A Randomized, Controlled, Open-label Short-term Study to Evaluate Changes in Exposure to Harmful and Potentially Harmful Constituents in Adult Smokers Who Completely Switch to on!® Nicotine Pouches in a Clinical Setting

NCT05664672

30JUL2021

Statistical Analysis Plan

A Randomized, Controlled, Open-label Short-term Study to Evaluate Changes in Exposure to Harmful and Potentially Harmful Constituents in Adult Smokers Who Completely Switch to on!® Nicotine Pouches in a Clinical Setting

SAP Status: Final
SAP Version: 1.0
SAP Date: 30July2021

Investigational Product: on! ® Nicotine Pouches
Protocol Reference: ALCS-REG-20-15-OTDN
Covance Study: 8461631

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LIST OF IN-TEXT TABLES AND FIGURES

LIST OF ABBREVIATIONS

Abbreviations pertain to the statistical analysis plan (SAP) only (not the tables, figures, and listings [TFLs]).

ADaM	Analysis Data Model
AE	adverse event
BLQ	below the limit of quantitation
BOEs	biomarkers of exposure
CC	continue smoking cigarettes
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
COVID-19	coronavirus disease 2019
CPD	cigarettes smoked per day
CSR	clinical study report
CV	coefficient of variation
DMP	data management plan
ECG	electrocardiogram
eCRF	electronic case report form
GLSM	geometric least squares mean
ICF	informed consent form
ICH	International Council for/Conference on Harmonisation
LLOQ	lower limit of quantitation
ln	natural log
LSM	least squares mean
MedDRA	Medical Dictionary for Regulatory Activities
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
NP	nicotine pouches
NPPD	number of NP per day
NPPU	number of NP per use
PD	pharmacodynamic(s)
PEAE	Product-emergent adverse event
SAP	statistical analysis plan
SD	standard deviation
SDV	source document verification
TFL	table, figure, and listing
UBC	usual brand cigarettes
WHODrug	World Health Organization Drug Dictionary

1. INTRODUCTION

This SAP has been developed after review of the clinical study protocol (Amendment 1 dated 28 April 2021 and Amendment 2 dated 30 June 2021) and electronic case report form (eCRF).

This SAP describes the planned analysis of the pharmacodynamic (PD), safety, and tolerability data from this study. A detailed description of the planned TFLs to be presented in the clinical study report (CSR) is provided in the accompanying TFL shells document.

In general, the analyses are based on information from the protocol, unless they have been modified by agreement with Altria Client Services, LLC.

This SAP must be finalized prior to the lock of the clinical database. Additionally, the SAP and TFL shells should be finalized prior to any programming activities commencing.

This SAP supersedes any statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified accordingly in the CSR. Any substantial deviations from this SAP will be agreed with Altria Client Services, LLC. and identified in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E3 guideline *Structure and Content of Clinical Study Reports*, ICH E8 guideline *General Considerations for Clinical Trials*, ICH E9 guideline *Statistical Principles for Clinical Trials*.[1,2,3]

The document history is presented in Appendix 1.

2. STUDY OBJECTIVES

The primary objective of the study is:

- To compare 24-hour urinary total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) in subjects using nicotine pouches (NP) for 7 days versus subjects who continue to smoke cigarettes for 7 days.

The secondary objectives of the study are:

- To compare biomarkers of exposure (BOEs) (except total NNAL) in subjects using NP for 7 days versus subjects who continue to smoke cigarettes for 7 days
- To compare BOEs in subjects using NP for 7 days versus subjects who stopped using any tobacco products for 7 days
- To characterize product use behaviors (such as: number of cigarettes smoked per day, number of NP use per day, number of NPs per use, average duration of each NP use).

3. STUDY ENDPOINTS

Primary endpoint:

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

Secondary endpoints:

- Amount excreted in 24 hours of urinary NE, 2-AN, 4-ABP, HEMA, CEMA, S-PMA, 3 HMPMA, 3-HPMA, 2-HPMA, AAMA, GAMA, 2-MHBMA, 2 OHFle, 2-Naphthol, 1 OHPhe, 3-HB[a]P, mutagenicity, and 1-OHP excreted on Day 7
- COHb on Day 7
- Product use behavior from Day 1 to Day 7 (ie, number of cigarettes smoked per day[CPD], number of NP per day [NPPD], number of NP per use [NPPU], and average duration of each NP use)

4. STUDY DESIGN

This will be an open-label, randomized, 5 parallel-groups clinical study evaluating changes in exposure to selected HPHCs and product use behavior in adult smokers.

Study population will be randomized into 5 groups:

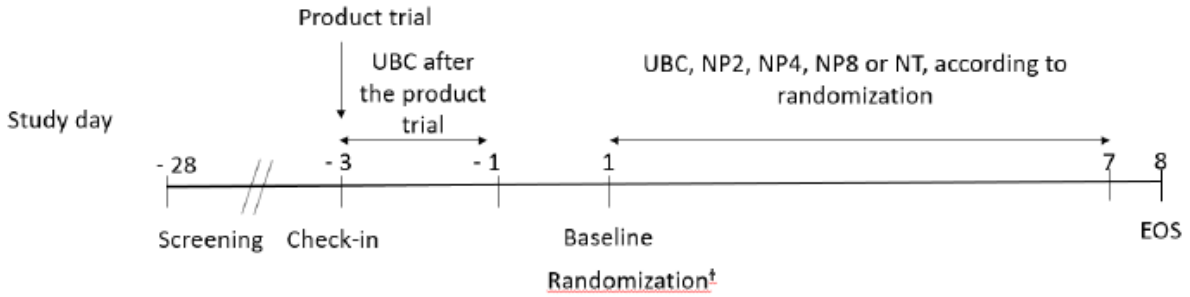
- Group 1 (n = 30): continue smoking cigarettes (CC); subjects will be asked to continue smoking their usual brand cigarettes (UBCs) ad libitum for 7 days.
- Group 2 (n = 30): 2 mg NP (NP2); subjects will exclusively use 2 mg NP, using at least 3 pouches per day for 7 days.
- Group 3 (n = 30): 4 mg NP (NP4); subjects will exclusively use 4 mg NP, using at least 3 pouches per day for 7 days.
- Group 4 (n = 30): 8 mg NP (NP8); subjects will exclusively use 8 mg NP, using at least 3 pouches per day for 7 days.
- Group 5 (n = 30): No Tobacco (NT); subjects will completely stop all tobacco product usage for 7 days.

