cotinine
    - Trans-3'-Hydroxycotinine
    - Trans-3'-Hydroxycotinine-O-glucuronide
    - Nicotine-N-glucuronide
    - Cotinine-N-glucuronide
- Total NNAL
- Ulinary S-PMA

Nicotine Equivalents:

Nicotine equivalents (mg) is calculated as the molar sum of total nicotine, total cotinine, and total ti·ans-3'-hydroxycotinine excreted in the spot urine sample.

The concenti·ation of each metabolite is first adjusted by the spot urine volume to obtain the amount excreted in the sampling period, then divided by the molecular weight of the metabolite to obtain the amount of each in moles. The sum in moles is then converted to mass of nicotine equivalents by multiplying by the molecular weight of nicotine.

Nicotine equivalents (mg) = [Total Nicotine (mg) / 162.23 (mg/mmol) + Total cotinine (mg) / 176.22 (mg/mmol) + Total ti·ans3'-hydroxycotinine (mg) / 192.22 (mg/mmol)] x 162.23 (mg/mmol).

Adjustments of Urinary BOEs by Urine Creatinine:

For mi na1yBOEs (Total NNAL, Nicotine Equivalents, and S-PMA) the biomarker concenti·ation will be adjusted by mi ne creatinine that was measured from the mi ne samples and the derived variable will be used as the analysis variables for descriptive and inferential statistics.

The following f01mula will be used for creatinine adjustment:

[mass biomarker / g creatinine] = [mass biomarker/mL] / [mg creatinine/dL] x 10^5

The exponent power (5) in 10^5 will be adjusted if biomarker concentration is rep01t ed in a unit other than mass/mL, e.g. mass/dL. If a mi ne creatinin e value is missing or outside the acceptance range (Adult males: 20-25 mg/kg/day, Adult females: 15-20 mg/kg/day), the c01Tesponding crea tinine adjusted biomarker value will be considered as missing.

Covance will use the above f01m ula to conduct som e sampl e calculations and submit the results to ALCS for review. Appropriate modifications will be made if deemed necessary after the review.

Blood: COHb

Respiratory: Exhaled CO

Statistical Analysis Endpoints:

- Uline Creatinine Adjusted Total NNAL
- Uline Creatinine Adjusted Nicotine Equivalents
- Uline Creatinine Adjusted S-PMA
- Unadjusted COHb
- Unadjusted Exhaled CO
- Total FTCD Score
- CPD
- VBM-FG2 use and other tobacco product use
- Quit Attempts and Quitting Intentions

The word "Adjusted" or "Unadjusted" will not be used while refen-ing the above statistical analyses endpoints later on but it will be adjusted/unadjusted based on the above list. The first 5 endpoints will be refen ed to as 5 BOEs.

9.1 Urine Sample Collection for Biomarker Analysis

A urine sampl e will be collected at Visits 2 through 7. Urine will be collected upon au ival at the study site. Palticipants will be instrncted to not void their bladders for approximately 2 hours before the study visit. The total volumes for each urine void will be recorded.

9.2 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.

9.3 Exhaled CO Measurement

Exhaled CO measurement tests should occur immediately after blood collection. A standard exhaled CO Test will be perf01med with Micro+™ Smokerlyzer® CO monitors (or equivalent) following the manufacturer's instmctions.

10. DEFINITION OF ANALYSIS POPULATIONS

Safety population includes subjects who have tried the test product during the study, including those subjects who pa1ticipated only in the screening phase.

Intent to treat (ITT) population includes eve1y subject who is randomized according to the randomization schedule.

Modified Intent to Treat (mITT)population includes eve1y subject who has completed the baseline visit and has at least one post-baseline outcome meas ures.

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

All protocol deviations that occur dming the study will be considered for their seve1ity and impact and will be taken into consideration when subjects are assigned to analysis populations. Details of subject assignment to the analysis populations will be listed.

