Statistical Analysis Plan

A Longitudinal Ambulatory Study to Assess Changes in Cigarette Consumption Behavior and Biomarkers of Exposure during a 6-Week Switch to Very Low Nicotine Cigarettes

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Statistical Analysis Plan Signature Page

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1. INTRODUCTION

The following statistical analysis plan (SAP) provides the framework for the summarization of the data from this study. The SAP may change due to unforeseen circumstances. Any changes made from the planned analysis within protocol, after locking of the database will be documented in the clinical study report (CSR).

Any additional analyses not addressed within this SAP and/or driven by the data, or requested by the SPONSOR, will be considered out of scope and must be described in the CSR.

2. STUDY PURPOSE, HYPOTHESIS, OBJECTIVES AND ENDPOINTS

2.1 Study Purpose

The purpose of this study is to examine whether measures of cigarette consumption behavior (cigarettes per day and smoking topography) are changed when smokers switch from smoking conventional cigarettes to smoking cigarettes with a very low nicotine (VLN) content (0.4 mg nicotine per gram of tobacco). Secondary purposes are to examine changes in biomarkers of exposure (BoE), nicotine pharmacokinetics (PK) and subjective measures of dependence, smoking urges, withdrawal symptoms and perceived health risks, when subjects switch to smoking VLN cigarettes.

2.2 Hypothesis

It is anticipated that when adult smokers switch to smoking VLN cigarettes, after habitually consuming their usual quantity and brand of cigarettes, their daily cigarette consumption will be reduced. It is further anticipated that puffing topography parameters will be unchanged following smoking VLN cigarettes for 6 weeks (i.e. no smoking compensation will occur).

2.3 Objectives

Primary objectives:

1. To characterize cigarette consumption behavior (cigarettes per day and puffing topography) before, during and after a switch from usual brand (UB) to VLN cigarettes for 6 weeks.

Secondary objectives:

1. To evaluate changes in tobacco-related biomarkers of exposure (BoE) before, during and after a 6-week switch from UB to VLN cigarettes.
2. To evaluate nicotine PK before, during and after a 6-week switch from UB to VLN cigarettes.
3. To evaluate changes in subjective effects before, during and after a 6-week switch from UB cigarettes to VLN cigarettes.

2.4 Endpoints

Product Use Endpoints (Primary Objective 1):

- Cigarettes smoked per day (CPD). Both compliant and non-compliant smoking captured in the electronic diaries (e-diaries).

- Number of collected used cigarette butts (apparent compliant, apparent non-compliant, and total)

- Puffing topography parameters (puff duration, puff volume, peak puff flow rate, average flow rate and inter-puff interval)

BoE Endpoints (Secondary Objective 1):

- In urine:
    - Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL;4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone [NNK] biomarker)
    - Total N-Nitrosonornicotine (NNN)
    - 3-hydroxypropylmercapturic acid (3-HPMA; acrolein biomarker),
    - S-phenylmercapturic acid (S-PMA; benzene biomarker),
    - 1-hydroxypyrene (1-OHP; hydroxypyrene biomarker)
    - Total nicotine equivalents (Tneq)
    - Creatinine concentration (for normalization of urinary BoE endpoints)
- Carboxyhemoglobin in blood
- Cotinine in plasma

Nicotine PK Endpoints(Secondary Objective 2)

- Nicotine PK parameters will include Cmax, AUC0-180 and Tmax

Subjective Effects Endpoints (Secondary Objective 3)

- Fagerström Test for Cigarette Dependence (FTCD)
- Brief Questionnaire of Smoking Urges (QSU-Brief)
- Minnesota Nicotine Withdrawal Scale - Revised (MNWS-R)
- Perceived health risk scale
- Safety endpoints will include adverse events (AEs).

3. STUDY DESIGN

This is an open-label, randomized, forced-switching study to be conducted at multiple study sites. Seventy (70) self-affirmed exclusive filtered non-mentholated cigarette smokers and 70 self-affirmed exclusive filtered mentholated cigarette smokers will be enrolled and begin the study at Week -1.

All potential subjects will provide informed consent and successfully complete the Screening procedures prior to participation in the study. Subjects will also engage in a

brief product trial with the VLN cigarettes. Subjects who react negatively (i.e., unwilling to use and/or cannot tolerate the product [experience AEs that will prevent them from continuing to use the product as judged by the Investigator]) to the VLN cigarettes during the product trial period will not continue in the study.

At the start of Week -1, all subjects will be asked to smoke their UB cigarettes as per their usual daily consumption for the following week. Subjects will receive an e-diary to record daily cigarette use (CPD). Training in completion of the e-diary will be provided at the visit at the start of Week -1.

Subjects will return at the end of Week -1, at the time indicated by the clinical research unit (CRU), for collection of blood and 24-hour urine samples for baseline BoE assessments. Subjective questionnaires for dependence, withdrawal symptoms, urges to smoke, and perceived health risk will also be completed at scheduled times. A randomly-selected subset of 18 non-menthol and 18 menthol smoker subjects will complete an assessment of puffing topography with their UB cigarettes during this visit. A further subset of 12 of the non-menthol and 12 of the menthol smoker subjects who complete the topography assessment will also complete a nicotine PK assessment at the end of this visit. Subjects who undergo topography and PK assessments will be assigned to switch to smoking VLN cigarettes.

On Day -1 of Week 1, subjects will be randomly selected to either remain smoking their non-menthol (20 subjects) or menthol (20 subjects) UB cigarettes, or to switch to smoking non-menthol (50 subjects) or menthol (50 subjects) VLN cigarettes as per their UB cigarette flavor. Subjects will return at the end of Weeks 2 and 6, at the time indicated by the CRU, for collection of blood and 24-hour urine samples for BoE assessments. Subjective effects questionnaires will also be completed at scheduled times. Subjects will continue recording their CPD in their e-diaries. The same subset of 18 non-menthol and 18 menthol smoker subjects selected to complete a puffing topography assessment with their UB cigarette on Week-1, will complete an assessment of puffing topography with the VLN cigarettes at these visits, and a further subset of 12 non-menthol and 12 menthol smoker subjects will also complete an assessment of nicotine PK at the end of these visits. Subjects undergoing topography and PK assessments will have been assigned to switch to smoking VLN cigarettes.

Additionally, all subjects will visit the clinic at the end of Week 4 to receive further supplies of cigarettes (if assigned to the VLN groups) and to complete subjective effects questionnaires.
Subjects randomized to the VLN groups will be provided with a supply of VLN cigarettes at each visit, which will be 150 % of their usual daily consumption as reported during Week 1. If a subject runs out of cigarettes between clinic visits, they may visit the clinic to receive additional test cigarettes. All subjects will be asked to smoke their cigarettes *ad libitum*, recording their actual daily consumption in their e-diaries. Non-compliant nicotine product consumption should also be recorded. Used

cigarette butts will also be collected during ambulatory periods to verify product use and/or assess compliance. During Week 1 (all subjects) and all subsequent weeks (subjects randomized to continue smoking UB cigarettes) subjects will be asked not to change their UB cigarette brand or flavor.

The CRU will attempt to contact all subjects who participated in the study (including subjects who terminate the study early) using their standard procedures approximately 7 days after the last contact to determine if any AE has occurred since the last study visit.

4. SAMPLE SIZE ESTIMATION

4.1 Cigarette Consumption

An intended sample size of 50 subjects in each of the two groups who switch from smoking usual brand to VLN cigarettes has been set for this study. This is based on powering the primary objective of a within-group comparison of cigarette consumption at baseline and end-of-study. The calculation was based on the number of pairs required to perform a one-tailed paired t-test with 80% power and an alpha level of 0.05 for a decrease in cigarette consumption of 3 CPD compared to available historical consumption data. The sample size was determined to be adequate based on potential non-compliance with the use of VLN cigarettes. A lower number (20) of smokers will be randomized to the continue-to-smoke usual brand groups, given the lower variability in consumption data and lower non-compliance anticipated in these groups. This will provide sufficient power for the secondary objective of between-group comparisons in cigarette consumption.

4.2 Puffing Topography

An intended sample size of 12 subjects in each of the two groups who switch from smoking usual brand to VLN cigarettes has been set for this study. This is based on powering the primary objective of a within-group comparison of puffing topography parameters at baseline and end-of-study. The calculation was based on the number of pairs required to perform a two-tailed paired t-test with 80% power and an alpha level of 0.05 to detect significant differences between UB and VLN cigarettes and is based on available puffing topography data (5). This sample size will also provide sufficient power to detect differences in nicotine PK between UB and VLN cigarettes.

5. ANALYSIS POPULATIONS

The statistical analysis will be based on separate, hierarchically organized, analysis populations defined as the following:

Safety population: All enrolled subjects who smoked at least one cigarette of any type. This population will be used for safety analysis.

Intent-to-treat (ITT) population: All subjects who had at least one valid recording of cigarette consumption (a period of one week of >70% completion of their e-diary).

Per-protocol (PP) population: All subjects who had valid recording of cigarette consumption and completed the study according to the protocol. Data will be excluded from this population:

- If a subject self-reports smoking a significant number of cigarettes other than those which they have been assigned according to the protocol, or if this is apparent following checking of their collected used cigarette butts

- If there is a significant discrepancy between the self-reported number of cigarettes smoked per day and the number of used cigarette butts collected

- If a subject is non-compliant based on a published method of assessing compliance. After switching, subjects will be deemed non-compliant if their ratio of [plasma cotinine/CPD VLN]/[plasma cotinine/CPD baseline] exceeds 0.2.

If it is determined that a subject is pregnant during the study, the pregnant subject's data will be listed but excluded from all PK parameter summaries.

PK Population: Subjects in the PP or ITT population who have at least one PK blood draw resulting in at least one quantifiable plasma nicotine concentration. This population will be used for PK analysis (secondary endpoint analysis) and all available data will be included in the concentration and PK parameter tables to the extent possible.

5.1 Preliminary Analyses

Topline preliminary reports will be prepared using final PK and puffing topography data. The PK and puffing topography TFLs listed in Section 13 will be included in the topline reports.

6. PRODUCT DESCRIPTION

The following investigational products will be used during this study:

Product	Short Description	Long Description
Non-mentholated VLN cigarette	VLN non-mentholated	Non-mentholated VLN cigarettes
Mentholated VLN cigarette	VLN mentholated	Mentholated VLN cigarettes
UB non-mentholated cigarette	UB non-mentholated	Subjects' UB non-mentholated filtered cigarettes
UB mentholated cigarette	UB mentholated	Subjects' UB mentholated filtered cigarettes

For the PK and safety text and analysis, table and listing headers, and AE (on rare occasion this may also apply to additional safety endpoints), the product will be described using the short description.

For figures, listings, and footnotes, the long description will be used, wherever feasible.

7. PRODUCT USE

7.1 Product Use Measurements and Collection Schedule

7.1.1 Product Use History

Subjects will be required to report previous tobacco- and nicotine-product use histories to satisfy the study inclusion and exclusion criteria. In addition, the subject will be asked if he/she is planning to quit smoking within the next 3 months. Those planning to quit will be excluded from participating in the study.

The subjects' tobacco use and smoking history (including a color photocopy of their UB cigarette package along with a ruler) will be recorded at Screening. Verification of the subject's UB cigarette brand will be made at the end of Week -1 clinic visit.

7.1.2 Product Use Recording

Subjects will be provided with e-diaries to record their daily cigarette consumption, both when in clinical confinement during study visits and during ambulatory periods. Subjects will be instructed to record both compliant and non-compliant (if any) daily numbers of cigarettes smoked. Non-compliant consumption in the subjects randomized to smoke VLN cigarettes is defined as nicotine product consumption other than their UB cigarettes during the baseline period (Week -1) or VLN cigarettes following switching (Weeks 1 to 6). Non-compliant consumption in the subjects randomized to continue to smoke their UB cigarettes is defined as nicotine product consumption other than their UB cigarettes between Week -1 and Week 6.
For the purposes of data analysis, the e-diary record of cigarette consumption will be used as the primary variable.

Subjects will be provided with metal canisters in which to store their used cigarette butts during the ambulatory study periods. This is for the purposes of assessing both compliance with the study requirements and the accuracy of their self-reported (electronic diary) cigarette consumption. Subjects will be requested to collect butts of all cigarettes smoked, both compliant and non-compliant.

At the end of each collection period, the total number of butts in the canisters for the whole of that period will be counted and recorded. The number of each type of cigarette (study cigarette and non-study cigarette) will also be recorded. The cigarette butt count will be reconciled against that subject's e-diary record of cigarette consumption.

7.1.3 Puffing Topography

At clinic visits at the end of Weeks -1, 2 and 6, a randomly-selected subset of 18 non-menthol and 18 menthol smoker subjects will complete a puffing topography evaluation session with either their UB (Week -1) or the VLN (Weeks 2 and 6) cigarettes. These subjects will be/have been assigned to switch to smoking VLN cigarettes. These assessments will only be performed at a single clinical site (Lincoln) and will take place during the 24-hour confinement period.

During the puffing topography assessment, subjects will engage in a 1 hour ad libitum smoking session with their UB (Week -1) or the VLN (Weeks 2 and 6) cigarettes. In these sessions, subjects will smoke cigarettes with the mobile smoking puff analyzer (SPA-M; Sodim). The topography device will be monitored to ensure the device is actively recording during each session.