The goal is to recruit approximately 150 subjects (not more than 60% of either gender) with the aim of at least 100 subjects completing the study (20 subjects, minimum per group).

A schematic of the study design is presented in Figure 1.

Figure 1: Study Design

Figure 1: Study Schematic



[‡]Randomization is expected to occur on Day 1, however, in order to make study product preparation for Day 1 easier and more manageable for the site, randomization of study subjects will also be allowed after 19:00 on Day -1.
Abbreviations: EOS = end of the study; NP2 = 2 mg nicotine pouches; NP4 = 4 mg nicotine pouches; NP8 = 8 mg nicotine pouches; NT = no tobacco; UBC = usual brand cigarette.

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first product administration. Subjects will be admitted into the study site on Day-3 where they will engage a brief product trial using 1 Mint on!® 8 mg NP and be confined to the study site until discharge on Day 8.

The total duration of study participation for each subject (from screening through last visit) is anticipated to be approximately 5 weeks.

The start of the study is defined as the date the first subject signs an informed consent form (ICF). The point of enrollment occurs at the time of subject check-in visit. The study completion is defined as the date of the last subject's last assessment (scheduled or unscheduled).

5. SAMPLE SIZE JUSTIFICATION

Up to 150 subjects will be enrolled in order that 20 subjects per group complete the study.

This study is being conducted to assess the differences in BOE values after adult smokers switched to on! ® NP with the total NNAL (ng/24 h, measured at Day 7) as the primary endpoint. The sample size estimation is based on total NNAL data, assuming a two-sided test, 85% power and α =0.017 Type I error rate to account for the multiplicity adjustment for the comparisons (each of the 3 NP groups versus CC group), a sample size of approximately 20 subjects per group is needed to detect a statistically significant difference between the NP groups and CC group. Thirty subjects will be randomized to make sure 20 subjects per group complete the study. The sample size calculation used to derive the sample size for this study was based on summary statistics data of total NNAL from a previous study with a similar study design[4], where the mean ± standard deviation of total NNAL at Day 7 were 476.1 ± 296.58 ng/24 h for the CC group and 167.3 ± 100.17 ng/24 h and 176.9 ± 135.17 ng/24 h for the groups that used a chewable OTDN product with 2 flavors, respectively.

6. STUDY PRODUCT GROUPS

The study product groups, abbreviations, and ordering to be used in the TFLs are presented in Table 1.

Table 1: Presentation of study product groups in TFLs

Study Product Groups	Abbreviation	Order in TFLs
Group 1: Subjects continue smoking their UBCs	CC	1
Group 2: Subjects exclusively use 2mg NP	NP2	2
Group 3: Subjects exclusively use 4mg NP	NP4	3
Group 4: Subjects exclusively use 8mg NP	NP8	4
Group 5: Subjects stop all tobacco product usage	NT	5

All TFLs will be based on actual product use (eg, if subject was assigned to receive NT but was wrongfully assigned to NP2 they would be summarized and listed under NP2 for safety tables only, excluded from biomarkers of exposure population).

7. STUDY RANDOMIZATION

On Day 1, the subjects will be randomized to 1 of the following 5 groups in a 1:1:1:1:1 ratio, with not more than 60% of either gender. Subjects will be stratified by gender and screening visit self-reported CPD (≤16; >16). Randomization is expected to occur on Day 1, however, in order to make study product preparation for Day 1 easier and more manageable for the site, randomization of study subjects will also be allowed after 19:00 on Day -1.

Group Number	Study Product	Number of Subjects
Group 1	CC	30
Group 2	NP2	30
Group 3	NP4	30
Group 4	NP8	30
Group 5	NT	30

8. DEFINITIONS OF POPULATIONS

Any protocol deviations, including those due to coronavirus disease 2019 (COVID-19) and related restrictions (see Section 9.1.1), will be considered prior to database lock for their importance and taken into consideration when assigning subjects to populations.

If it is determined that a subject was pregnant or COVID-19 positive during the study, all of the subject's safety and biomarker data will be reported, but will be excluded from the biomarker summarization and statistical analyses.

Details of subject assignment to the analysis populations will be listed.

8.1. All Subjects Population

The all subjects population will include all subjects who signed the informed consent form and had any study assessment recorded in the database per the protocol.

8.2. Safety Population

The safety population will include all subjects from Groups 1, 2, 3, and 4 who used at least 1 of the assigned study product and all Group 5 subjects. The safety population also includes the subjects who participated only in Product Trial Period but withdrew before randomization.

8.3. Product Use Population

The Product Use Population will include all subjects from Groups 1, 2, 3, and 4 who used at least 1 of the assigned study products and all Group 5 subjects. This population will be used for the product use behavior endpoint analysis.