11. STATISTICAL METHODOLOGY

11.1 General

Data listings will be provided for all subjects up to the point of withdrawal, with any subjects excluded from the relevant population highlighted. Summa1y statistics and statistical analyses will generally only be perf01med for subjects included in the relevant analysis population. For the calculation of summa1y statistics and statistical analysis, unrounded data will be used. For continuous data, summa1y statistics will include the number of non-missing values (N), mean, median, standard deviation (SD), minimum (min), max imum (max). For categorical data, frequency counts and percentages will be presented.

Mean change from base line is the mean of all individual subjects' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual subject' s baseline value from the value at the timepoint. The individual subject' s change from baseline values will be used to calculate the mean chan ge from baseline using a SAS® procedure such as Proc Univariate.

Mean percent chan ge from baseline is the mean of all individual subjects' percent change from baseline values. Each percent change from baseline will be calculated by subtracting the individual subject's baseline value from the value at the desired timepoint and then dividing this calculated value by the individual subject's baseline value and multiplying by 100. These

individual subjects' percent changes from baseline values will be used to calculate the mean percent change from baseline using a SAS® procedure such as Proc Univariate.

Missing values will not be imputed.

Data analysis will be perf01med us ing SAS® Versio n 9.1 .3 or higher.

11.2 Definition of Baseline for Calculating Change

The Baseline Period is from Day 1 to Day 8. The baseline for calculating change from baseline will be defined in the following table.

Metric	**Baseline**	**Corresponding post-baseline visits**
Quit Attempts and Quitting Intentions	Day 1 (Visit 2)	Day 36 (Visit 7)
Fagerstrom Test for Cigarette Dependence (FTCD)	Day 8 (Visit 3)	Day 36 (Visit 7)
BOE	Day 8 (Visit 3)	Visits 4, 5, 6, 7
CPD daily tracking from IVRS	The average of available data from Day 2 through Day 8	Daily CPD Day 9 to 36 or the average of last week at Visits 4, 5, 6, 7
Vital Signs	Day 8, including unscheduled (rechecked) values	Visits 4, 5, 6, 7
*see Section 11.4.3 for more details		

Rationale for the baseline choices for calculating change:

Quit attempts and intentions: Day **1** is the only one measurement in baseline.

FTCD: There are 2 measurements in the baseline, Day 1 and 8. Day 8 is selected because it is anticipated that there will be changes in CPD, a key component of the FTCD score, when adult smokers are asked to track their daily cigarette consumption. Day 1 value does not reflect this change.

BOE: Day 8 is the last of the 2 baseline values and is closer to the post-baseline values.

CPD daily tracking: The weekly average was selected to adjust for the daily variability and also because total NNAL (primary end-point) has a longer half-life and the average CPD might be better representative of changes in exposure to total NNAL than the individual values.

11.3 Criteria for Evaluation

11.3.1 Primary Endpoint

The primary outcome measure or endpoint is differences in the percent change from Baseline to the EOS in urinary total NNAL between Test and Control Groups.

11.3.2 Secondary Endpoints

The secondary outcome measures or endpoints 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 EOS in BOE (urinary NE, S-PMA, blood COHb, exhaled CO) and CPD between the Test and Control Groups.
- Differences from Baseline to EOS in all BOE and CPD between the Test and Control Groups.
- Proportion of subjects in subgroups based on cigarette consumption change from Baseline to EOS (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 EOS (no change, reduction, increase) within each group.
- Changes from Baseline (Day 8) to EOS in total scores of Fagerstrom Test for Cigarette Dependence (see Appendix 1), within and between the Test and Control Groups.
- Changes from Baseline (Day 1) to EOS on the Quit Attempts and Quitting Intentions, within and between the Test and Control Groups.