Topography assessments will be started at least one hour following either the subject's breakfast or lunch. The puffing topography session for each subject at Weeks 2 and 6 should be within ± 2 hours of the time of their Week -1 session. Additional details and instructions for puffing topography procedures will be provided separately.

The following topography parameters will be assessed:

- Puff duration
- Puff volume
- Peak puff flow rate
- Average flow rate
- Inter-puff interval

7.2 Data Summarization and Presentation of Primary Endpoints

Study product use (study product, CPD and cigarette butts) will be listed by subject and study week. CPD and cigarette butts will be summarized by study week and study product using descriptive statistics (number of observations [n], arithmetic mean [Mean], standard deviation [SD], coefficient of variation [CV%], standard error of the mean [SEM], minimum, median, and maximum). The total duration of the product use (sum of the duration of each product use) will also be summarized. The descriptive statistics will be presented for both PP and ITT populations.

Topography parameters (puff duration, puff volume, peak puff flow rate, average flow rate, and inter-puff interval) will be listed by subject and summarized by study product and time point (Week -1, 2, or 6).

7.3 Statistical Analysis of Primary Endpoints

Paired t-tests will be used to compare cigarette consumption (CPD) and puffing topography parameters at the Week 2 and Week 6 time points with the baseline (Week -1) values. This analysis will be conducted on the evaluable subjects in the PP population. If data are unexpectedly found not to be normally distributed, an appropriate non-parametric test will be performed. Differences will be considered statistically significant at an alpha level of 0.05. Means, difference of means, 90% confidence interval for difference, and p-value will be presented.

The following SAS codes will be used for the analysis:

```
Proc ttest data=< >;
 By product_group;
 Paired week_X*baseline;
Run;
```

Where week_X will be either Week 2 or Week 6. Product Groups are VLN non-mentholated, VLN non-mentholated, and VLN combined which pooled non-mentholated and mentholated groups. The primary analysis will be based on the VLN combined product group.

In addition, a linear mixed model analysis of variance will be used to compare the between product group differences in the absolute change from baseline values of the consumption and puffing topography parameters. Product group, week, and product group by week interaction will be the fixed factors in the model. A restricted maximum likelihood estimation method with an unstructured (UN) covariance structure will be applied. If the model does not converge, the first order autoregressive AR(1) and/or compound symmetry CS covariance structures will be tested as alternatives. The least-square mean difference, 95% confidence interval and p-value will be provided for the product group difference. The pairwise comparisons (VLN non-mentholated versus UB non-mentholated, VLN mentholated versus UB mentholated, and VLN combined versus UB combined) will be performed at week Week 2 and Week 6. Least-square means (LSMeans), difference of LSMeans, 90% confidence interval for difference, and p-value for difference will be presented.

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

```
Proc mixed data=< >;
Class subject product_group week;
Model response = product_group week product_group*week /ddfm=kr;
Repeated week/type=<type> subject=subject;
LSmeans product_group*week/CL alpha=0.05 CL pdiff;
Run;
```

The primary analysis will be the pairwise comparisons of VLN combined versus UB combined (pooled non-mentholated and mentholated groups).

8. BIOMARKERS

8.1 Urine Biomarkers

8.1.1 Urine Biomarkers Measurements and Collection Schedule

Urine will be collected over 24-hour periods for urine BoE measurements, during the clinic visits at the end of Weeks -1, 2 and 6. The urine samples collected during a single 24-hour period will be pooled together and weighed. The total weight of all urine collected over each 24 hour period will be documented. Concentrations of the following biomarkers will be measured: total NNAL, total NNN, 3-HPMA, S-PMA, 1-OHP, and Tneq. Creatinine in urine will also be measured and used to report BoE as amount per unit of creatinine.

8.1.2 Bioanalytical Method

Urine concentrations will be determined using validated analytical methods at Celerion Bioanalytical Services, Lincoln, NE and Celerion, Switzerland.

Urine nicotine, cotinine, *trans*-3'-hydroxycotinine, nicotine-*N*-glucuronide, cotinine-*N*-glucuronide, *trans*-3'-hydroxycotinine-*O*-glucuronide, NNN, NNAL, 1-OHP, and creatinine concentrations will be analyzed by liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods at Celerion, Lincoln, NE using validated analytical methods with appropriate quality controls according to applicable portions of Celerion Standard Operating Procedures which were written based on the FDA Guidance for Industry: Bioanalytical Method Validation (May, 2001) and the FDA Good Laboratory Practice regulations (Title 21 CFR Part 58).

Approximate lower limit of quantitation (LLOQ) values for each analyte are shown in the table below. LLOQs will be reported out to the most current validation data and included in the bioanalytical report.

Analyte	LLOQ
Nicotine	50.0 ng/mL
Cotinine	50.0 ng/mL
trans-3'-hydroxycotinine	50.0 ng/mL
Nicotine-*N*-glucuronide	50.0 ng/mL
Cotinine-*N*-glucuronide	200 ng/mL
trans-3'-hydroxycotinine-*O*-glucuronide	200 ng/mL
NNN	0.200 pg/mL
NNAL	5.00 pg/mL
1-OHP	10.0 pg/mL
Creatinine	120 µg/mL (effective LLOQ)

Urine nicotine, cotinine, trans-3'-hydroxycotinine, nicotine-N-glucuronide, cotinine-N-glucuronide, trans-3'-hydroxycotinine-O-glucuronide, NNN, NNAL, 1-OHP, and creatinine concentrations will be determined using validated analytical methods at Celerion, Lincoln, NE and Celerion, Switzerland.

Urine 3-HPMA and S-PMA concentrations will be analyzed by LC-MS/MS methods at Celerion, Switzerland. The analysis will be performed according to the standards described in the Swiss Ordinance relating to Good Laboratory Practice, adopted 18 May 2005 [RS 813.112.1]. This Ordinance is based on the OECD Principles of Good Laboratory Practice, as revised in 1997 and adopted 26 November 1997 by decision of the OECD Council [C(97)186/Final].The OECD Principles of Good Laboratory Practice are accepted by Regulatory Authorities throughout the European Union, the United States of America and Japan. In addition, the analysis of clinical trial samples will be conducted in accordance with the relevant standards of Good Clinical Practice and Standard Operating Procedures based on the recommendations of the EMA 'Reflection paper for laboratories that perform the analysis or evaluation of clinical trial samples' (EMA/INS/GCP/532137/2010), the EMA 'Guideline on bioanalytical method validation' (EMEA/CHMP/EWP/192217/2009) and the FDA 'Guidance for Industry, Bioanalytical Method Validation', (U.S. Department of Health and Human Services, Food and Drug Administration, CDER, CVM, May 2018).

Approximate LLOQ values for each analyte are shown in the table below. LLOQs will be reported out to the most current validation data and included in the bioanalytical report.

Analyte	LLOQ
3-HPMA	20 ng/mL
S-PMA	0.025 ng/mL

8.1.3 Urine Biomarkers Analysis

The following variables will be determined for each urine biomarker at each collection week:

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

Nicotine equivalents will be calculated as the molar sum of nicotine, cotinine, trans 3'hydroxycotinine and their glucuronides excreted in urine over 24 hours:

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 Tneq 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)

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

Creatinine-adjusted concentrations will be calculated as shown in Section 8.1.4. Absolute and percent change from baseline will be calculated as shown in Section 8.1.5.

8.1.4 Creatinine Adjusted Urine Biomarker Concentrations

Creatinine concentrations will be used to adjust the concentration values of all urine biomarkers (Total NNAL, total NNN, 3-HPMA, S-PMA, 1-OHP, and Tneq) as follows:

$$\text{Urine biomarker (mass/mg creatinine)} = \frac{\text{urine biomarker (mass/mL) x 100}}{\text{creatinine (mg/dL)}}$$

8.1.5 Change from Baseline Urine Biomarker Concentration

Urine biomarker change from baseline on Weeks 2 and 6 will be calculated as follows, where Baseline = Week -1:

Absolute change from baseline = Post Product Use Value – Baseline Value

Percent change from baseline (%) = (Post Product Use Value – Baseline Value) / Baseline Value x 100 %

8.2 Blood Biomarkers

8.2.1 Blood Biomarkers Measurements and Collection Schedule

Blood samples for COHb in whole blood and cotinine in plasma will be collected on Weeks -1, 2, and 6. Samples will be collected at approximately 13:00, following the subject's lunchtime meal, and will be preceded by at least a 30 minute abstention from study product use.

8.2.2 Bioanalytical Method

Whole blood COHb and plasma cotinine will be analyzed by spectrophotometric measurement and LC-MS/MS, respectively, at Celerion Bioanalytical Services, Lincoln, NE, using validated analytical methods with appropriate quality controls according to applicable portions of Celerion Standard Operating Procedures which were written based on the FDA Guidance for Industry: Bioanalytical Method Validation (May, 2001) and the FDA Good Laboratory Practice regulations (Title 21 CFR Part 58). The LLOQ for COHb will be 0.2%. The LLOQ for plasma cotinine will be 1.00 ng/mL.

8.2.3 Blood Biomarkers Analysis

Absolute and percent change from baseline in blood biomarkers will be calculated as described for urine in Section 8.1.5.

8.3 Data Summarization and Presentation of Biomarkers of Exposure

Blood biomarker concentrations, urine biomarker concentrations, urine creatinine concentrations, and the creatinine-adjusted urine biomarker concentrations will be listed by product, subject and week for all biomarkers. All BLQ values will be presented as "BLQ" in the listings.

Blood biomarker concentrations, blood biomarker absolute change from baseline and blood biomarker percent change from baseline as well as urine biomarker mass excreted per 24 hours, absolute change from baseline, percent change from baseline of total mass excreted per 24 hours, creatinine-normalized excretion level, creatinine-normalized excretion absolute change from baseline, and creatinine-normalized excretion percent change from baseline will be summarized by product group and week for all biomarkers using descriptive statistics (n, mean, SD, CV%, SEM, minimum, median, and maximum). The descriptive statistics will be presented for both PP and ITT populations.

8.4 Statistical Analysis of Biomarkers of Exposure

Paired t-tests will be used to compare urinary NNAL, NNN, 3-HPMA, S-PMA, 1-OHP, Tneq mass excreted, and blood COHb measures at the Week 2 and 6 time points with the baseline (Week -1) values. This analysis will be conducted on the evaluable subjects in the PP population. If data are unexpectedly found not to be normally distributed, an appropriate non-parametric test will be performed. Differences will be considered statistically significant at an alpha level of 0.05. The same SAS codes used in Section 7.3 for paired t-test will be used for the analysis.

In addition, a linear mixed model analysis of variance will be used to compare the between product group differences in the absolute change from baseline values of each of the urinary and blood BoEs. The same statistical model and SAS codes used in Section 7.3 for product group comparisons will be used for the analysis.

9. PHARMACOKINETIC ANALYSIS

9.1 Measurements and Collection Schedule

For a randomly-selected subset of 12 non-menthol and 12 menthol smoker subjects, PK blood sampling will occur following the completion of the 24-hour urine collection period on clinic visits at Weeks -1, 2, and 6. The selected subjects will remain in the clinic for a further night, in which they will abstain from smoking any cigarettes/using any nicotine-containing products for at least 12 hours prior to the PK assessment session. During this session, subjects will smoke a single cigarette (either their UB on Week -1 or the VLN on Weeks 2 and 6) *ad libitum* during a 5-minute period. Serial blood samples will be collected for plasma nicotine analysis at 5 minutes prior to and at 2, 5, 7, 10, 12, 15, 20, 30, 45, 60, 90, 120, 150, and 180 minutes relative to the start of cigarette smoking.

All concentration data will be included in the calculation of the individual PK parameters, the individual concentration-time plots (based on actual sample times), and in the mean concentration-time plots (based on nominal sample times). However, if there are any significant deviations from nominal sample times, some concentration data may be excluded from mean concentration-time plots and/or additional concentration-time plots of the mean data may be provided. All deviations and excluded data will be provided and discussed in the CSR.

9.2 Bioanalytical Method

Plasma concentrations of nicotine will be determined using a LC-MS/MS method at Celerion Bioanalytical Services, Lincoln, NE, using a validated analytical method with appropriate quality controls according to applicable portions of Celerion Standard Operating Procedures which were written based on the FDA Guidance for Industry: Bioanalytical Method Validation (May, 2001) and the FDA Good Laboratory Practice regulations (Title 21 CFR Part 58). The analytical range (LLOQ

– upper limit of quantitation [ULOQ]) for nicotine is expected to be 0.200 – 25.0 ng/mL.

9.3 NonCompartmental Pharmacokinetic Analysis and Parameter Calculation

9.3.1 Plasma Nicotine Pharmacokinetic Parameters

The appropriate noncompartmental PK parameters will be calculated from the plasma nicotine concentration-time data using Phoenix® WinNonlin® Version 7.0 or higher. Actual sample times will be used in the calculations of the PK parameters. Concentration data will be presented: 1) unadjusted for baseline and 2) baseline-adjusted. The baseline is the plasma nicotine concentration value obtained before the start of cigarette smoking (-5 minutes) and the adjustment will be subject-specific. For the calculation of PK parameters, plasma nicotine concentrations below the limit of quantification (BLQ) will be set to one-half (½) the LLOQ. All PK parameters included in the protocol are listed in Table 6.1 below, and are defined as appropriate for study design.