8.4. Biomarker of Exposure Population

The BOE population will include all subjects from Groups 1, 2, 3, and 4 who used at least 1 of the assigned study products and all Group 5 subjects. To be included in the BOE population, subjects must have baseline (Day -1) and at least 1 postbaseline evaluable BOE data. This population will be used for biomarker endpoint analysis.

9. STATISTICAL METHODOLOGY

9.1. General

Listings will be provided for all data captured in the database. Listings will include all subjects assigned to safety population and include data up to the point of study completion or discontinuation. Subjects are considered to have completed the study if they complete the scheduled end of study visit (rather than early termination visit). Any subject who discontinues the study will be identified accordingly in the listings. Summaries and statistical analyses will include the subjects assigned to the relevant population based on data type.

Data analysis will be performed using the SAS® statistical software package Version 9.4 (or higher if a new version is issued during the study).

Analysis Data Model (ADaM) datasets will be prepared using Clinical Data Interchange Standards Consortium (CDISC) ADaM Version 2.1 (or higher if a new version is issued during the study) and CDISC ADaM Implementation Guide Version 1.1 (or higher if a new version is issued during the study). Pinnacle 21 Community Validator Version 4.2.1 (or higher if a new version is issued during the study) will be utilized to ensure compliance with CDISC standards.

Where reference is made to ‘valid’ data, this refers to non-missing data which meet the predetermined criteria (eg, are not flagged for exclusion).

Where reference is made to 'all calculations', this includes, but is not limited to, summary statistics, statistical analyses, baseline derivation, changes from baseline, and any parameter derivations.

All figures will be produced on linear-linear or discrete-linear scales, as applicable, unless specifically stated otherwise.

9.1.1. Handling of Data Quality Issues Due to Coronavirus Disease 2019 and Related Restrictions

Due to COVID-19 and related restrictions, there is a high risk for impact to data integrity, with the recognized potential for:

- Missed visits, caused by, for example:
  - Subject unable to travel to site due to restrictions, the need to quarantine, or COVID-19 infection
  - Subject unwilling to go to site due to fear of COVID-19 infection
  - Site postponing subject's visit due to investigator not being available (eg, if they have been dispatched to hospital handling COVID-19 infections)
- Site unable to replenish supply of investigational product
- Incomplete data entry by sites due to limited resources to support study or no access to source documents or to eCRF
- Outstanding source document verification (SDV) due to sponsor or country restrictions on remote SDV, or no or limited access to site(s) for on-site visits
- Unanswered queries

At the time of the reporting of the study results, all protocol deviations due to COVID-19 or related restriction will be assessed for their severity and impact on the analyses. If needed, appropriate statistical methods will be applied as a mitigating action (eg, data might be categorized into 2 analysis groups, with and without COVID-19 and related restrictions impact); however, this will exclude any imputations of the missing values. Any mitigating actions will be agreed with Altria Client Services, LLC. in advance and identified in the CSR.

9.1.2. Calculation of the Summary Statistics

For continuous data the following rules will be applied:

- Missing values will not be imputed, unless specifically stated otherwise.
- Unrounded data will be used in the calculation of summary statistics.

- If the number of subjects with valid observations (n) <3, summary statistics will not be calculated, with the exception of n, minimum, and maximum.

- In general, as early termination data are not associated with any scheduled timepoint, they will be excluded from all calculations of summary statistics and statistical analyses. Exceptions may be made where justified.

For categorical data the following rules will be applied:

- For ordered categorical data (eg, adverse event [AE] severity), all categories between the possible minimum and maximum categories will be included, even if n = 0 for a given category.

- For non-ordered categorical data (eg, race), only those categories for which there is at least 1 subject represented will be included; unless specifically stated otherwise.

- Missing values will not be imputed, unless specifically stated otherwise. A 'missing' category will be included for any parameter for which information is missing. This will ensure that the population size totals are consistent across different parameters.

9.1.3. Repeat and Unscheduled Readings

For vital signs and 12-lead ECG data only, any pre-use value recorded in addition to the original value or a post-use value recorded within 15 minutes of the original value will be defined as a repeat value; any post-use value recorded more than 15 minutes after the original value will be defined as an unscheduled value. For all other data types (eg, laboratory parameters), any value recorded in addition to the original value will be defined as an unscheduled value.

As unscheduled values are not associated with any scheduled timepoint, they will be excluded from all calculations, with the exception of the baseline derivation (see Section 9.1.4).

9.1.4. Definitions of Baseline and Change from Baseline

The baseline will be defined as the last value recorded prior to study product use. If the date/time of the value is incomplete or missing, it will be excluded from the baseline calculation, unless the incomplete date/time indicates the value was recorded prior to study product use.

Individual changes from baseline will be calculated by subtracting the individual subject's baseline value from the value at the post-use timepoint.

The summary statistics for change from baseline will be derived from individual subjects' values (eg, mean change from baseline will be the mean of the individual changes from baseline for all subjects, rather than difference between the mean value at the post-use timepoint and mean value at baseline).

See Section 9.1.3 for more detail on handling repeat and unscheduled readings in the calculations.

9.2. Subject Disposition and Population Assignment

Subject disposition and population assignment will be listed.

A summary table by study product groups will be provided, based on the safety population.

Screen failure data summary table will be provided separately, based on the all subjects who screen failed.

9.3. Screening Demographics and Baseline Characteristics

The screening demographics and baseline characteristics including age, sex, race, ethnicity, height, body weight, and body mass index will be listed.

A summary table by study product groups will be provided, based on the safety population.

9.4. Prior and Concomitant Medication

Prior medication will be defined as medication that ends prior to study product use. Concomitant medication will be defined as medication that starts during or after study product use or starts but does not end prior to study product use.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug) Global, Format B3, Version September 2020 (or later if a new version is issued during the study; see the data management plan [DMP] for more details). Prior and concomitant medications will be listed.