11.3.3 Safety Endpoints

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

11.4 Statistical Analyses of Endpoints

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

11.4.1 Statistical Analyses of Primary Endpoint

A linear mixed model for repeated measures analysis of variance will be used for the analysis of the plimary outcome measure. SAS procedure Proc Mixed will be used for the statistical computing. The null hypothesis is that smokers allowed *ad libitum* use of VBM-FG2 discs (test) will not differ in the primary biomarker (percent change from baseline to EOS in urinary total

NNAL) compared to smokers not allowed use ofVBM-FG2 discs (control). The alternative hypothesis is that smokers allowed *ad libitum* use ofVBM-FG2 discs will differ in the prima1y biomarker compared to smokers not allowed use ofVBM-FG2 discs. The model will include percent (or absolute) change from baseline to EOS in urina1y total NNAL as a response variable, product, visit , and product by visit interaction as fixed effects; and subject as random effect. In the expanded model, several additional factors will be considered. Details about the models are as follows:

Model 1:

Percent (or absolute) change from baseline in total NNAL = study group + visit + study group*visit + subject + random enor

Model 2:

Percent (or absolute) change from baseline in total NNAL = study group + visit + study group*visit + subject + CPD + sex + race + body mass index (BMI) + age + random enor

where

CPD = fixed covariate representing average number of cigarettes per day for past week from IVRS
study group = fixed effect te1m (test or control)
sex = fixed effect (male or female)

race= fixed effect (White or Non-White)

BMI = fixed effect covariate

age = fixed effect covariate (continuous)

visit= fixed effect te1m representing days (ordinal categ01ical variable)
subject = random subject effect

baseline = Total NNAL meas ure at Day 8

If the study group*visit interaction te1m is not statistica lly significant (P-value $>$ 0.10), then the interaction te1m will be removed from the model and all compa1isons will be done using the overall product means. If the interaction effect is significant (P-value 0.10), then the comparisons will be conducted for each study visit. Comparisons between products will be done based on 5% level ofsignificance.

Least squares mean and standard enor for theproduct effect will be estimated by study group and visit with P-values. P-values will also be provided for other effects in Model 2. While group comparison will be made on multiple visits in the model, the difference in change from baseline to the las t visit will be the prima1y comparison and other compa1isons will be secondary.

The models will be applied on both the mITT and the Per-protocol populations.

11.4.2 Statistical Analyses of Secondary Endpoints

Difference in baseline:

Paired T Test will be used to examine the difference in all 5 BOEs between Day 1 and Day 8.

Paired T test will also be used to examine the differences in CPD between the once weekly recall at Day 8 (from questionnaire) and the average daily tracking of CPD from Days 2 through 8 (from IVRS).

Difference in change from baseline:

Linear mixed model for repeated measures analyses of variance will be used for the analyses of the seconda1y outcome measures: percent change from baseline and absolute change from baseline in all other BOEs. The same model will be used for percent change from baseline and absolute change from baseline in CPD and Total score of FTCD, the model details are as follows:

For other BOEs:

Model 1:

Percent (or absolute) change from baseline = study group + visit+ study group*visit + subject + random enor

Model 2:

Percent (or absolute) change from baseline = study group+ visit+ study group*visit + subject + CPD + sex + race + BMI + age + random enor

For CPD and Total Score ofFTCD:

Model 1:

Percent (or absolute) change from baseline = study group+ visit+ study group*visit +subject+ random enor

Model 2:

Percent (or absolute) change from baseline = study group+ visit+ study group*visit +subject+ sex + race + BMI + age + random enor

where

CPD = fixed effect covariate representing average number of cigarettes per day for the past two days from IVRS

study group = fixed effect te1m (test or control)

sex = fixed effect (male or female)

age = fixed effect covariate (continuous)

race= fixed effect (White or Non-White)

BMI = fixed effect covariate (continous)

visit= fixed effect te1m representing days (ordinal categ01ical variable)

subject = random effect

baseline = Day 8 value for BOE and average of Day 2 to 8 for CPD (IVRS)

If the study group*visit interaction te1m is not statistically significant (P-value > 0.10), then the interaction te1m will be removed from the model and all compa1isons will be done using the overall product means. If the interaction effect is significant (P-value 0.10), then the comparisons will be conducted for each study visit.