Table 6.1. Noncompartmental Pharmacokinetic Parameters to be Calculated

Parameter	Definition	Method of Determination
AUC0-180	Area under the concentration-time curve from time 0 to 180 minutes	Calculated using the Linear Trapezoidal with Linear Interpolation Method
Cmax	The maximum observed concentration	Taken directly from bioanalytical data
Tmax	The time to reach Cmax	Taken from the concentration versus time data as the actual time corresponding to the maximum observed concentration

For the calculation of PK parameters, subjects must have at least 3 postproduct use data points. If the preproduct data point is missing then a value of ½ the LLOQ will be imputed. Subjects for whom there are insufficient data to calculate the PK parameters will be included in the concentration tables only.

Baseline adjustment

For PK parameters calculated using the baseline-adjusted concentrations, adjustment will be done using the reported nicotine half-life of 120 minutes (elimination rate constant, $\lambda z = 0.0058$ min^{-1}) with the following equation:

$$C_{t(adj)} = C_t - C_0 \times e^{-\lambda z \times t1}$$

where $C_{t(adj)}$ is adjusted concentration, C_t is observed concentration, C_0 is the concentration at the pre-product use time point, t is actual sampling time since product administration, and t1 is the actual sampling time since pre-product administration sample time.

After correction for pre-product use values, some concentrations may be BLQ and some may be negative values. All values obtained will be reported as is even if these values are BLQ or negative. Negative values will be assigned a value of zero in summary statistics and for PK parameter calculations.

9.4 Data Summarization and Presentation of PK Concentrations and Parameters

All nicotine PK concentrations and/or PK parameters descriptive statistics will be generated using SAS® and/or Phoenix® WinNonlin® as appropriate.

The plasma concentrations of nicotine will be listed by subject and summarized by study product group, time point and sex for all subjects in the PK Population. Plasma concentrations of nicotine will be presented with the same level of precision as received from the bioanalytical laboratory. Summary statistics, including n, Mean, SD, CV%, SEM, minimum, median, and maximum will be calculated for all nominal concentration time points. Excluded subjects will be included in the concentration listings, but will be excluded from the summary statistics and noted as such in the tables. All BLQ values will be presented as "BLQ" in the concentration listings and footnoted accordingly. The descriptive statistics will be presented for the PK population in both PP and ITT populations.

Mean and individual concentration-time profiles will be presented on a linear scale and semi-log scale. Linear profiles will be presented with and without SD.

Plasma nicotine PK parameters will be listed and summarized by study product group and sex for all subjects in the PK Population (from ITT and PP populations). Pharmacokinetic parameters will be reported to 3 significant figures for individual parameters, with the exception of T_{max}, which will be presented with 2 decimal places. Summary statistics (n, Mean, SD, CV%, SEM, minimum, median and maximum), will be calculated for plasma nicotine PK parameters AUC0-180, Cmax and Tmax. In addition, geometric mean (Geom Mean) and geometric CV% (Geom CV%) will be calculated for AUC0-180 and Cmax. Excluded subjects will be listed in the PK parameter tables, but will be excluded from the summary statistics and noted as such in the tables. The descriptive statistics will be presented for the PK population in both PP and ITT populations.

The level of precision for each concentration and PK parameter statistic will be presented as follows: minimum/maximum in same precision as bioanalytical data/PK parameter, mean/median in one more level of precision than minimum/maximum, SD in one more level of precision than mean/median, n will be presented as an integer and CV% will be presented to the nearest tenth.

9.5 Statistical Analysis of PK Parameters

Paired t-tests (on AUC and Cmax) will be used to compare baseline adjusted nicotine PK parameters at the Week 2 and 6 time points with the baseline (Week -1) values. This analysis will be conducted on subjects in the PK population (from the PP population only). If data are unexpectedly found not to be normally distributed, an appropriate non-parametric test will be performed. Differences will be considered statistically significant at an alpha level of 0.05. Geometric means, geometric mean ratio (GMR), 90% confidence interval for GMR, and p-value will be presented. The analysis is based on the log-transformed data. The same SAS codes used in Section 7.3 for paired t-test will be used for the analysis.

10. SUBJECTIVE EFFECTS

10.1 Measurements and Collection Schedule

The FTCD, QSU-Brief, MNWS-R, perceived health risk scale will be completed at the end of each clinic visit, at the end of Weeks -1 (Baseline), 2, 4 and 6.

10.2 Data Summarization and Presentation of Subjective Effects

10.2.1 Analysis variables

Total score for FTCD will be calculated for each subject at each time point and used as the analysis variable for FTCD questionnaire

The factor scores for QSU-brief: Responses will be used for the QSU-brief questionnaire. There are two factor scores: Factor 1 ('anticipation of pleasure from smoking' calculated as the average of the response scores from Questions 1, 3, 6, 7, and 10) and Factor 2 ('relief of nicotine withdrawal' calculated as the average of the response scores from Questions 2, 4, 5, 8, and 9).

Total score for MNWS-R (calculated as the sum of the responses for each question) will be used as the analysis variable for MNWS-R questionnaire.

Response for perceived health risk scale will be used as the analysis variable.

Questionnaire answers will be listed by subjects for each questionnaire. Change from baseline will be calculated for each post-baseline time point for the analysis variables. All data will be listed by subject and summarized by time point using descriptive statistics. The descriptive statistics will be presented for both PP and ITT populations.

10.3 Statistical Analysis of Subjective Effects

Paired t-tests will be used to compare subjective effects measures at the Week 2 and 6 time points with the baseline (Week -1) values. This analysis will be conducted on the evaluable subjects in the PP population. If data are unexpectedly found not to be

normally distributed, an appropriate non-parametric test will be performed. Differences will be considered statistically significant at an alpha level of 0.05. The same SAS codes used in Section 7.3 for paired t-test will be used for the analysis.

In addition, a linear mixed model analysis of variance will be used to compare the between product group differences in the absolute change from baseline values of each of the urinary and blood BoEs. The same statistical model and SAS codes used in Section 7.3 for product group comparisons will be used for the analysis.

11. SAFETY

All case report form (CRF) data will be listed by subject and chronologically by assessment time points. This will include rechecks, unscheduled assessments, and early termination.

Applicable continuous variables will be summarized using n, arithmetic mean, SD, minimum, median, and maximum.

The level of precision will be presented as follows: minimum/maximum in the same precision as in the database, mean/median in one more precision level than minimum/maximum, SD in one more precision level than mean/median, and n will be presented as an integer.

Where individual data points are missing because of dropouts or other reasons, the data will be summarized based on reduced denominators.

11.1 Subject Discontinuation

Subjects will be summarized by number of subjects enrolled, completed, and discontinued the study with discontinuation reasons by product group and overall.

11.2 Demographics

Descriptive statistics will be calculated for continuous variables (age, weight, height, and body mass index) by product group and overall. Age will be derived from date of birth to date of informed consent.

Frequency counts will be provided for categorical variables (race, ethnicity, and gender) by product group and overall.

11.3 Tobacco Product Use History

Descriptive statistics will be calculated for number of cigarettes smoked per day and number of years used tobacco product based on the self-reported tobacco product use history by product group and overall.

Frequency counts will be provided for categorical variables (Cigarette brand, brand style, flavor, and size) by product group and overall.

11.4 Adverse Events

All adverse events (AEs) occurring during this clinical trial will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) Version 21.0.

All AEs captured in the database will be listed in by-subject data listings including verbatim term, coded term, product, severity, relationship to study medication, and action; however, only product-use-emergent AEs (PUEAEs) will be summarized.

A PUEAE is defined as an AE that is starting or worsening at the time of or after study product administration. Each PUEAE will be attributed to a product based on the onset date and time of the AE. If an AE increases in severity, that AE will be given a resolution date and time and a new record will be initiated with the new severity. If the severity of an AE remains the same or decreases, the AE will be kept open through to resolution.

If the onset time of an AE is missing and the onset date is the same as the product administration date, then the AE will be considered product use emergent in the prior product. If onset time of an AE is missing and the onset date does not fall on an administration date, then the AE will be considered product use emergent for the last product administered. If the onset date of an AE is missing, then the AE will be considered product use emergent and attributed to the product on the study.

PUEAEs will be tabulated by System Organ Class (SOC) and Preferred Term. Summary tables will include number of subjects reporting the AE and as percent of number of subjects used study product. The number of AEs will be tabulated in a similar manner. Tables which tabulate the number of TEAEs by severity and relationship to study product will also be included.

Serious adverse events (SAEs), if present, will also be listed. Applicable narratives will be included in the CSR.

11.5 Clinical Laboratory Tests (Serum Chemistry, Hematology, Urinalysis)

Clinical laboratory tests will be performed at Screening and end-of-study.

Clinical laboratory test results will be summarized overall by time point and listed by subject.

Out-of-range values and corresponding recheck results will be listed.

11.6 Vital Signs

Vital signs (respiratory rate, pulse rate, blood pressure, and oral temperature) will be measured in the sitting position at Screening, at each study visit (weeks -1, 2, 4) and at the end-of-study (Week 6).

Vital signs will be listed by subject and time point of collection and be summarized by product group and time point.

11.7 Electrocardiogram

Electrocardiogram will be performed at Screening and listed by subject.

11.8 Concomitant Medications

All concomitant medications recorded during the study will be coded with the WHO Dictionary Version 01SEP2018 and listed.

11.9 Physical Examination

Physical examinations will be performed at Screening. Symptom-driven physical examination may performed at Week -1, end-of-study (Week 6) and follow-up. All data found in the CRF will be listed. Changes in physical examinations (if any) will be described in the text of the final report.

12. SUMMARY OF CHANGES FROM PROTOCOL-PLANNED ANALYSIS

The analyses described in this SAP are aligned with those analyses described in the protocol.

13. SUMMARY TABLES AND FIGURES

Summary tables and figures are numbered following the International Conference on Harmonization (ICH) structure but may be renumbered as appropriate during the compilation of the tables and figures for the CSR. Note that all summary tables and figures will be generated using SAS® Version 9.3.

13.1 In-text Summary Tables and Figures

The following is a list of table and figure titles that will be included in the text of the CSR. Tables and figures will be numbered appropriately during compilation of the CSR.

Section 10:

Table 10-1 Subject Disposition Summary (Safety and PP population)

Section 11:

Figure 11-15 Arithmetic Mean Baseline-Adjusted Plasma Nicotine Concentration-Time Profiles Following Following Use of UB (Week -1) and VLN Cigarettes (Weeks 2 and 6) (Pharmacokinetic Population from PP)

Section 12:

Table 12-1 Adverse Event Frequency - Number of Subjects Reporting the Event (% of Subjects Used Product) (Safety Population)

13.2 Section 14 Summary Tables and Figures

The following is a list of table and figure titles that will be included in Section 14 of the report. Table and figure titles may be renumbered as appropriate during the compilation of the report.

14.1 Demographic Data Summary Tables

Table 14.1.1 Summary of Disposition (Safety and PP Populations)

Table 14.1.2 Demographic Summary (Safety and PP Populations)

Table 14.1.3 Tobacco/Nicotine Product Use History Summary (Safety and PP Populations)

14.2 Pharmacokinetic and Pharmacodynamic Data Summary Tables and Figures

14.2.1 Product Use Tables

Table 14.2.1.1.1.1 Summary of Number of Cigarettes Smoked per Week by Study Product Group and Study Week (PP Population)

Table 14.2.1.1.1.2 Summary of Number of Cigarettes Smoked per Week by Study Product Group and Study Week (ITT Population)

Table 14.2.1.1.2 Statistical Comparison of Number of Cigarettes Smoked per Week at Weeks 2 and 6 Versus Week -1 by Study Product Group (PP Population)

Table 14.2.1.1.3 Statistical Comparison of Number of Cigarettes Smoked per Week Among Study Product Groups at Weeks 2 and 6 (PP Population)

Table 14.2.1.2.1.1 Summary of Number of Cigarette Butts Collected per Week by Study Product Group and Study Week (PP Population)

Table 14.2.1.2.1.2 Summary of Number of Cigarette Butts Collected per Week by Study Product Group and Study Week (ITT Population)

Table 14.2.1.2.2 Statistical Comparison of Number of Cigarette Butts Collected per Week at Weeks 2 and 6 Versus Week -1 by Study Product Group (PP Population)

14.2.2 Product Use Figures

14.2.3 Puff Topography Parameter Tables

14.2.4 Puff Topography Parameter Figures

14.2.5 Biomarker Tables

Urine NNAL

Urine NNN

Urine 3-HPMA

Urine S-PMA

Urine 1-OHP

Urine Tneq

Blood COHb

14.2.6 Biomarker Figures

14.2.7 Plasma Nicotine Tables

Concentrations

Pharmacokinetics

14.2.8 Plasma Nicotine Figures

Figure 14.2.8.1	Mean (SD) Unadjusted Plasma Nicotine Concentration Versus Time Profiles Following Use of UB (Week -1) and VLN Cigarettes (Weeks 2 and 6) (Linear Scale) (Pharmacokinetic Population from PP)
Figure 14.2.8.2	Mean Unadjusted Plasma Nicotine Concentration Versus Time Profiles Following Use of UB (Week -1) and VLN Cigarettes (Weeks 2 and 6) (Linear Scale) (Pharmacokinetic Population from PP)
Figure 14.2.8.3	Mean Unadjusted Plasma Nicotine Concentration Versus Time Profiles Following Use of UB (Week -1) and VLN Cigarettes (Weeks 2 and 6) (Semi-Log Scale) (Pharmacokinetic Population from PP)
Figure 14.2.8.4	Mean (SD) Baseline Adjusted Plasma Nicotine Concentration Versus Time Profiles Following Use of UB (Week -1) and VLN Cigarettes (Weeks 2 and 6) (Linear Scale) (Pharmacokinetic Population from PP)
Figure 14.2.8.5	Mean Baseline Adjusted Plasma Nicotine Concentration Versus Time Profiles Following Use of UB (Week -1) and VLN Cigarettes (Weeks 2 and 6) (Linear Scale) (Pharmacokinetic Population from PP)
Figure 14.2.8.6	Mean Baseline Adjusted Plasma Nicotine Concentration Versus Time Profiles Following Use of UB (Week -1) and VLN Cigarettes (Weeks 2 and 6) (Semi-Log Scale) (Pharmacokinetic Population from PP)

Programmer's note: each figure will have 6 profiles: UB Non-Mentholated (Week -1), VLN Non-Mentholated (Week 2), VLN Non-Mentholated (Week 6), UB Mentholated (Week -1), VLN Mentholated (Week 2), and VLN Mentholated (Week 6).