9.5. Pharmacodynamic Assessments

9.5.1. Pharmacodynamic Analysis

Descriptive statistics, including the number of subjects with non-missing data, number of subjects with missing data, mean, standard error of the mean, standard deviation (SD), median, minimum, maximum, coefficient of variation (CV%), and 95% CI, will be used to summarize the following PD parameters. The change from baseline for each parameter will be calculated and summarized in a similar manner.

Primary endpoint:
• 24-hour total urinary NNAL (mg/24 hours) excreted on Day 7

Secondary endpoints:
• Amount excreted in 24-hours of urinary NE, 2-AN, 4-ABP, HEMA, CEMA, S-PMA, 3 HMPMA, 3-HPMA, 2-HPMA, AAMA, GAMA, 2-MHBMA, 2 OHFle, 2-Naphthol, 1 OHPhe, 3-HB[a]P, mutagenicity, and 1-OHP excreted on Day 7
• COHb on Day 7

• Product use behavior from Day 1 to Day 7 (ie, number of cigarettes smoked per day[CPD], number of NP per day [NPPD], number of NP per use [NPPU], and average duration of each NP use)

9.5.2. Pharmacodynamic Derivations

Urine Biomarker Analysis Variables:

The following variables will be determined for each urine biomarker except mutagenicity testing.

- Measured concentration
- Total biomarker mass excreted per 24 hours
- Total mass excreted per 24 hours absolute change from Baseline
- Measured concentration adjusted for urine creatinine

Urine biomarker concentration values reported as below the limit of quantitation (BLQ) will be set to one-half of the lower limit of quantitation prior to calculating the 24-hour mass excreted. Total urine weight (g) collected during the 24 hours will be converted to 24 hours urine volume using the assumed density of 1 gram (g) equals 1 milliliter (mL).

Biomarker change from baseline values will be calculated.

If subjects' 24-hour urine samples are collected in any of the below circumstances, the urine biomarker total amount excreted in 24-hour for that timepoint will not be calculated and will be treated as missing. Creatinine-adjusted biomarker concentrations (except mutagenicity) might be calculated if more than 5% (of all study samples) of the 24-hour urine samples are collected in any of these circumstances:

1) incomplete;

2) outside the 24-hour window (less than or more than 24 hours +/- 30 minutes);

3) the first void of the day was pooled not according to the protocol.

For creatinine values that are BLQ, the values will not be used to adjust the NE concentration values. The creatinine-adjusted urinary biomarker values will be treated as missing.

Urine Biomarker Total Amount Excreted in 24 hours:

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

The concentration of each metabolite will first be multiplied by the 24-hour urine volume to obtain the total amount excreted in 24 hours, then divided by the molecular weight of the metabolite to obtain the total amount of each in moles. The sum in moles will then be converted to mass of NE by multiplying by the molecular weight of nicotine.

Nicotine (mg/24h)	=	nicotine concentration [ng/mL] × 24h urine volume [mL] ÷ 1000 000
Nicotine-glucuronide (mg/24h)	=	nicotine glucuronide concentration [ng/mL] × 24h urine volume [mL] ÷ 1000 000
Cotinine (mg/24 hours)	=	cotinine concentration [ng/mL] × 24h urine volume [mL] ÷ 1000 000
Cotinine-glucuronide (mg/24h)	=	cotinine glucuronide concentration [ng/mL] × 24h urine volume [mL] ÷ 1000 000
Trans-3'-hydroxycotinine (mg/24h)	=	trans-3'-hydroxycotinine concentration [ng/mL] × 24h urine volume [mL] ÷ 1000 000
Trans-3'-hydroxycotinine-glucuronide (mg/24h)	=	trans-3'-hydroxycotinine glucuronide concentration [ng/mL] × 24h urine volume [mL] ÷ 1000 000
Nicotine equivalents (mg/24 hours)	=	(nicotine [mg/24h]/162.23 [mg/mmol] + nicotine-gluc [mg/24h]/338.36 [mg/mmol] + cotinine [mg/24h]/176.22 [mg/mmol] + cotinine-gluc [mg/24h]/352.34 [mg/mmol] + trans-3'-hydroxycotinine [mg/24h]/192.22 [mg/mmol] + trans-3'-hydroxycotinine-gluc [mg/24h]/368.34 [mg/mmol]) x 162.23 (mg/mmol)

For other urine biomarkers except mutagenicity, the total amount excreted in 24 hours will be calculated as follows:

Urine Biomarker (unit2/24 hours)	=	Urine biomarker concentration [unit1/mL] × 24h urine volume [mL] ÷ 1000

Where: if unit1 = pg, then unit2 = ng; if unit1 = ng, then unit2 = µg

Urine Biomarker Adjusted by Urine Creatinine:

If creatinine adjustment is needed, NE concentration will be reported in µg/mL as follows:

NE concentration (µg/mL)	=	(nicotine [ng/mL]/162.23 [mg/mmol] + nicotine-gluc [ng/mL]/338.36 [mg/mmol] + cotinine [ng/mL]/176.22 [mg/mmol] + cotinine-gluc [ng/mL]/352.34 [mg/mmol] + trans-3'-hydroxycotinine [ng/mL]/192.22 [mg/mmol] + trans-3'-hydroxycotinine-gluc [ng/mL]/368.34 [mg/mmol]) × 162.23 (mg/mmol) × 1 µg/1000 ng

Then the NE will be adjusted as follows:

$$\text{Adjusted Nicotine equivalents (mg NE/g creatinine)} = \frac{\text{NE concentration (µg/mL)} \times 100}{\text{Creatinine concentration (mg/dL)}}$$

For other biomarkers:

$$\text{Adjusted Urine biomarker (unit2/g creatinine)} = \frac{\text{Urine biomarker concentration (unit1/mL)} \times 100}{\text{Creatinine concentration (mg/dL)}}$$

Where: if unit1 = pg, then unit2 = ng, and if unit1 = ng, then unit2 = µg.