Least squared mean and standard enor for the product effect will be estimated by study group and visit with p-values for statistical significance.P-value will also be provided for other effects in the model.

All seconda1y and explorat01y analyses will be conducted on the Per-protocol population only.

A linear regression analysis will be conducted within each group at each timepoint to examine the relationships between levels of all 5 BOEs (dependent variable) with either weekly cigarette counts (Day 1 and 8 from questionnaire) or daily cigarette counts (from IVRS) (independent variable). For total NNAL, the c01Tesponding dail y cigarette counts from IVRS will be the average of past 7 days. For other biomarkers, it will be the average of past 2 days. The regression analysis will be conducted on the Per-protocol population.

The prop01tion of subjects in subgroups will be provided with prop01tion and sample size based on:

1) Cigarette consumption change from Baseline (average of Days 2 to 8 from IVRS) to the last week (no change, <50% reduction, 2::50% reduction , 100% reduction, increase);
2) Total NNAL change from Day 8 to the last visit(no change, reduction, increase);
3) Total scores ofFTCD change from Day 8 to the last visit (increase, no change, decrease)
4) Prop01tion of subjects in subgroups based on Changes from Baseline (Day 1) to EOS (increase, no change, decrease) on the change in Quit Attempts from Day 1 to last visit.
5) Prop01tion of subjects in subgroups based on Changes from Baseline (Day 1) to EOS (yes to no, no to yes, and same) on the change in Quitting Intentions from Day 1 to last visit.

The Mantel-Haenszel Chi-Square Test will be used for (1), (2), (3), and (4); Fisher exact test will be used for (5) to test the frequency differences between the two groups.

Additional statistical analyses:

Wilcoxon signed rank test will be used to test the FTCD score difference between the 2 baseline measures (Visit 2 and 3) for the test group. If there is no statistical significance, the average score will be related to the average amount ofVBM-FG2 in the past week via linear regression. Otherw ise the FTCD score for Visit 3 will be used.

For the test group only, a simple linear regression model will be used to examine the relationship between COHb and Exhaled CO at each post-baseline visit.

A stepwise multiple linear regression model will also be used to examine the relationship between each of the 5 BOEs (response variable) and a number of factors including average CPD, average VBM-FG2 use, average use of other products, age, sex, BMI and race at each post-baseline visit for the test group only. The average amount of tobacco product use will be for the pas t 7 days when total NNAL is the dependent variable and will be for the past two days when other BOE is the dependent variable.

Demographics and Characterization of Tobacco Product Use and Exposure Patterns

Demographic baseline characteristics will be summarized by study group with descriptive statistics. For continuous data, descriptive statistics will include N, mean, median, SD, min, max, coefficient of variation (CV%), and 95% confidence interval (CI). For categorical data, frequency counts and percentages will be presented. Fisher's exact test will be used to test for the differences in categorical variables (sex, race: White versus Non-white, quit attempt, cigarette consumption per day: =<20 and >20) between the 2 study groups and t test, to test for the differences in continuous variables (age, body weight, height, BMI, Number of times stopped smoking cigarettes for 24 hours or longer in an attempt to quit in past 6 months, Number of years smoked since turning 21 years).

Descriptive statistics will be provided to summarize the use of all tobacco products including cigarettes, VBM-FG2 discs and other products by study group and visit. The mean for each variable will be plotted by study group over time.

For subjects in the test group, a simple linear regression model will be used to examine the relationship between visit average of CPD (from IVRS) and visit average of VBM-FG2 use for all post-baseline visits in the study.

For subjects in the test group, a frequency table will be provided with the responses (definitely would buy and probably would buy) in the VBM-FG2 Potential Purchase Interest Questionnaire as the row variable and their average VBM-FG2 use level (4 discs versus <4) in the last 2 visits as the column variable . Fisher exact test will be used to test for the association.