14.2.9 Subjective Effect Tables

FTCD

Table 14.2.9.1.1.1	Summary of FTCD Score by Study Product Group and Study Week (PP Population)
Table 14.2.9.1.1.2	Summary of FTCD Score by Study Product Group and Study Week (ITT Population)
Table 14.2.9.1.2	Statistical Comparison of FTCD Score at Weeks 2 and 6 Versus Week -1 by Study Product Group (PP Population)
Table 14.2.9.1.3	Statistical Comparison of FTCD Score Among Study Product Groups at Weeks 2 and 6 (PP Population)

QSU-Brief

14.3 Safety Data Summary Tables

14.3.1 Displays of Adverse Events

14.3.2 Listings of Deaths, other Serious and Significant Adverse Events

14.3.3 Narratives of Deaths, other Serious and Certain other Significant Adverse Events

14.3.4 Abnormal Laboratory Value Listing (each subject)

14.3.5 Displays of Other Laboratory, Vital Signs, Electrocardiogram, Physical Examination, and Other Safety Data

Table 14.3.5.2 Clinical Laboratory Summary – hematology (Safety Population)
Table 14.3.5.3 Clinical Laboratory Summary – Urinalysis (Safety Population)
Table 14.3.5.4 Vital Sign Summary (Safety Population)

13.3 Section 16 Data Listings

Note: Hepatitis and HIV results that are provided by the clinical laboratory will not be presented in subject CRF or data listings and will not be included in any database transfer.

Data listings are numbered following the ICH structure but may be renumbered as appropriate during the compilation of the TFLs for the CSR. The following is a list of appendix numbers and titles that will be included as data listings:

16.1 Study Information

Appendix 16.1.9 Statistical Methods

Appendix 16.1.10.1 Clinical Laboratory Reference Ranges

16.2 Subject Data Listings

16.2.1 Subject Discontinuation

Appendix 16.2.1.1 Subject Discontinuation (Safety Population)

Appendix 16.2.1.2 Subject Discontinuation (Screen Failure)

16.2.2 Protocol Deviations

Appendix 16.2.2 Protocol Deviations

16.2.3 Subjects Excluded from Pharmacokinetic, Biomarker, Product Use, or Subjective Effect Analysis

Appendix 16.2.3.1 Subjects Excluded from Product Use Analysis
Appendix 16.2.3.2 Subjects Excluded from Puff Topography Analysis
Appendix 16.2.3.3 Subjects Excluded from Biomarker Analysis
Appendix 16.2.3.4 Subjects Excluded from Pharmacokinetic Analysis
Appendix 16.2.3.5 Subjects Excluded from Subjective Effect Analysis

Note: Appendices 16.2.2 and 16.2.3.1 through 16.2.3.3 are generated in MS Word for inclusion in the study report.

16.2.4 Demographic Data

Appendix 16.2.4.1 Demographics (Safety Population)

Appendix 16.2.4.2 Physical Examination (Safety Population)
Appendix 16.2.4.3 Medical History (Safety Population)
Appendix 16.2.4.4 Tobacco/Nicotine Product Use History (Safety Population)

16.2.5 Compliance and/or Concentration Data

Appendix 16.2.5.1 Inclusion / Exclusion Criteria Not Met (Safety Population)
Appendix 16.2.5.2.1 VLN Product Trial (Safety Population)
Appendix 16.2.5.2.2.1 Product Dispensed (Safety Population)
Appendix 16.2.5.2.2.2.1 Product Returned (I of II) (Safety Population)
Appendix 16.2.5.2.2.2.2 Product Returned (I of II) (Safety Population)
Appendix 16.2.5.2.2.3 Puff Topography (Safety Population)
Appendix 16.2.5.3.1 Plasma/Blood Sampling (Safety Population)
Appendix 16.2.5.3.2 24-Hour Urine Collection (Safety Population)
Appendix 16.2.5.4 Prior and Concomitant Medications (Safety Population)

16.2.6 Individual Pharmacokinetic/Pharmacodynamic/Product Use Response Data

Appendix 16.2.6.1 Number of Cigarettes Smoked and Number of Cigarette Butts Collected per Week (Safety Population)
Appendix 16.2.6.2 Puff Topography Parameters (Safety Population)
Appendix 16.2.6.3 Urinary Total NNAL (Safety Population)
Appendix 16.2.6.4 Urinary Total NNN (Safety Population)
Appendix 16.2.6.5 Urinary 3-HPMA (Safety Population)
Appendix 16.2.6.6 Urinary S-PMA (Safety Population)
Appendix 16.2.6.7 Urinary 1-OHP (Safety Population)
Appendix 16.2.6.8.1.1 Urinary Nicotine and Metabolites (I of II) (Safety Population)
Appendix 16.2.6.8.1.2 Urinary Nicotine and Metabolites (II of II) (Safety Population)
Appendix 16.2.6.8.2 Urinary Tneq (Safety Population)
Appendix 16.2.6.9 Blood COHb (Safety Population)
Appendix 16.2.6.10 Plasma Cotinine (Safety Population)
Appendix 16.2.6.11.1 Unadjusted Plasma Nicotine Concentrations Versus Time (Linear and Semi-Log Scale) for Subject <#>
Appendix 16.2.6.11.2 Baseline Adjusted Plasma Nicotine Concentrations Versus Time (Linear and Semi-Log Scale) for Subject <#>
Appendix 16.2.6.12 FTCD Response and Score (Safety Population)
Appendix 16.2.6.13 QSU-Brief Response and Factor Score (Safety Population)
Appendix 16.2.6.14 MNWS-R Response and Total Score (Safety Population)
Appendix 16.2.6.15 Perceived Health Risk Scale (Safety Population)

16.2.7 Adverse Events Listings

Appendix 16.2.7.1 Adverse Events (Safety Population)

16.2.8 Listings of Individual Laboratory Measurements and Other Safety Observations

Appendix 16.2.8.1.1 Clinical Laboratory Report - Serum Chemistry (Safety Population)
Appendix 16.2.8.1.2 Clinical Laboratory Report - Hematology (Safety Population)
Appendix 16.2.8.1.3 Clinical Laboratory Report - Urinalysis (Safety Population)
Appendix 16.2.8.1.4 Clinical Laboratory Report – Comments (Safety Population)
Appendix 16.2.8.1.5 Urine Drug Screens (Safety Population)
Appendix 16.2.8.1.6 Pregnancy Tests (Safety Population)
Appendix 16.2.8.1.7 Serum FSH (Safety Population)
Appendix 16.2.8.1.8 Urine Cotinine Screens (Safety Population)
Appendix 16.2.8.1.9 Serology Sample Collection (Safety Population)
Appendix 16.2.8.1.10 Exhaled CO Measurement (Safety Population)
Appendix 16.2.8.2 Vital Signs (Safety Population)
Appendix 16.2.8.3 12-Lead Electrocardiogram (Safety Population)
Appendix 16.2.8.4 Phone Call (Safety Population)

14. TABLE AND FIGURE SHELLS

The following table shells provide a framework for the display of data from this study. The shells may change due to unforeseen circumstances. These shells may not be reflective of every aspect of this study, but are intended to show the general layout of the tables that will be presented and included in the final report. Unless otherwise noted, all tables will be presented in Times New Roman font size 8. These tables will be generated using Celerion ADaM Version 1.0.

14.1 In-text Summary Tables Shells

In-text Table 10-1 will be in the following format:

Table 10-1 Disposition Summary

Population	Disposition	VLN Non-Mentholated	VLN Mentholated	UB Non-Mentholated	UB Mentholated	Overall
Safety	Enrolled	X (100%)	X (100%)	X (100%)	X (100%)	X (100%)
	Completed	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
	Discontinued Early	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
	Reason for Discontinuation	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
ITT	Enrolled	X (100%)	X (100%)	X (100%)	X (100%)	X (100%)
	Completed	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
	Discontinued Early	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
	Reason for Discontinuation	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
PP	Enrolled	X (100%)	X (100%)	X (100%)	X (100%)	X (100%)
	Completed	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
	Discontinued Early	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
	Reason for Discontinuation	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)

VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Source: Table 14.1.1
Program: /CAXXXXX/sas_prg/stsas/intexttest/t_disp.sas DDMMMYYYY HH:MM

In-text Table 11-1 will be in the following format:

Table 11-1 Demographic and Smoking History Summary

Population	Trait	Category/Statistics	VLN Non-Mentholated	VLN Mentholated	UB Non-Mentholated	UN Mentholated	Overall
Safety	Gender	Male	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)
		Female	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)
	Race	Asian	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)
		Black or African American	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)
		White	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)
	Ethnicity	Not Hispanic or Latino	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)
		Hispanic or Latino	X(XX%)	X(XX%)	X(XX%)	X(XX%)	X(XX%)
	Age (yrs)	n	X	X	X	X	X
		Mean	XX.X	XX.X	XX.X	XX.X	XX.X
		SD	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
		Minimum	XX	XX	XX	XX	XX
		Median	XX.X	XX.X	XX.X	XX.X	XX.X
		Maximum	XX	XX	XX	XX	XX
	BMI (kg/m²)	n	X	X	X	X	X
		Mean	XX.XXX	XX.XXX	XX.XXX	XX.XXX	XX.XXX
		SD	X.XXXX	X.XXXX	X.XXXX	X.XXXX	X.XXXX
		Minimum	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
		Median	XX.XXX	XX.XXX	XX.XXX	XX.XXX	XX.XXX
		Maximum	XX.X	XX.X	XX.X	XX.X	XX.X
	CPD	n	X	X	X	X	X
		Mean	XX.X	XX.X	XX.X	XX.X	XX.X
		SD	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
		Minimum	XX	XX	XX	XX	XX
		Median	XX.X	XX.X	XX.X	XX.X	XX.X
		Maximum	XX	XX	XX	XX	XX
	Duration (Years)	n	X	X	X	X	X
		Mean	XX.X	XX.X	XX.X	XX.X	XX.X
		SD	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
		Minimum	XX	XX	XX	XX	XX
		Median	XX.X	XX.X	XX.X	XX.X	XX.X

Population	Trait	Category/Statistics	VLN Non-Mentholated	VLN Mentholated	UB Non-Mentholated	UN Mentholated	Overall
		Maximum	XX	XX	XX	XX	XX

BMI = Body mass index, CPD = Cigarettes per day
Age is calculated at the date of the informed consent.
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes

Source: Tables 14.1.2 and 14.1.3
Program: /CAXXXXX/sas_prg/stsas/intexttest/t_dem.sas DDMMMYYYY HH:MM

Programmer Note: ITT and PP population will also be presented in the table.

In-text Table 11-2 will be in the following format:

Table 11-2 Summary of Number of Cigarettes Smoked per Week by Study Product Group and Study Week (PP Population)

Study Week	Statistics	VLN Non-Mentholated	VLN Mentholated	UB Non-Mentholated	UB Mentholated
Week -1*	n	X	X	X	X
	Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
	Median	XX.X	XX.X	XX.X	XX.X
	Range	XX, XX	XX, XX	XX, XX	XX, XX
Week 1	n	X	X	X	X
	Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
	Median	XX.X	XX.X	XX.X	XX.X
	Range	XX, XX	XX, XX	XX, XX	XX, XX

*Subjects used their own usual brand cigarettes at Week -1.
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Source: Table 14.2.1.1.1.1
Program: /CAXXXXX/sas_prg/stsas/intexttest/t_dem.sas DDMMMYYYY HH:MM

Programmer Note: All study weeks will be presented in the table.

In-text Table 11-3 will be in the following format:

Table 11-3 Statistical Comparison of Number of Cigarettes Smoked per Week at Weeks 2 and 6 Versus Week -1 by Study Product Group (PP Population)

Study Week	Product Group	Means		Difference (Test Week – Baseline)	XX% Confidence Interval	p-value
		Test Week	Baseline			
Week 2	VLN Non- Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
	VLN Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
	VLN Combined	XXX	XXX	XXX	XXX - XXX	X.XXXX
Week 6	VLN Non- Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
	VLN Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
	VLN Combined	XXX	XXX	XXX	XXX - XXX	X.XXXX

Baseline = Week -1
Subjects used their own usual brand cigarettes at Week -1.
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
Paired t-test method is used to perform the analysis.