Urine Mutagenicity:

250 mL urine sample will be concentrated to 1 mL and used for urine mutagenicity testing. The measurement results will be reported as revertants/µL. The urine mutagenicity count in the 24 hour urine will be calculated as follow:

Urine mutagenicity (revertants/250 mL) = Urine mutagenicity (revertants/µL) x 1000

Note: the coeffiecient 1000 is for 1 mL = 1000 µL. If the volume after concentration is X mL, the coefficient will be X*1000.

Urine mutagenicity (revertants/24 hour) = Urine mutagenicity (revertants/250 mL) x [24h urine volume(mL) ÷ 250]

Note: the coeffiecient 250 is the volume of urine sample used for mutagenicity test. If the sample volume is XXX mL, the coefficient will be XXX.

Blood Biomarker Analysis Variables:

The following variables will be determined for blood biomarkers:

- Measured concentration
- Measured concentration absolute change from Baseline

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

Biomarker Values Change from Baseline:

The absolute change from baseline of urine biomarker amount excreted in 24 hours and blood biomarker concentration will be calculated as follows:

Absolute change from baseline = Post Randomization Value – Baseline Value

where Baseline = Day -1

9.5.3. Presentation of Pharmacodynamic Data

All PD parameters and their changes from baseline will be listed.

Summary tables and mean ± SD figures by study product groups and timepoint will be provided for all PD parameters and their changes from baseline.

Values below the limit of quantification (BLQ) will be set to one-half (1/2) of LLOQ for the calculation of summary statistics.

The descriptive statistics tables for blood and urine biomarkers and products used per day will be generated with the following level of precision for the summary statistics:

The derived values (amount excreted in urine biomarkers and change from baseline) will have two decimal points.

- Number of observations (n)/number of missing values (n missing) without a decimal;
- Mean/median with one more decimal/significant figure than minimum/ maximum;
- Q1 and Q3 with one more decimal/significant figure than minimum/ maximum;
- Standard deviation/standard error of the mean (SD/SEM) with one more decimal/significant figure than mean/median.
- Coefficient of variation (CV%) with one decimal;
- Minimum/maximum in same precision as in the database
- 95% confidence intervals (CI) with one more decimal/significant figure than minimum/ maximum

9.5.4. Pharmacodynamic Statistical Methodology

Linear mixed models for analysis of covariance will be used to compare the Day 7 biomarker values between groups as described in the study objectives. In the statistical models, the outcome variable will be included as a dependent variable; group and gender will be included as fixed effects; and baseline values of corresponding biomarker will be included as covariates. Pairwise comparisons (NP2 vs. CC, NP4 vs. CC, NP8 vs. CC, NP2 vs. NT, NP4 vs. NT, NP8 vs. NT, CC vs. NT) will be performed using a Dunnett's test at a 2-sided significance level of 0.05 to adjust for multiplicity. CC & NT will be considered as the control groups. The test is for each of the other groups to compare with the control groups. The analysis will be conducted on the biomarker of exposure population dataset.

The following SAS codes will be used to perform the analysis.

```
Proc mixed data = data;
Class group gender;
Model PD = gender group baseline / ddfm=kr;
LSmeans group / CL alpha=0.05 pdiff adjust=dunnett;
Run;
```

A standard residual analysis using Proc Mixed procedure will be used to examine validity of normality assumptions for the primary endpoint. A natural logarithmic transformation (except urine mutagenicity) might be applied to the endpoint in the linear mixed model if the normality assumption does not hold. Square Root transformation will be used for urine mutagenicity statistical analysis.

Product use behavior endpoints will be summarized using descriptive statistics by group and study day.

9.6. Safety Assessments

9.6.1. Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1 (or higher if a new version is issued during the study; see the DMP for more details).

A product-emergent adverse event (PEAE) will be defined as an AE that starts during or after study product use, or starts prior to study product use and increases in severity after study product use.

A product-related PEAE will be defined as a PEAE with a relationship of unlikely, possible, likely and definitely related to the study product, as determined by the investigator.

All AEs will be listed. In addition to the data recorded in the database, the listings will include derived onset time and duration. Onset time will be calculated from the time of study product use for PEAEs only.

The frequency of subjects with PEAEs and the number of PEAEs will be summarized for the following categories:

- PEAEs (overall, serious, leading to discontinuation, and leading to death) by study products
- PEAEs by severity (mild, moderate, severe, total) and study products
- Product-related PEAEs (mild, moderate, severe, total) by study products
- Product-related PEAEs by severity and study products

The frequency of subjects will be summarized separately for PEAEs and product-related PEAEs by the following:

- System organ class, preferred term, and study products
- Preferred term and study products

For the AE data the following rules will apply:

- For the derivation of relationship (applicable to AEs captured on the 'change in the severity' eCRF form only): The relationship to study product is not captured on the AE change in severity eCRF form because it is always assumed to be the same as the relationship captured on the first eCRF form completed for this AE (initial severity). Therefore, for these cases the missing relationship will be set to that captured on the first form completed for this AE.
- For the derivation of product-emergent status (applicable to all AEs): If the start date/time of an AE is incomplete or missing, an AE will be assumed to not be a PEAE,

unless the incomplete start date/time or the end date/time indicates an AE started after study product use.