11.4.3 Safety and Tolerability Assessments

Adverse Events

All AEs occmTing during this clinical trial after the subject has signed the ICF document must be recorded in the Case Report F01m, incl uding the date and time of onset and outcome of each event. Events captured between Screening (Visit I) and Visit 2 occmTing prior to study prod uct usage will be documented as baseline signs and symptoms and not AEs, unless they are "possibly," "likely," or " definitely" associated with product trial use in Screening Part I. Any AEs that are "possibly," "likely," or " definitely" associated with product tii·al use in Screening Pait I will be listed and summa1i zed with post-usage product-emergent AEs (PEAEs) but will be flagged with time of occunence as Screening Pait I.

All AEs will be listed. Product-emergent AEs will be summarized by product, severity, and relationship to the study product. The frequency of PEAEs (the number of PEAEs, the number of subjects experiencing a PEAE, and the percentage of subjects expe1i encing a PEAE) will be summa1ized by study group, Medical Dictionary for Regulat01y Act ivities (MedDRA) system organ class, and prefen ed te1m. The summary and frequency PEAE tables will be presented for all causalities and for those considered related to the study product. Any severe or serious AEs will be tabulated.

Clinical Laboratory Parameters

Chemistty and hematology data will be summarized by study group. In addition, all chemistty, hematology, and mi nalysis data outside the clinical reference ranges will be listed by parameter and product.

Values for any chemistty , hematology, or urinalysis parameter outside the clinical reference range will be flagged on the individual subject data listings.

Vital Signs

Vital signs data will be summarized by study group together with changes from baseline. Figures of mean vital signs along with SD bars will be presented by study group. Vital sign values outside the clinical reference range will be flagged on the individual subject data listings.

Electrocardiogram

The ECG data will be obtained directly from the 12-lead ECG trace and will include Ventt·icular Hea1tRate, PR, QRS, QT, QT con ected using Bazett' s f01m ula (QTcB), and/or QT c01Tected using Flidericia's f01m ula (QTcF) intervals.

The ECG data will be listed for each subject.

Other Assessments

All other safety assessments not detailed in this section will be listed but not summarized or statistically analyzed.

12. INTERIM ANALYSES

An interim data analysis will be conducted after the first 50 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. Therefore, no P-value adjustment will be conducted for statistical testing. 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 baseline demographics and smoking characteristics, safety variables, and the secondary endpoint variables that are categorical. The TFLs for interim analysis and final analysis (all study subjects) are presented in Appendix 2.

13. CHANGES FROM THE PROTOCOL-SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol-specified statistical analyses.

14. DATA PRESENTATION

14.1 Unscheduled Visits

Values obtained during unscheduled visits will not be presented in summary tables , unless requested by the Sponsor.

14.2 Insufficient Data for Presentation

Some of the TFLs might not have sufficient numbers of subjects or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the center of the table, such as, "No serious adverse events occmTed for this study."

15. REFERENCES

I. FDA Guidance for fudustry: Bioanalytical Method Validation (May 200I)

2. FDA Good Laboratory Practice regulations (Title 21 CFR Part 58; April 2013)

APPENDIX 1: FAGERSTROMTEST FOR NICOTINE DEPENDENCE

1. **How soon after you wake up do you smokeyour first cigarette?**
   D Within 5 minutes (3)
   D 6 - 30 minutes (2)
   D 31 - 60 minutes (I)
   D After 60 minutes (0)

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.)?
   D Yes (1)
   0 No (0)

3. **Which cigarette would you hate most to give up?**
   D The first one in the morning (1)
   D All others (0)

4. **How many cigarettes per day do you smoke?**
   D 10 or less (0)
   D 11 to 20 Cl)
   D 21 to 30 (2)
   D 31 or more (3)

5. **Do you smokemore frequently during the first hours after waking than during the rest of the day?**
   D Yes (I)
   0 No (O)

6. . **Do you smoke**if **you are so** ill **that you are in bed most of the day?**
   D Yes (I)
   0 No (O)

Scoring:
Level of nicotine dependence:
0 - 2 Very low depe ndence
3 - 4 Low dependence
5 Medium dependence
6 - 7 High dependence
8- 10 Very high dependence

APPENDIX 2: LIST OF TFLS FOR INTERIM AND FINAL ANALYSES

Following is the list of TFLs that will be produced during the interim analyses.