Source: Table 14.2.1.1.2
Program: /CAXXXXX/sas_prg/stsas/intexttest/t_dem.sas DDMMMYYYY HH:MM

In-text Table 11-4 will be in the following format:

Table 11-4 Summary of Puffing Topography Parameters by Study Product Group and Study Week (PP Population)

Parameter	Study Week	Statistics	VLN Non-Mentholated	VLN Mentholated	VLN Combined	UB Non-Mentholated	UB Non-Mentholated	UB Combined
Puff Duration (unit)	Week -1*	n	X	X	X	X	X	X
		Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
		Median	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
		Range	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX
	Week 2	n	X	X	X	X	X	X
		Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
		Median	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
		Range	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX
	Week 6	n	X	X	X	X	X	X
		Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
		Median	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
		Range	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX

*Subjects used their own usual brand cigarettes at Week -1.
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Source: Table 14.2.3.1.1
Program: /CAXXXXX/sas_prg/stsas/intexttest/t_dem.sas DDMMMYYYY HH:MM

Programmer Note: All topography parameters will be presented in the table.

In-text Table 11-5 will be in the following format:

Table 11-5 Statistical Comparison of Puffing Topography Parameters at Weeks 2 and 6 Versus Week -1 by Study Product Group (PP Population)

Parameter	Study Week	Product Group	Means		Difference (Test Week – Baseline)	XX% Confidence Interval	p-value
			Test Week	Baseline			
Puff Duration (unit)	Week 2	VLN Non- Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
		VLN Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
		VLN Combined	XXX	XXX	XXX	XXX - XXX	X.XXXX
		UB Non-Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
		UB Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
		UB Combined	XXX	XXX	XXX	XXX - XXX	X.XXXX
	Week 6	VLN Non- Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
		VLN Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
		VLN Combined	XXX	XXX	XXX	XXX - XXX	X.XXXX
		UB Non-Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
		UB Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
		UB Combined	XXX	XXX	XXX	XXX - XXX	X.XXXX

Baseline = Week -1
Subjects used their own usual brand cigarettes at Week -1.
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes
Paired t-test method is used to perform the analysis.

Source: Table 14.2.3.2
Program: /CAXXXXX/sas_prg/stsas/intexttest/t_dem.sas DDMMMYYYY HH:MM

Programmer Note: All topography parameters will be presented in the table.

In-text Tables 11-6, 11-8, 11-10, 11-12, 11-14, 11-16, 11-18 will be in the following format:

Table 11-6 Summary of Urinary NNAL Mass Excreted (unit) by Study Product Group and Study Week (PP Population)

Study Week	Statistics	VLN Non-Mentholated	VLN Mentholated	VLN Combined	UB Non-Mentholated	UB Non-Mentholated	UB Combined
Week -1*	n	X	X	X	X	X	X
	Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
	Median	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
	Range	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX
Week 2	n	X	X	X	X	X	X
	Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
	Median	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
	Range	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX
Week 6	n	X	X	X	X	X	X
	Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
	Median	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
	Range	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX

*Subjects used their own usual brand cigarettes at Week -1.
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Source: Table 14.2.5.1.1.1
Program: /CAXXXXX/sas_prg/stsas/intexttest/t_dem.sas DDMMMYYYY HH:MM

In-text Tables 11-7, 11-9, 11-11, 11-13, 11-15, 11-17, 11-19 will be in the following format:

Table 11-7 Statistical Comparison of Urinary NNAL Mass Excreted (unit) at Weeks 2 and 6 Versus Week -1 by Study Product Group (PP Population)

Study Week	Product Group	Means		Difference (Test Week – Baseline)	XX% Confidence Interval	p-value
		Test Week	Baseline			
Week 2	VLN Non- Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
	VLN Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
	VLN Combined	XXX	XXX	XXX	XXX - XXX	X.XXXX
	UB Non-Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
	UB Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
	UB Combined	XXX	XXX	XXX	XXX - XXX	X.XXXX
Week 6	VLN Non- Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
	VLN Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
	VLN Combined	XXX	XXX	XXX	XXX - XXX	X.XXXX
	UB Non-Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
	UB Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
	UB Combined	XXX	XXX	XXX	XXX - XXX	X.XXXX

Baseline = Week -1
Subjects used their own usual brand cigarettes at Week -1.
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes
Paired t-test method is used to perform the analysis.

Source: Table 14.5.1.2
Program: /CAXXXXX/sas_prg/stsas/intexttest/t_dem.sas DDMMMYYYY HH:MM

In-text Table 11-20 will be in the following format:

Table 11-20 Summary of Baseline Adjusted Plasma Nicotine Pharmacokinetic Parameters Prior to and Following Use of VLN Cigarettes (Pharmacokinetic Population)

Study Week	Pharmacokinetic Parameters	Product <Y>	Product <X>
Week -1	Param1 (units)	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
	Param2 (units)	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
	Param3 (units)	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
Week 2	Param1 (units)	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
	Param2 (units)	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
	Param3 (units)	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
Week 6	Param1 (units)	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
	Param2 (units)	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]
	Param3 (units)	XXX.X (XX.X) [n=xx]	XXX.X (XX.X) [n=xx]

*Subjects used their own usual brand cigarettes at Week -1.
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes
AUCs and Cmax values are presented as geometric mean and geometric CV%.
Tmax values are presented as median (min, max).
Source: Tables 14.2.7.5.1, 14.2.7.6.1, 14.2.7.7.1, 14.2.7.8.1, 14.2.7.9.1, and 14.2.7.10.1

Notes for Generating the Actual Table:

The following PK parameters will be presented in the following order and with following units: AUC0-180 (min*ng/mL), Cmax (ng/mL) and Tmax (min)
n will be presented as an integer (with no decimal);
Please remove footnote 'other parameters are presented…' as this is not applicable.
Please add column to indicate study week
Summary statistics will be presented by sex and overall with the same precision as defined in post-text shells
4 products will be presented in Table 11-20: VLN Non-Mentholated, VLN Non-Mentholated, UB Non-Mentholated, and UB Non-Mentholated.

```
Program:  /CAXXXXX/sas_prg/pksas/intext-pk-tables.sas     DDMMMYYYY  HH:MM
Program:  /CAXXXXX/sas_prg/pksas/adam_intext_pkparam.sas      DDMMMYYYY  HH:MM
```

In-text Table 11-21 will be in the following format:

Table 11-21 Statistical Comparison of Baseline Adjusted Plasma Nicotine Pharmacokinetic Parameters at Weeks 2 and 6 Versus Week -1 (Pharmacokinetic Population from PP)

Parameter	Study Week	Product Group	LSMeans		GMR (Test Week / Baseline)	XX% Confidence Interval	p-value
			Test Week	Baseline			
AUC0-180	Week 2	VLN Non- Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
		VLN Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
		VLN Combined	XXX	XXX	XXX	XXX - XXX	X.XXXX
		UB Non-Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
		UB Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
		UB Combined	XXX	XXX	XXX	XXX - XXX	X.XXXX
	Week 6	VLN Non- Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
		VLN Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
		VLN Combined	XXX	XXX	XXX	XXX - XXX	X.XXXX
		UB Non-Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
		UB Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
		UB Combined	XXX	XXX	XXX	XXX - XXX	X.XXXX

Baseline = Week -1
Subjects used their own usual brand cigarettes at Week -1.
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes
Analysis is based on the log-transformed data.
Paired t-test method is used to perform the analysis.

Source: Table 14.2.7.11
Program: /CAXXXXX/sas_prg/stsas/intexttest/t_dem.sas DDMMMYYYY HH:MM

Programmer Note: Cmax will also be presented in the table.

In-text Tables 11-22, 11-26, and 11-28 will be in the following format:

Table 11-22 Summary of FTCD Score by Study Product Group and Study Week (PP Population)

Study Week	Statistics	VLN Non-Mentholated	VLN Mentholated	VLN Combined	UB Non-Mentholated	UB Mentholated	UB Combined
Week -1*	n	X	X	X	X	X	X
	Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
	Median	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
	Range	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX
Week 2	n	X	X	X	X	X	X
	Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
	Median	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
	Range	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX
Week 6	n	X	X	X	X	X	X
	Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
	Median	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
	Range	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX

*Subjects used their own usual brand cigarettes at Week -1.
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Source: Table 14.2.9.1.1
Program: /CAXXXXX/sas_prg/stsas/intexttest/t_dem.sas DDMMMYYYY HH:MM

In-text Tables 11-23, 11-27, and 11-29 will be in the following format:

Table 11-23 Statistical Comparison of FTCD Score at Weeks 2 and 6 Versus Week -1 by Study Product Group (PP Population)

Study Week	Product Group	Means		Difference (Test Week – Baseline)	XX% Confidence Interval	p-value
		Test Week	Baseline			
Week 2	VLN Non- Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
	VLN Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
	VLN Combined	XXX	XXX	XXX	XXX - XXX	X.XXXX
	UB Non-Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
	UB Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
	UB Combined	XXX	XXX	XXX	XXX - XXX	X.XXXX
Week 6	VLN Non- Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
	VLN Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
	VLN Combined	XXX	XXX	XXX	XXX - XXX	X.XXXX
	UB Non-Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
	UB Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
	UB Combined	XXX	XXX	XXX	XXX - XXX	X.XXXX

Baseline = Week -1
Subjects used their own usual brand cigarettes at Week -1.
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes
Paired t-test method is used to perform the analysis.

Source: Table 14.9.1.2
Program: /CAXXXXX/sas_prg/stsas/intexttest/t_dem.sas DDMMMYYYY HH:MM

In-text Table 11-24 will be in the following format:

Table 11-24 Summary of QSU-brief Factor Score by Study Product Group and Study Week (PP Population)

Factor	Study Week	Statistics	VLN Non-Mentholated	VLN Mentholated	VLN Combined	UB Non-Mentholated	UB Mentholated	UB Combined
Factor 1	Week -1*	n	X	X	X	X	X	X
		Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
		Median	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
		Range	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX
	Week 2	n	X	X	X	X	X	X
		Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
		Median	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
		Range	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX
	Week 6	n	X	X	X	X	X	X
		Mean (SD)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)	XX.X (XX.XX)
		Median	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
		Range	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX	XX, XX

*Subjects used their own usual brand cigarettes at Week -1.
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Source: Table 14.2.9.2.1
Program: /CAXXXXX/sas_prg/stsas/intexttest/t_dem.sas DDMMMYYYY HH:MM

Programmer Note: Factor 2 will also be presented in the table.

In-text Table 11-25 will be in the following format:

Table 11-25 Statistical Comparison of QSU-brief Factor Score at Weeks 2 and 6 Versus Week -1 by Study Product Group (PP Population)

Factor	Study Week	Product Group	Means		Difference (Test Week – Baseline)	XX% Confidence Interval	p-value
			Test Week	Baseline			
Factor 1	Week 2	VLN Non- Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
		VLN Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
		VLN Combined	XXX	XXX	XXX	XXX - XXX	X.XXXX
		UB Non-Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
		UB Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
		UB Combined	XXX	XXX	XXX	XXX - XXX	X.XXXX
	Week 6	VLN Non- Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
		VLN Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
		VLN Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
		UB Non-Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
		UB Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX
		UB Mentholated	XXX	XXX	XXX	XXX - XXX	X.XXXX

Baseline = Week -1
*Subjects used their own usual brand cigarettes at Week -1.
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes
Paired t-test method is used to perform the analysis.

Source: Table 14.2.9.2.2
Program: /CAXXXXX/sas_prg/stsas/intexttest/t_dem.sas DDMMMYYYY HH:MM

Programmer Note: Factor 2 will also be presented in the table.