- For the derivation of product-related status (applicable to PEAEs only): If the study product relationship for a PEAE is missing, a PEAE will be assumed to not be a product-related PEAE.

- For the derivation of onset time (applicable to PEAEs only): If the start date/time of a PEAE is missing, onset time will not be calculated. If the start date/time of a PEAE is incomplete, where possible, the minimum possible onset time will be calculated and presented in '≥DD:HH:MM' format (eg, if the date/time of study product use is 01MAY2019/08:00 and recorded start date/time of a PEAE is 03MAY2019, then the minimum possible onset time will be calculated by assuming a PEAE started at the first hour and minute of 03MAY2019 [03MAY2019/00:00], thus will be presented as onset time ≥01:16:00 in the listing). If the start date of a PEAE is the same as the date of study product use but the start time of a PEAE is missing, an onset time will be presented as '≥00:00:01'. Any clock changes will be accounted for in the derivation.

- For the derivation of duration (applicable to all AEs): If the end date/time of an AE is missing, duration will not be calculated. If the start or end date/time of an AE is incomplete, where possible, the maximum possible duration will be calculated and presented in '≤DD:HH:MM' format (eg, if the start of an AE date/time is 01MAY2019/08:00 and its recorded end date/time is 03MAY2019, then the maximum possible duration will be calculated by assuming an AE ended at the last hour and minute of 03MAY2019 [03MAY2019/23:59], thus will be presented as duration ≤02:15:59 in the listing). Any clock changes will be accounted for in the derivation.

- For the calculation of PEAE summary statistics: If the severity of a PEAE is missing, that PEAE will be counted under the 'missing' category.

- For the calculation of PEAE summary statistics: If a subject experienced multiple PEAEs with the same preferred term for the same product, this will be counted as 1 PEAE for that product under the maximum severity recorded.

9.6.2. Clinical Laboratory Parameters

All clinical laboratory parameters, will be listed, as applicable; any value outside the clinical reference range will be flagged. Separate listings will be provided for any parameter for which there is any individual subject value outside the respective clinical reference range.

9.6.3. Vital Signs Parameters

All vital signs parameters, and changes from baseline, will be listed, as applicable; any value outside the clinical reference range will be flagged.

Summary tables by product and timepoint will be provided for all vital signs parameters.

9.6.4. 12-lead Electrocardiogram Parameters

All 12-lead ECG parameters and interpretation will be listed; any value outside the clinical reference range will be flagged.

9.6.5. Other Assessments

Medical history will be listed. Fagerstrom questionnaires will be summarized by product group and listed individually.

All other safety and tolerability assessments not detailed in the above sections will be listed only.

9.6.6. Safety Statistical Methodology

No inferential statistical analyses are planned.

10. INTERIM ANALYSIS

No interim analysis planned.

11. SIGNIFICANT CHANGES FROM THE PROTOCOL-SPECIFIED ANALYSES

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

12. REFERENCES

1. ICH. ICH Harmonised Tripartite Guideline: Structure and content of clinical study reports (E3). 30 November 1995.

2. ICH. ICH Harmonised Tripartite Guideline: General considerations for clinical trials (E8). 17 July 1997.

3. ICH. ICH Harmonised Tripartite Guideline: Statistical principles for clinical trials (E9). 5 February 1998.

4. Altria; Study Report No: ALCS-RDS-18-04-VRV.

13. APPENDICES

Appendix 1: Document History

Status and Version	Date of Change	Summary/Reason for Changes
Final Version 1.0	02Aug2021	TFL shells page 2: Change from: All TFLs will be created as .rtf files using A4 paper size, with all margins set to 2.54 cm. To: All TFLs will be created as .rtf files using US Letter paper size, with all margins set to 2.54 cm.
Final Version 1.0	26Oct2021	Per internal review, update: Table 14.1.1 Summary of Subject Disposition and Population Assignment (Safety Population) to: Table 14.1.1 Summary of Subject Disposition and Population Assignment (All Subject Population) So that Screen fails can be included.
Final Version 1.0	27Oct2021	Per internal review, update: Listing 16.2.1 Subject Disposition (Safety Population) to: Listing 16.2.1 Subject Disposition (All Subject Population) So that Screen fails can be included.
Final Version 1.0	27Oct2021	Per internal review, update: Listing 16.2.7.1.1 Adverse Events (Safety Population) Add: 2 columns: 1) Was a Conmed Given due to this Event? 2) Did the AE Cause the Subject to be Discontinued from the Study?
Final Version 1.0	28Oct2021	Per internal review, update: Listing 16.2.4.1 Subject Eligibility (Safety Population) To: Listing 16.2.4.1 Subject Eligibility (All Subjects Population)
Final Version 1.0	23Nov2021	Remove the "Unlikely" relationship wording in all AE summary and listing footnotes. Affecting Tables 14.3.1.1 through 14.3.1.5 and Listing 16.2.7.1.1
Final Version 1.0	23Nov2021	Change all "Product Trial*" Columns to "Not Assigned*" per sponsor's request for better reflecting the data. Also update the footnote * to "*Only include subjects that enrolled in the study but dropped prior to randomization." Update the # footnote to: "#Subjects who only enrolled in the study but dropped prior to randomization are excluded from the Overall summary."
Final Version 1.0	12Jan2022	Added PD parameter derivation missing for all the Urine biomarkers in the Primary and Secondary endpoints for inferential stats analysis: Total NNAL (ng/24 hours) = Total NNAL concentration [pg/mL] × 24h urine volume [mL] ÷ 1000