- Table 14.1-1 Summaiy of Subject Disposition
- Table 14.1-2 Summaiy of Screening Demographics
- Table 14.1-3 Summaiy of Baseline Smoking Characterist ics
- Tab le 14.2.1-3.1 Individual Data and Summaiy Statistics of S-PMA
- Table 14.2.1-3.2 Individual Data and Summaiy Statistics of Change from Baseline S-PMA
- Table 14.2.1-3.3 Individual Data and Summaiy Statistics of Percent Change from Baseline S-PMA
- Table 14.2.1-4.1 Individual Data and Summaiy Statistics of Carboxyhemoglobin
- Table 14.2.1-4.2 Individual Data and Summaiy Statistics of Change from Baseline Carboxyhemoglobin
- Table 14.2.1-4.3 Individual Data and Summaiy Statistics of Percent Change from Baseline Carboxy hemog lobin
- Table 14.2.1-5.1 Individual Data and Summaiy Statistics of Exhaled Carbon Monoxide
- Table 14.2.1-5.2 Individual Data and Summaiy Statistics of Change from Baseline Exhaled Carbon Monoxide
- Table 14.2.1-5.3 Individual Data and Summaiy Statistics of Percent Change from Baseline Exhaled Carbon Monoxide
- Table 14.2.1-6.1 Individual Data and Summaiy Statistics of Cigarettes per Day
- Table 14.2.1-6.2 Individual Data and Summaiy Statistics of Change from Baseline Cigarettes per Day
- Table 14.2.1-6.3 Individual Data and Summaiy Statistics of Percent Change from Baseline Cigarettes per Day
- Table 14.2.1-7.1 Individual Data and Summaiy Statistics of Total Score of Fagerstrom Test for Cigarette Dependence
- Table 14.2.1-7.2 Individual Data and Summaiy Statistics of Change from Baseline Total Score of Fagerstrom Test for Cigarette Dependence
- Table 14.2.1-7.3 Individual Data and Summaiy Statistics of Percent Change from Baseline Total Score of Fagerstrom Test for Cigarette Dependence
- Table 14.2.1-X Individual Data and Summaiy Statistics of Urine Creatinine (Interim only)
- Table 14.2.1-8.1 Individual Data and Summaiy Statistics of VBM-FG2 Discs per Day

- Table 14.2.1-8.2 Individual Data and Summary Statistics of Change from Baseline VBM-FG2 Discs per Day
- Table 14.2.1-8.3 Individual Data and Summary Statistics of Percent Change from Baseline VBM-FG2 Discs per Day
- Listing 16.2.8-12 Other Tobacco or Nicotine Containing Product Use Questionnaire by Subject
- Table 14.2.1-12 Individual Data and Summaiy Statistics for Number of Quit Attempts with Change from Baseline
- Table 14.2.1-13 Frequency and Percentage of Subjects with Change from Baseline in Quitting Intentions
- Table 14.3.1-1 Summaiy of Product-Emergent Adverse Events
- Table 14.3.1-2 Frequency of Product-Emergent Adverse Events (All Causalities)
- Table 14.3.1-3 Frequency of Product-Emergent Adverse Events by Severity (All Causalities)
- Table 14.3.1-4 Frequency of Product-Emergent Adverse Events (Possibly, Likely, or Definitely Related to Study Product)
- Table 14.3.1-5 Frequency of Product- Emergent Adverse Events by Severity (Possibly, Likely, or Definitely Related to Study Product)
- Table 14.3.2-2 Serious Adverse Events

The TFLs that will be produced duri ng the final analyses (all subjects) have been provided in the accompanying TFL shells document.