In-text Table 12-1 will be in the following format:

Table 12-1 Adverse Event Frequency - Number of Subjects Reporting the Event (% of Subjects Used Product)

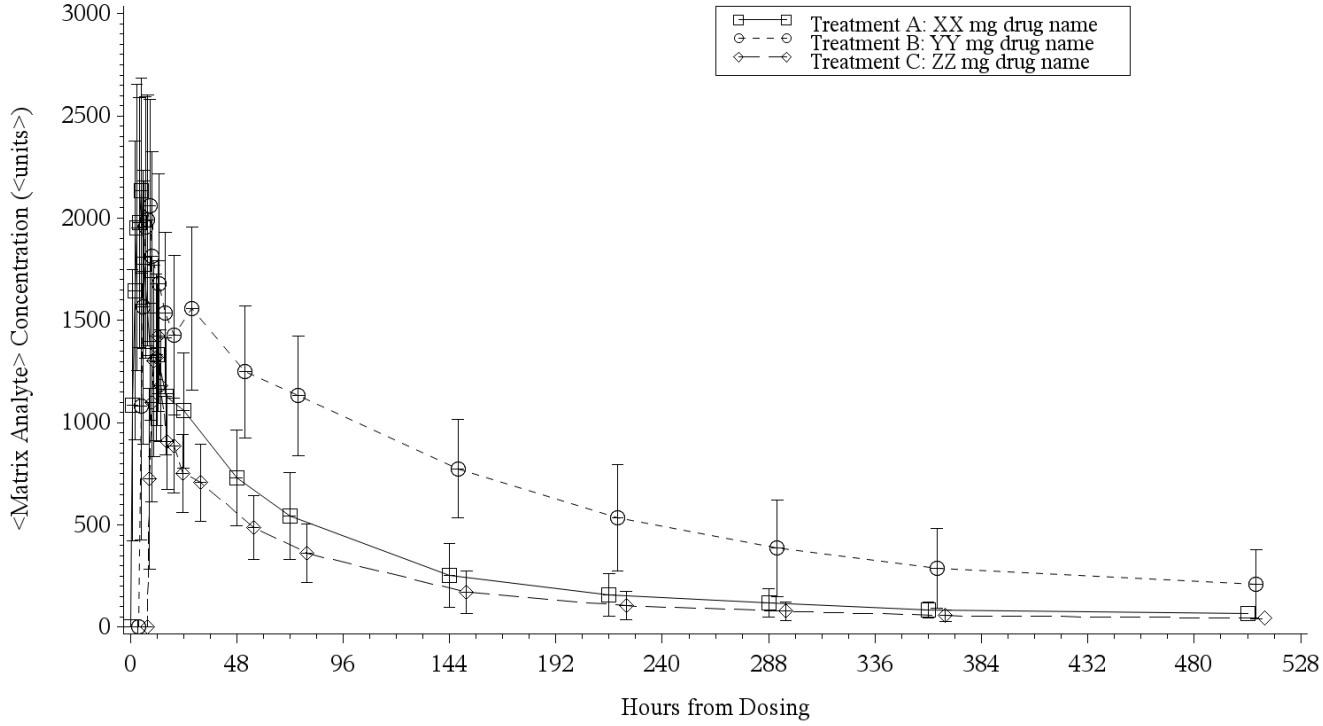
Adverse Events*	Baseline	VLN Non-Mentholated	VLN Mentholated	UB Non-Mentholated	UB Mentholated	Overall#
Number of Subjects Used Study Product	XX (100%)	XX (100%)	XX (100%)	XX (100%)	XX (100%)	XX (100%)
Number of Subjects With Adverse Events	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
General disorders and administration site conditions	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Vessel puncture site pain	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Vessel puncture site reaction	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)

*Adverse events are classified according to MedDRA® Version 21.0
Subjects used their own usual brand cigarettes at Week -1.
Although a subject may have had 2 or more clinical adverse experiences, the subject is counted only once within a category. The same subject may appear in different categories.
Overall includes AEs after the start of Week1 product use.

Source: Table 14.3.1.1
Program: /CAXXXXX/sas_prg/stsas/intexttest/t_ae.sas DDMMMYYYY HH:MM

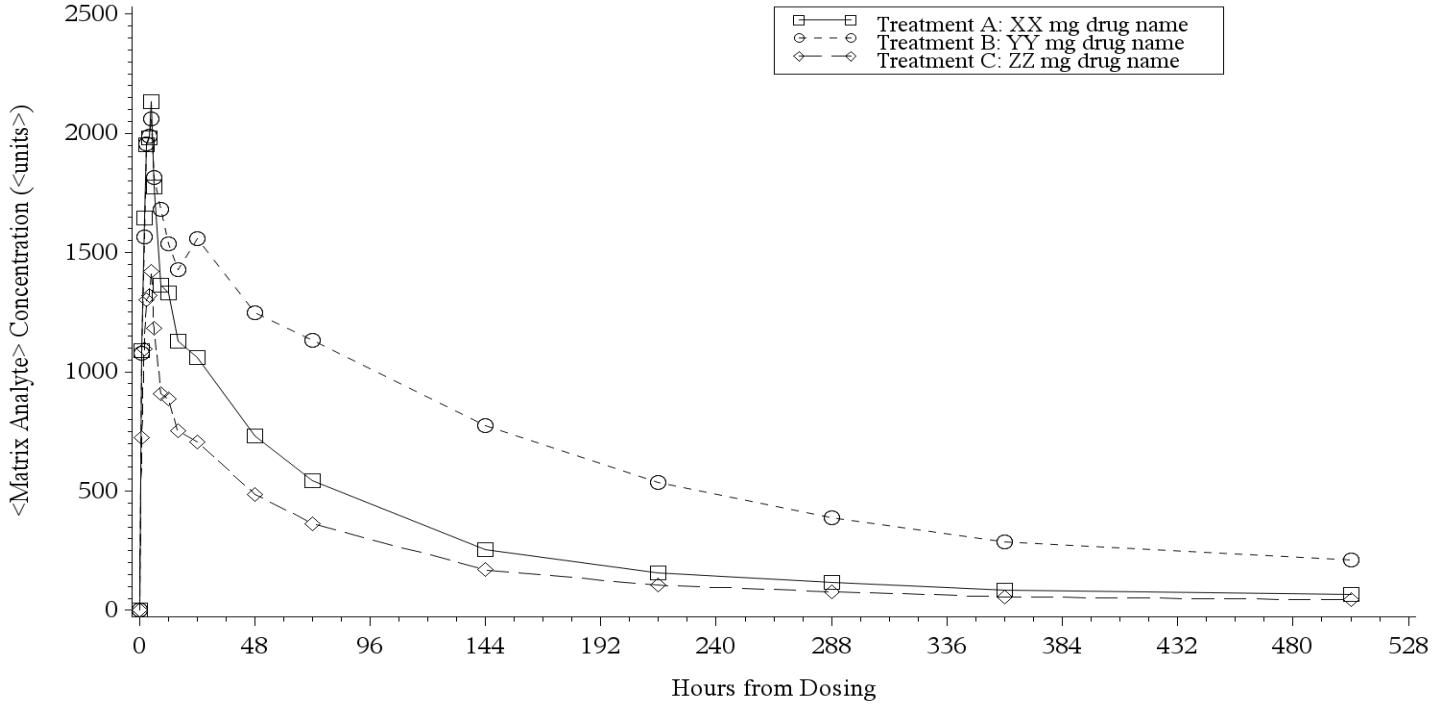
14.2 Figures Shells

Figures 14.2.2.1.1, 14.2.2.2.1, 14.2.6.1.1, 14.2.6.2.1, 14.2.6.3.1, 14.2.6.4.1, 14.2.6.5.1, 14.2.6.6.1, 14.2.6.7.1, 14.2.8.1, 14.2.8.4, 14.2.10.1.1, 14.2.10.2.1.1, 14.2.10.2.2.1, 14.2.10.3.1, and 14.2.10.4.1 will be in the following format:



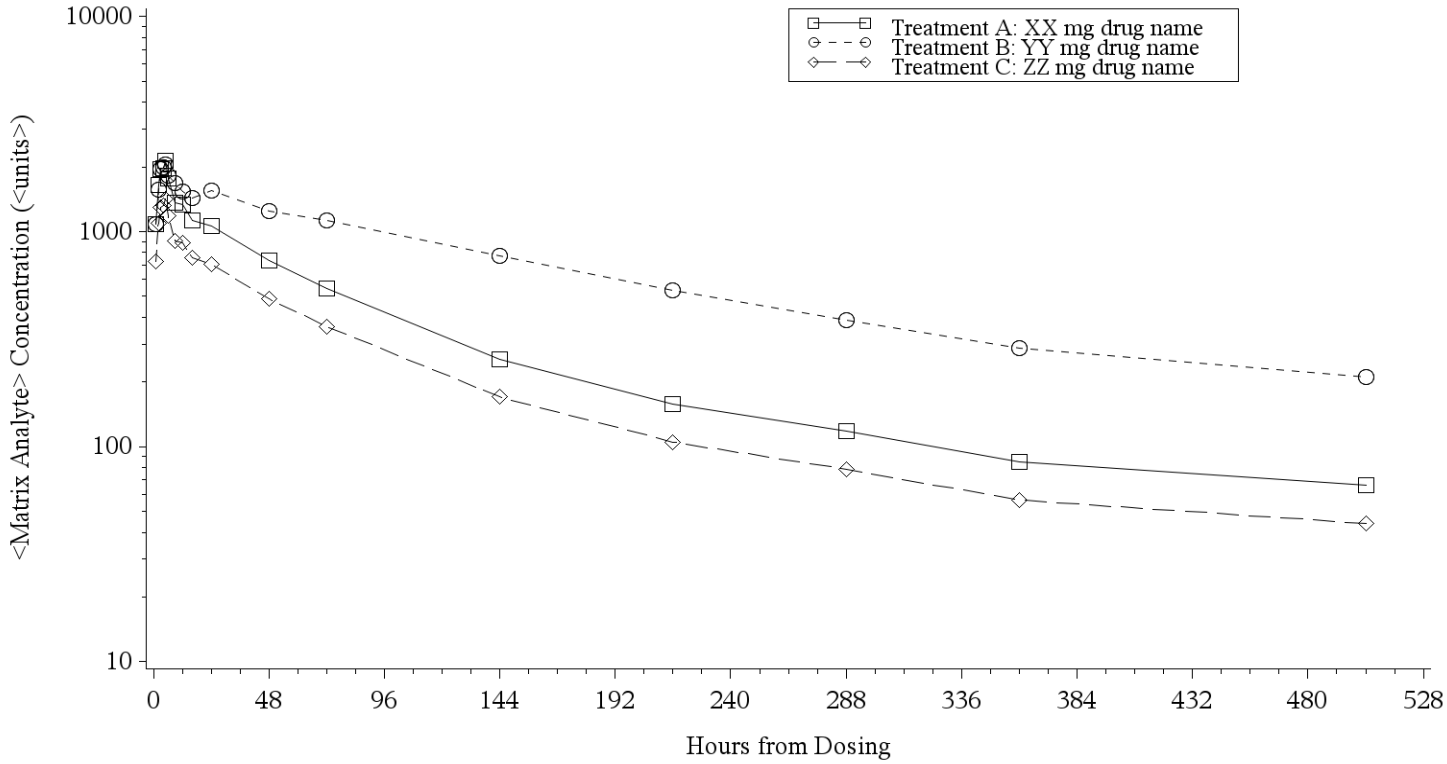
Programmer's note: in the legend and footnotes, "Treatment" will be referred to as "Product" with the appropriate descriptions. The x-axis will be labeled "Time (Minutes)".

In-text Figures 11-1 through and 11-15 and post-text Figures 14.2.8.2, 14.2.8.5,14.2.2.1.2, 14.2.2.2.2, 14.2.4.1 through 14.2.4.5, 14.2.6.1.2, 14.2.6.2.2, 14.2.6.3.2, 14.2.6.4.2, 14.2.6.5.2, 14.2.6.6.2, 14.2.6.7.2, 14.2.10.1.2, 14.2.10.2.1.2, 14.2.10.2.2.2, 14.2.10.3.2, and 14.2.10.4.2will be presented in the following format:



Programmer's note: in the legend and footnotes, "Treatment" will be referred to as "Product" with the appropriate descriptions. The x-axis will be labeled "Time (Minutes)".

Figures 14.2.8.3 and 14.2.8.6 will be presented in the following format:



Programmer's note: in the legend and footnotes, "Treatment" will be referred to as "Product" with the appropriate descriptions. The x-axis will be labeled "Time (Minutes)".

14.3 Section 14 Summary Tables Shells

Post-text Table 14.1.1 will be in the following format:

Part 1 of X

Table 14.1.1 Summary of Disposition (Safety and PP Populations)

		Study Product Group				
Population	Category	VLN Non-Mentholated	VLN Mentholated	UB Non-Mentholated	UB Mentholated	Overall
Safety	Enrolled	XX(100%)	XX(100%)	XX(100%)	XX(100%)	XX(100%)
	Completed	XX(XX%)	XX(XX%)	XX(XX%)	XX(XX%)	XX(XX%)
	Discontinued Early	X(X%)	X(X%)	X(X%)	X(X%)	X(X%)
	<Reason1>	X(X%)	X(X%)	X(X%)	X(X%)	X(X%)
	<Reason2>	X(X%)	X(X%)	X(X%)	X(X%)	X(X%)
mITT	Enrolled	XX(100%)	XX(100%)	XX(100%)	XX(100%)	XX(100%)
	Completed	XX(XX%)	XX(XX%)	XX(XX%)	XX(XX%)	XX(XX%)
	Discontinued Early	X(X%)	X(X%)	X(X%)	X(X%)	X(X%)
	<Reason1>	X(X%)	X(X%)	X(X%)	X(X%)	X(X%)
	<Reason2>	X(X%)	X(X%)	X(X%)	X(X%)	X(X%)
PP	Enrolled	XX(100%)	XX(100%)	XX(100%)	XX(100%)	XX(100%)
	Completed	XX(XX%)	XX(XX%)	XX(XX%)	XX(XX%)	XX(XX%)
	Discontinued Early	X(X%)	X(X%)	X(X%)	X(X%)	X(X%)
	<Reason1>	X(X%)	X(X%)	X(X%)	X(X%)	X(X%)
	<Reason2>	X(X%)	X(X%)	X(X%)	X(X%)	X(X%)

Note: VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /XAXXXXX/ECR/sas_prg/stsas/tab prog_name.sas DDMMMYYYY HH:MM

Post-text Table 14.1.2 will be in the following format:

Table 14.1.2 Demographic Summary (Safety and PP Populations)

			Study Product Group				
Population	Trait		VLN Non-Mentholated	VLN Mentholated	UB Non-Mentholated	UB Mentholated	Overall
Safety	Gender	Male	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
		Female	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
	Race	American Indian	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
		Asian	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
		Black	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
	Age* (yrs)	n	X	X	X	X	X
		Mean	X.X	X.X	X.X	X.X	X.X
		SD	X.XX	X.XX	X.XX	X.XX	X.XX
		Minimum	XX	XX	XX	XX	XX
		Median	X.X	X.X	X.X	X.X	X.X
		Maximum	XX	XX	XX	XX	XX
	Weight (kg)	n	X	X	X	X	X
		Mean	X.X	X.X	X.X	X.X	X.X
		SD	X.XX	X.XX	X.XX	X.XX	X.XX
		Minimum	XX	XX	XX	XX	XX
		Median	X.X	X.X	X.X	X.X	X.X
		Maximum	XX	XX	XX	XX	XX
	Height (cm)	n	X	X	X	X	X
		Mean	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
		SD	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX
		Minimum	XX.X	XX.X	XX.X	XX.X	XX.X
		Median	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
		Maximum	XX.X	XX.X	XX.X	XX.X	XX.X

Note: * Age is derived from birth date to date of informed consent.
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes

```
      UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
      UB mentholated = Subjects' UB mentholated filtered cigarettes

Program:  /CAXXXXX/ECR/sas_prg/stsas/tab programname.sas  DDMMMYYYY  HH:MM
```

Programmer Note: Summary for ITT and PP population will also be presented in the table.