		2-AN (ng/24 hours) = 2-AN concentration [pg/mL] × 24h urine volume [mL] ÷ 1000 4-ABP (ng/24 hours) = 4-ABP concentration [pg/mL] × 24h urine volume [mL] ÷ 1000 HEMA (µg/24 hours) = HEMA concentration [ng/mL] × 24h urine volume [mL] ÷ 1000 CEMA (µg/24 hours) = CEMA concentration [ng/mL] × 24h urine volume [mL] ÷ 1000 S-PMA (µg/24 hours) = 3-PMA concentration [ng/mL] × 24h urine volume [mL] ÷ 1000 3-HMPMA (µg/24 hours) = 3-HMPMA concentration [ng/mL] × 24h urine volume [mL] ÷ 1000 3-HPMA (µg/24 hours) = 3-HPMA concentration [ng/mL] × 24h urine volume [mL] ÷ 1000 2-HPMA (µg/24 hours) = 2-HPMA concentration [ng/mL] × 24h urine volume [mL] ÷ 1000 AAMA (µg/24 hours) = AAMA concentration [ng/mL] × 24h urine volume [mL] ÷ 1000 GAMA (µg/24 hours) = GAMA concentration [ng/mL] × 24h urine volume [mL] ÷ 1000 2-MHBMA (µg/24 hours) = 2-MHBMA concentration [ng/mL] × 24h urine volume [mL] ÷ 1000 2-OHFlu (µg/24 hours) = 2-OHFlu concentration [ng/mL] × 24h urine volume [mL] ÷ 1000 2-Naphthol (µg/24 hours) = 2-Naphthol concentration [ng/mL] × 24h urine volume [mL] ÷ 1000 1 OHPhe (µg/24 hours) = 1 OHPhe concentration [ng/mL] × 24h urine volume [mL] ÷ 1000 3-HB[a]P (pg/24 hours) = 3-HB[a]P concentration [fg/mL] × 24h urine volume [mL] ÷ 1000 1-OHP (µg/24 hours) = 1-OHP concentration [ng/mL] × 24h urine volume [mL] ÷ 1000
Final Version 1.0	18Jan2022	Corrected typo on the Secondary endpoints naming on page 6 and 12 of SAP: Change 2 OHFle to 2 OHFlu to match the protocol.
Final Version 1.0	20Jan2022	Update Fagerstrom Summary and listing per sponsor request: Table 14.3.4.1 Summary of Fagerstrom Test (Safety Population) Add as last row: "Total Score" with statistics "N, Mean, SD, Median, Minimum, Maximum". Listing 16.2.4.8 Fagerstrom Test (Safety Population) Add "Total Score" as the last Column
Final Version 1.0	20Jan2022	Per sponsor request: added section 8.5 in the SAP. 8.5 Creatinine Adjusted Urine Biomarker of Exposure Population The creatinine adjusted urine BOE population will include all subjects from Groups 1, 2, 3, and 4 who used at least 1 of the assigned study products and all Group 5 subjects. To be included in the creatinine adjusted urine BOE population, subjects must have baseline (Day -1) and at least 1

		postbaseline evaluable creatinine adjusted urine BOE data. This population will be used for creatinine adjusted urine biomarker endpoint analysis. Added Creatinine Adjusted urine BOE Population flag in the Population assignment spreadsheet. Added Creatinine Adjusted urine BOE results into PD summary tables, figures, listings and stats analysis table. Will renumber the following to "a" and number the following to 'b', except for the listing. These TFLs include: Table 14.2.2.1a Summary of Biomarker of Exposure (Biomarker of Exposure Population) Table 14.2.2.2a Summary of Changes from Baseline in Biomarker of Exposure (Biomarker of Exposure Population) Figure 14.2.2.1a Mean (± SD) Biomarker of Exposure (Biomarker of Exposure Population) Figure 14.2.2.2a Boxplots of Changes from Baseline in Biomarker of Exposure (Biomarker of Exposure Population) Table 14.2.2.4a Statistical Analysis of Biomarker of Exposure (Biomarker of Exposure Population) Listing 16.2.6.2.3 Biomarker of Exposure and Changes from Baseline (Safety Population) Table 14.2.2.1b Summary of Creatinine Adjusted Urine Biomarker of Exposure (Creatinine Adjusted Urine Biomarker of Exposure Population) Table 14.2.2.2b Summary of Changes from Baseline in Creatinine Adjusted Urine Biomarker of Exposure (Creatinine Adjusted Urine Biomarker of Exposure Population) Figure 14.2.2.1b Mean (± SD) of Creatinine Adjusted Urine Biomarker of Exposure (Creatinine Adjusted Urine Biomarker of Exposure Population) Figure 14.2.2.2b Boxplots of Changes from Baseline in Creatinine Adjusted Urine Biomarker of Exposure (Creatinine Adjusted Urine Biomarker of Exposure Population) Table 14.2.2.4b Statistical Analysis of Creatinine Adjusted Urine Biomarker of Exposure (Creatinine Adjusted Urine Biomarker of Exposure Population)
Final Version 1.0	17Feb2022	Clarification for Urine Biomarker adjusted by Urine Creatinine derivation (SAP page 15). Given the creatinine unit in the actual dataset was reported mg/L instead of our presumption of mg/dL, we will be using constant 1000 instead of the original 100 for derivation of creatinine adjusted BOE formula: Change from: Adjusted Nicotine equivalents (mg NE/g creatinine) = NE concentration (µg/mL) × 100 / Creatinine concentration (mg/dL) For other biomarkers: Adjusted Urine biomarker (unit2/g creatinine) = Urine biomarker concentration (unit1/mL) × 100/Creatinine concentration (mg/dL) To: Adjusted Nicotine equivalents (mg NE/g creatinine) = NE concentration (µg/mL) × 1000 / Creatinine concentration (mg/L)

		For other biomarkers: Adjusted Urine biomarker (unit2/g creatinine) = Urine biomarker concentration (unit1/mL) × 1000/Creatinine concentration (mg/L)
Final Version 1.0	2Mar2022	Updated Stats table per sponsor comment for better data presentation: Table 14.2.2.4a and Table 14.2.2.4b clarification: 1) If we're log transforming the PD results per sap, we'll need to also log transform the Baseline value as the covariate in the model. 2) We'll present the Adjusted P-value instead of the Normal P-value. 3) Present Adjusted Lower and Higher 95%CI intervals.
Final Version 1.0	2Mar2022	Added SAP Note to File per sponsor request: The SAP note to file is documented as a clarification for better presentation of the study data following FDA document "Guidance for Industry Q2B Validation of Analytical Procedures: Methodology" dated November 1996. For SAP finalized for ALCS-REG-20-15-OTDN (Labcorp: 8461631) V1.0 dated 30July2021, we're adding the following for Section 9.5.2 on page 13: Old language: Urine biomarker concentration values reported as below the limit of quantitation (BLQ) will be set to one-half of the lower limit of quantitation prior to calculating the 24-hour mass excreted. New language: Urine biomarker concentration values reported as below the limit of quantitation (BLQ) will be set to one-half of the lower limit of quantitation (LLOQ) prior to calculating the 24-hour mass excreted or creatine adjusted concentrations. Urine biomarker concentration values below the limit of detection (LOD, reported as 0) will be set to one-sixth (1/6) of the LLOQ prior to calculating the 24-hour mass excreted or creatinine adjusted concentrations (based on using ½ of LOD, with LOD being generally considered 1/3 of LLOQ as stated in the above FDA guidance for industry). Given the data for mutagenicity is received in rev/mL unit. We update the SAP language for Section 9.5.2 on page 16: We remove the following old language: 250 mL urine sample will be concentrated to 1 mL and used for urine mutagenicity testing. The measurement results will be reported as revertants/µL. The urine mutagenicity count in the 24 hour urine will be calculated as follow: Urine mutagenicity (revertants/250 mL) = Urine mutagenicity (revertants/µL) x 1000 Note: the coeffiecient 1000 is for 1 mL = 1000 µL. If the volume after concentration is X mL, the coefficient will be X*1000. Urine mutagenicity (revertants/24 hour) = Urine mutagenicity (revertants/250 mL) x [24h urine volume(mL) ÷ 250] Replace with new language: Urine mutagenicity (revertants/24 hour) = Urine mutagenicity (revertants/mL) x 24h urine volume(mL) Also add data handling method: Urine mutagenicity values reported as NR by Celerion will be set to 0 prior to calculating the 24-hour urine mutagenicity value.
Final Version 1.0	24Mar2022	Added "N-miss and 95%CI for biomarker summary and behavior use summary tables" to be consistent with SAP and Protocol language.

		The impacting tables are: Table 14.2.2.1a & 1b, Table 14.2.2.2a & 2b and Table 14.2.2.4.
Final Version 1.0	24Mar2022	Update per sponsor request for: Table 14.2.2.4a Statistical Analysis of Biomarker of Exposure (Biomarker of Exposure Population) Table 14.2.2.4b Statistical Analysis of Creatinine Adjusted Urine Biomarker of Exposure (Creatinine Adjusted Urine Biomarker of Exposure Population) Change all CC vs NT comparison to NT vs CC.
Final Version 1.0	29Mar2022	Updated per sponsor request and clarification: Table 14.2.2.2a & 2b are confusing for reviewers. Please modify: 1) Change the footnote from 'Baseline was defined as the last value recorded prior to product use' to 'Baseline was defined as the value measured on Day -1, before randomization. Table 14.2.2.2a & 2b are confusing for reviewers. Please modify: 2) Timepoints from 'Baseline' to 'Day -1 (Baseline)', and from 'Day 7' to 'Day 7 (Change from Baseline)'.
Final Version 1.0	11Apr2022	Corrected Population typo: Change: Figure 14.2.2.3 Mean (± SD) Product Use Behavior (Biomarker of Exposure Population) To: Figure 14.2.2.3 Mean (± SD) Product Use Behavior (Product Use Population)

NA = not applicable

Statistical Analysis Plan (SAP) Approval Form

Type of Approval: SAP

Sponsor Name:	Altria Client Services LLC		
Sponsor Protocol/CIP ID:	ALCS-REG-20-15-OTDN	**Covance Study ID:**	8461631
SAP text filename:	ALCS-REG-20-15-OTDN_SAP_Final_30July2021.docx	**TFL shells filename:**	ALCS-REG-20-15-OTDN_TFL_Final_30July2021.docx
Version:	1.0	**Date:**	2Aug2021

Covance Approval(s):

Lead Statistician

Approval Signature Print Name Job Title Date	DocuSigned by: [redacted] 8/2/2021 150855A1D5984AA... [redacted], Biostatistician, Labcorp Drug Development, Inc.

Sponsor Approval(s):

By signing below when the statistical analysis plan (SAP) is considered final, the signatories agree to the analyses to be performed for this study and to the format of the associated tables, figures, and listings (TFLs). Once the SAP has been signed, programming of the Analysis Dataset Model (ADaM) datasets and TFLs based on these documents can proceed. Any modifications to the SAP text and TFL shells made after signing may result in a work-scope change.

Approval Signature Print Name Job Title Date	DocuSigned by: [redacted] 8/2/2021 D01C7C978D01409... [redacted], Lead statistician, Altria Client Services LLC.

Please scan/email completed form(s) to the Lead Statistician listed below:

Printed Name/Title:	[redacted] Biostatistician
Email:	[redacted]

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