Post-text Table 14.1.3 will be in the following format:

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Table 14.1.3 Tobacco/Nicotine Product Use History Summary (Safety and PP Populations)

			Study Product Group				
Population	Trait		VLN Non-Mentholated	UB Non-Mentholated	VLN Mentholated	UB Mentholated	Overall
Safety	Brand	XXXXX	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
		XXXXXX	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
	Brand Style	XXXXX	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
		XXXXXX	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
	Flavor	XXXXX	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
	Size	XXXXX	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
		XXXXX	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
	Duration (yrs)	n	X	X	X	X	X
		Mean	X.X	X.X	X.X	X.X	X.X
		SD	X.XX	X.XX	X.XX	X.XX	X.XX
		Minimum	XX	XX	XX	XX	XX
		Median	X.X	X.X	X.X	X.X	X.X
		Maximum	XX	XX	XX	XX	XX
	CPD	n	X	X	X	X	X
		Mean	X.X	X.X	X.X	X.X	X.X
		SD	X.XX	X.XX	X.XX	X.XX	X.XX
		Minimum	XX	XX	XX	XX	XX
		Median	X.X	X.X	X.X	X.X	X.X
		Maximum	XX	XX	XX	XX	XX

Note: CPD = Cigarettes per day
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes
Program: /CAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM

Programmer Note: Summary for ITT and PP population will also be presented in the table.

Post-text Tables 14.2.1.1.1.1-2 and 14.2.1.2.1.1-2 will be in the following format:

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Table 14.2.1.1.1.1 Summary of Number of Cigarettes Smoked per Week by Study Product Group and Study Week (PP Population)

Study Week	Statistics	Study Product Group: VLN Non-Mentholated	VLN Mentholated	VLN Combined	UB Non-Mentholated	UB Mentholated	UB Combined
Week -1*	n	X	X	X	X	X	X
	Mean	X.X	X.X	X.X	X.X	X.X	X.X
	SD	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
	CV%	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
	SEM	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
	Minimum	XX	XX	XX	XX	XX	XX
	Median	X.X	X.X	X.X	X.X	X.X	X.X
	Maximum	XX	XX	XX	XX	XX	XX
Week 1	n	X	X	X	X	X	X
	Mean	X.X	X.X	X.X	X.X	X.X	X.X
	SD	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
	CV%	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
	SEM	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
	Minimum	XX	XX	XX	XX	XX	XX
	Median	X.X	X.X	X.X	X.X	X.X	X.X
	Maximum	XX	XX	XX	XX	XX	XX

Note: *Subjects used their own usual brand cigarettes at Week -1.
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM

Programmer Note: All study weeks will be presented in the table.

Post-text Tables 14.2.1.1.2 and 14.2.1.2.2 will be in the following format:

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Table 14.2.1.1.2 Statistical Comparison of Number of Cigarettes Smoked per Week at Weeks 2 and 6 Versus Week -1 by Study Product Group (PP Population)

Study Week	Product Group	Means		Difference	XX%	p-value
		Test Week	Baseline	(Test Week – Baseline)	Confidence Interval	
Week 2	VLN Non-Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
	VLN Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
	VLN Combined	XXX	XXX	XXX	XXX – XXX	X.XXXX
	UB Non-Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
	UB Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
	UB Combined	XXX	XXX	XXX	XXX – XXX	X.XXXX
Week 6	VLN Non-Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
	VLN Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
	VLN Combined	XXX	XXX	XXX	XXX – XXX	X.XXXX
	UB Non-Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
	UB Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
	UB Combined	XXX	XXX	XXX	XXX – XXX	X.XXXX

Note: Baseline = Week -1
Subjects used their own usual brand cigarettes at Week -1.
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes
Paired t-test method is used to perform the analysis.

Program: /CAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM

Post-text Tables 14.2.1.1.3 and 14.2.1.2.3 will be in the following format:

Table 14.2.1.1.3 Statistical Comparison of Number of Cigarettes Smoked per Week Among Study Product Groups at Weeks 2 and 6 (PP Population)

Study Week	Comparison	LSMeans Test (n)	LSMeans Reference (n)	LSMean Difference (Test – Reference)	XX% Confidence Interval	p-value
Week 2	VLN Non-mentholated vs UB Non-mentholated	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX
	VLN Mentholated vs UB Mentholated	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX
	VLN Combined vs UB Combined	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX
Week 6	VLN Non-mentholated vs UB Non-mentholated	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX
	VLN Mentholated vs UB Mentholated	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX
	VLN Combined vs UB Combined	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX

Note: LSMeans, LSmean difference, CI and p-values are from the ANOVA.
n = Number of observation used in the analysis

Test = The first product in the comparison
Reference = The second product in the comparison

VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM

Post-text Tables 14.2.3.1.1-2 will be in the following format:

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Table 14.2.3.1.1 Summary of Puff Topography Parameters by Study Product Group and Study Week (PP Population)

			Study Product Group					
Parameter(unit)	Study Week	Statistics	VLN Non-Mentholated	VLN Mentholated	VLN Combined	UB Non-Mentholated	UB Mentholated	UB Combined
Puff Duration (XX)	Week -1*	n	X	X	X	X	X	X
		Mean	X.X	X.X	X.X	X.X	X.X	X.X
		SD	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
		CV%	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
		SEM	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
		Minimum	XX	XX	XX	XX	XX	XX
		Median	X.X	X.X	X.X	X.X	X.X	X.X
		Maximum	XX	XX	XX	XX	XX	XX
	Week 2	n	X	X	X	X	X	X
		Mean	X.X	X.X	X.X	X.X	X.X	X.X
		SD	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
		CV%	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
		SEM	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
		Minimum	XX	XX	XX	XX	XX	XX
		Median	X.X	X.X	X.X	X.X	X.X	X.X
		Maximum	XX	XX	XX	XX	XX	XX

Note: *Subjects used their own usual brand cigarettes at Week -1.
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM

Programmer Note: Study Week 6 and other topography parameters will also be presented in the table.

Post-text Table 14.2.3.2 will be in the following format:

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Table 14.2.3.2 Statistical Comparison of Puff Topography Parameters at Weeks 2 and 6 Versus Week -1 by Study Product Group (PP Population)

Parameter(unit)	Study Week	Product Group	Means: Test Week	Means: Baseline	Difference (Test Week – Baseline)	XX% Confidence Interval	p-value
Puff Duration (XX)	Week 2	VLN Non-Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
		VLN Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
		VLN Combined	XXX	XXX	XXX	XXX – XXX	X.XXXX
		UB Non-Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
		UB Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
		UB Combined	XXX	XXX	XXX	XXX – XXX	X.XXXX
	Week 6	VLN Non-Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
		VLN Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
		VLN Combined	XXX	XXX	XXX	XXX – XXX	X.XXXX
		UB Non-Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
		UB Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
		UB Combined	XXX	XXX	XXX	XXX – XXX	X.XXXX

Note: Baseline = Week -1
Subjects used their own usual brand cigarettes at Week -1.
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes
Paired t-test method is used to perform the analysis.

Program: /CAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM

Programmer Note: Other topography parameters will also be presented in the table.

Post-text Table 14.2.3.3 will be in the following format:

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Table 14.2.3.3 Statistical Comparison of Puff Topography Parameters Among Study Product Groups at Weeks 2 and 6
(PP Population)

Parameter(unit)	Study Week	Comparison	LSMeans Test (n)	LSMeans Reference (n)	LSMean Difference (Test – Reference)	XX% Confidence Interval	p-value
Puff Duration (XX)	Week 2	VLN Non-mentholated vs UB Non-mentholated	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX
		VLN Mentholated vs UB Mentholated	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX
		VLN Combined vs UB Combined	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX
	Week 6	VLN Non-mentholated vs UB Non-mentholated	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX
		VLN Mentholated vs UB Mentholated	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX
		VLN Combined vs UB Combined	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX

Note: LSMeans, LSmean difference, CI and p-values are from the ANOVA.
n = Number of observation used in the analysis

Test = The first product in the comparison
Reference = The second product in the comparison

VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM

Programmer Note: Other topography parameters will also be presented in the table.

Post-text Tables 14.2.5.1.1.1.1-2, 14.2.5.1.1.4.1-2, 14.2.5.2.1.1.1-2, 14.2.5.2.1.4.1-2, 14.2.5.3.1.1.1-2, 14.2.5.3.1.4.1-2, 14.2.5.4.1.1.1-2, 14.2.5.4.1.4.1-2, 14.2.5.5.1.1.1-2, 14.2.5.5.1.4.1-2, 14.2.5.6.1.1.1-2, 14.2.5.6.1.4.1-2, and 14.2.5.7.1.1.1-2 will be in the following format:

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Table 14.2.5.1.1.1.1 Summary of Urinary NNAL Mass Excreted (unit) by Study Product Group and Study Week (PP Population)

Study Week	Statistics	Study Product Group: VLN Non-Mentholated	VLN Mentholated	VLN Combined	UB Non-Mentholated	UB Mentholated	UB Combined
Week -1*	n	X	X	X	X	X	X
	Mean	X.X	X.X	X.X	X.X	X.X	X.X
	SD	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
	CV%	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
	SEM	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
	Minimum	XX	XX	XX	XX	XX	XX
	Median	X.X	X.X	X.X	X.X	X.X	X.X
	Maximum	XX	XX	XX	XX	XX	XX
Week 2	n	X	X	X	X	X	X
	Mean	X.X	X.X	X.X	X.X	X.X	X.X
	SD	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
	CV%	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
	SEM	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
	Minimum	XX	XX	XX	XX	XX	XX
	Median	X.X	X.X	X.X	X.X	X.X	X.X
	Maximum	XX	XX	XX	XX	XX	XX

Note: *Subjects used their own usual brand cigarettes at Week -1.
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM

Programmer Note: Week 6 will also be presented in the table.

Post-text Tables 14.2.5.1.1.2.1-2, 14.2.5.1.1.3.1-2, 14.2.5.1.1.5.1-2, 14.2.5.1.1.6.1-2, 14.2.5.2.1.2.1-2, 14.2.5.2.1.3.1-2, 14.2.5.2.1.5.1-2, 14.2.5.2.1.6.1-2, 14.2.5.3.1.2.1-2, 14.2.5.3.1.3.1-2, 14.2.5.3.1.5.1-2, 14.2.5.3.1.6.1-2, 14.2.5.4.1.2.1-2, 14.2.5.4.1.3.1-2, 14.2.5.4.1.5.1-2, 14.2.5.4.1.6.1-2, 14.2.5.5.1.2.1-2, 14.2.5.5.1.3.1-2, 14.2.5.5.1.5.1-2, 14.2.5.5.1.6.1-2, 14.2.5.6.1.2.1-2, 14.2.5.6.1.3.1-2, 14.2.5.6.1.5.1-2, 14.2.5.6.1.6.1-2, 14.2.5.7.1.2.1-2, and 14.2.5.7.3.1-2 will be in the following format:

Table 14.2.5.1.1.2.1 Summary of Urinary NNAL Mass Excreted Change from Baseline (unit) by Study Product Group and Study Week (PP Population)

		Study Product Group					
Study Week	Statistics	VLN Non-Mentholated	VLN Mentholated	VLN Combined	UB Non-Mentholated	UB Mentholated	UB Combined
Week 2	n	X	X	X	X	X	X
	Mean	X.X	X.X	X.X	X.X	X.X	X.X
	SD	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
	CV%	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
	SEM	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
	Minimum	XX	XX	XX	XX	XX	XX
	Median	X.X	X.X	X.X	X.X	X.X	X.X
	Maximum	XX	XX	XX	XX	XX	XX
Week 6	n	X	X	X	X	X	X
	Mean	X.X	X.X	X.X	X.X	X.X	X.X
	SD	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
	CV%	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
	SEM	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
	Minimum	XX	XX	XX	XX	XX	XX
	Median	X.X	X.X	X.X	X.X	X.X	X.X
	Maximum	XX	XX	XX	XX	XX	XX

Note: Baseline = Week -1
Subjects used their own usual brand cigarettes at Week -1.
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

```
Program:  /CAXXXXX/ECR/sas_prg/stsas/tab programname.sas  DDMMMYYYY  HH:MM
```

Post-text Tables 14.2.5.1.2, 14.2.5.2.2, 14.2.5.3.2, 14.2.5.4.2, 14.2.5.5.2, 14.2.5.6.2, and 14.2.5.7.2 will be in the following format:

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Table 14.2.5.1.2 Statistical Comparison of Urinary NNAL Mass Excreted (unit) at Weeks 2 and 6 Versus Week -1 by Study Product Group (PP Population)

Study Week	Product Group	Means		Difference (Test Week – Baseline)	XX% Confidence Interval	p-value
		Test Week	Baseline			
Week 2	VLN Non-Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
	VLN Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
	VLN Combined	XXX	XXX	XXX	XXX – XXX	X.XXXX
	UB Non-Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
	UB Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
	UB Combined	XXX	XXX	XXX	XXX – XXX	X.XXXX
Week 6	VLN Non-Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
	VLN Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
	VLN Combined	XXX	XXX	XXX	XXX – XXX	X.XXXX
	UB Non-Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
	UB Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
	UB Combined	XXX	XXX	XXX	XXX – XXX	X.XXXX

Note: Baseline = Week -1
Subjects used their own usual brand cigarettes at Week -1.
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes
Paired t-test method is used to perform the analysis.

Program: /CAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM

Post-text Tables 14.2.5.1.3, 14.2.5.2.3, 14.2.5.3.3, 14.2.5.4.3, 14.2.5.5.3, 14.2.5.6.3, and 14.2.5.7.3 will be in the following format:

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Table 14.2.5.1.3 Statistical Comparison of Urinary NNAL Mass Excreted (unit) Among Study Product Groups at Weeks 2 and 6 (PP Population)

Study Week	Comparison	LSMeans Test (n)	LSMeans Reference (n)	LSMean Difference (Test – Reference)	XX% Confidence Interval	p-value
Week 2	VLN Non-mentholated vs UB Non-mentholated	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX
	VLN Mentholated vs UB Mentholated	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX
	VLN Combined vs UB Combined	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX
Week 6	VLN Non-mentholated vs UB Non-mentholated	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX
	VLN Mentholated vs UB Mentholated	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX
	VLN Combined vs UB Combined	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX

Note: LSMeans, LSmean difference, CI and p-values are from the ANOVA.
n = Number of observation used in the analysis

Test = The first product in the comparison
Reference = The second product in the comparison

VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB Non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM

Post-text Tables 14.2.7.1.1 through 14.2.7.4.2 will be in the following format:

Table 14.2.7.1.1 Unadjusted Plasma Nicotine Concentrations (ng/mL) Following Use of UB Non-Mentholated Filtered Cigarettes and Non-Mentholated VLN Cigarettes (Pharmacokinetic Population from PP)

Subject	Sample Times (min)								
Number	XX	XX	XX	XX	XX	XX	XX	XX	XX
X	BLQ	XX	XX	XX	XX	XX	XX	XX	XX
X	BLQ	XX	XX	XX	XX	XX	XX	XX	XX
X	BLQ	XX	XX	XX	XX	XX	XX	XX	XX
n	XX	XX	XX	XX	XX	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
SD	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
CV%	.	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
SEM	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
Minimum	XX	XX	XX	XX	XX	XX	XX	XX	XX
Median	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
Maximum	XX	XX	XX	XX	XX	XX	XX	XX	XX

For the calculation of summary statistics, values that are below the limit of quantitation (BLQ) of <XX> are treated as 1/2 limit of quantitation.
. = Value missing or not reportable.

Notes for Generating the Actual Table:

Presentation of Data:
Concentrations will be presented to same precision as in bio data.
Summary statistics presentation with respect to the precision of the bioanalytical data: n = integer; Mean and Median +1; SD and SEM +2, Min and Max +0, CV% to 1 decimal. Summary statistics will be presented by sex and overall.

Programmer Note:
A row will be added above 'sample time' which will be labelled 'Week' and will have the following numbers: -1, 2, and 6
PK Time points are from Protocol: i.e. preproduct use and 2, 5, 7, 10, 12, 15, 20, 30, 45, 60, 90, 120, 150, and 180 minutes postproduct use
Note that 'sample time' is in 'min' not 'hr'
For Tables 14.2.7.3.1 through 14.2.7.4.2 the following footnote will be added if applicable: 'For the calculation of summary statistics, negative values are assigned a value of zero'

Table follows CPConc1 template

Per study design needs, the following changes are made to this table relative to Celerion standard: columns <Product Sequence> and <Study Period> will be removed. Summary statistics will be presented by sex and overall.

Program: /CAXXXXX/sas_prg/pksas/pk-conc-tables.sas DDMMMYYYY HH:MM
Program: /CAXXXXX/sas_prg/pksas/pk-conc-tables-sig.sas DDMMMYYYY HH:MM
Program: /CAXXXXX/sas_prg/pksas/adam_conc.sas DDMMMYYYY HH:MM

Post-text Tables 14.2.7.5.1 through 14.2.7.10.2 will be in the following format:

Table 14.2.7.5.1 Baseline Adjusted Plasma Nicotine Pharmacokinetic Parameters Following Use of UB Non-Mentholated Filtered Cigarettes (Week -1) (Pharmacokinetic Population from PP)

	Parameters					
Subject Number	param1 (units)	param2 (units)	param3 (units)	param4 (units)	param5 (units)	param6 (units)
X	XXX	X.XX	XXX	XXX	XX.X	X.XXX
X	XX.X	X.XX	XXX	XXX	XX.X	X.XXX
X	XXX	X.XX	XXX	XXX	XX.X	X.XXX
X	XX.X	X.XX	XXX	XXX	XX.X	X.XXX
X	XX.X	X.XX	XXX	XXX	XX.X	X.XXX
X	X.XX	X.XX	XXX	XXX	XX.X	X.XXX
X	XXX	X.XX	XXX	XXX	XX.X	X.XXX
n	XX	XX	XX	XX	XX	XX
Mean	XXX.X	X.XXX	XXX.X	XXX.X	XX.XX	X.XXXX
SD	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
CV%	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
SEM	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
Minimum	XX.X	X.XX	XXX	XXX	XX.X	X.XXX
Median	XX.XX	X.XXX	XXX.X	XXX.X	XX.XX	X.XXXX
Maximum	XXX	X.XX	XXX	XXX	XX.X	X.XXX
Geom Mean	XXX.X	X.XXX	XXX.X	XXX.X	XX.XX	X.XXXX
Geom CV%	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X

. = Value missing or not reportable.

Notes for Generating the Actual Table:

Presentation of Data:

- PK Parameters will be presented in the following order and with following units: AUC0-180 (min*ng/mL), Cmax (ng/mL), Tmax (min)

- n will be presented as an integer (with no decimal); Cmax will be presented with precision of the bioanalytical data
- AUC will be presented with, at maximum, the precision of the bioanalytical data, and, at minimum, 3 significant figures (to be determined by the PKist once bioanalytical data are received).
- Summary statistics for parameters will be presented (with respect to the precision of the PK parameter data) as: Mean, Median, and Geom Mean+1; SD and SEM +2, Min and Max +0. Geom Mean and Geom CV% will not be presented for Tmax.
- CV% and Geom CV% for all parameters will be presented with 1 decimal
- Summary statistics will be presented by sex and overall
- Table follows CPPar1 template

Per study design needs, the following changes are made to this table relative to Celerion standard: columns <Product Sequence> and <Study Period> will be removed. Summary statistics will be presented by sex and overall.

Program: /CAXXXXX/sas_prg/pksas/pk-tables.sas DDMMMYYYY HH:MM
Program: /CAXXXXX/sas_prg/pksas/adam_pkparam.sas DDMMMYYYY HH:MM

Post-text Table 14.2.7.11 will be in the following format:

Table 14.2.7.11 Statistical Comparison of Baseline Adjusted Plasma Nicotine Pharmacokinetic Parameters at Weeks 2 and 6 (VLN Cigarettes) Versus Week -1 (UB Cigarettes) (Pharmacokinetic Population from PP)

Study Week	Product Group	Geometric Means: Test Week	Geometric Means: Baseline	GMR (Test Week / Baseline)	XX% Confidence Interval	p-value
Week 2	VLN Non-Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
	VLN Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
	VLN Combined	XXX	XXX	XXX	XXX – XXX	X.XXXX
	UB Non-Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
	UB Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
	UB Combined	XXX	XXX	XXX	XXX – XXX	X.XXXX
Week 6	VLN Non-Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
	VLN Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
	VLN Combined	XXX	XXX	XXX	XXX – XXX	X.XXXX
	UB Non-Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
	UB Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
	UB Combined	XXX	XXX	XXX	XXX – XXX	X.XXXX

Note: Baseline = Week -1
Subjects used their own usual brand cigarettes at Week -1.
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes
Analysis is based on the log-transformed data.
Paired t-test method is used to perform the analysis.
Geometric means are calculated by exponentiating the means.
Geometric Mean Ratios (GMR) are calculated by exponentiating the mean of difference from paired t-test.
.
Program: /CAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM

Post-text Table 14.2.9.1.1.1-2, 14.2.9.3.1.1-2, and 14.2.9.4.1.1-2 will be in the following format:

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Table 14.2.9.1.1.1 Summary of FTCD Score by Study Product Group and Study Week (PP Population)

		Study Product Group					
Study Week	Statistics	VLN Non-Mentholated	VLN Mentholated	VLN Combined	UB Non-Mentholated	UB Mentholated	UB Combined
Week -1*	n	X	X	X	X	X	X
	Mean	X.X	X.X	X.X	X.X	X.X	X.X
	SD	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
	CV%	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
	SEM	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
	Minimum	XX	XX	XX	XX	XX	XX
	Median	X.X	X.X	X.X	X.X	X.X	X.X
	Maximum	XX	XX	XX	XX	XX	XX
Week 2	n	X	X	X	X	X	X
	Mean	X.X	X.X	X.X	X.X	X.X	X.X
	SD	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
	CV%	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
	SEM	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
	Minimum	XX	XX	XX	XX	XX	XX
	Median	X.X	X.X	X.X	X.X	X.X	X.X
	Maximum	XX	XX	XX	XX	XX	XX

Note: *Subjects used their own usual brand cigarettes at Week -1.
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM

Programmer Note: Study Week 6 will also be presented in the table.

Post-text Tables 14.2.9.1.2, 14.2.9.3.2, and 14.2.9.4.2 will be in the following format:

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Table 14.2.9.1.2 Statistical Comparison of FTCD Score at Weeks 2 and 6 Versus Week -1
by Study Product Group (PP Population)

Study Week	Product Group	Means: Test Week	Means: Baseline	Difference (Test Week – Baseline)	XX% Confidence Interval	p-value
Week 2	VLN Non-Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
	VLN Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
	VLN Combined	XXX	XXX	XXX	XXX – XXX	X.XXXX
	UB Non-Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
	UB Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
	UB Combined	XXX	XXX	XXX	XXX – XXX	X.XXXX
Week 6	VLN Non-Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
	VLN Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
	VLN Combined	XXX	XXX	XXX	XXX – XXX	X.XXXX
	UB Non-Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
	UB Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
	UB Combined	XXX	XXX	XXX	XXX – XXX	X.XXXX

Note: Baseline = Week -1
Subjects used their own usual brand cigarettes at Week -1.
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes
Paired t-test method is used to perform the analysis.

Program: /CAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM

Post-text Tables 14.2.9.1.3, 14.2.9.3.3, and 14.2.9.4.3 will be in the following format:

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Table 14.2.9.1.3 Statistical Comparison of FTCD Score Among Study Product Groups at Weeks 2 and 6 (PP Population)

Study Week	Comparison	LSMeans Test (n)	LSMeans Reference (n)	LSMean Difference (Test − Reference)	XX% Confidence Interval	p-value
Week 2	VLN Non-mentholated vs UB Non-mentholated	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX
	VLN Mentholated vs UB Mentholated	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX
	VLN Combined vs UB Combined	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX
Week 6	VLN Non-mentholated vs UB Non-mentholated	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX
	VLN Mentholated vs UB Mentholated	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX
	VLN Combined vs UB Combined	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX

Note: LSMeans, LSmean difference, CI and p-values are from the ANOVA.
n = Number of observation used in the analysis

Test = The first product in the comparison
Reference = The second product in the comparison

VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM

Post-text Table 14.2.9.2.1.1-2 will be in the following format:

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Table 14.2.9.2.1.1 Summary of QSU-Brief Factor Score by Study Product Group and Study Week (PP Population)

			Study Product Group					
Factor	Study Week	Statistics	VLN Non-Mentholated	VLN Mentholated	VLN Combined	UB Non-Mentholated	UB Mentholated	UB Combined
Factor 1	Week -1*	n	X	X	X	X	X	X
		Mean	X.X	X.X	X.X	X.X	X.X	X.X
		SD	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
		CV%	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
		SEM	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
		Minimum	XX	XX	XX	XX	XX	XX
		Median	X.X	X.X	X.X	X.X	X.X	X.X
		Maximum	XX	XX	XX	XX	XX	XX
	Week 2	n	X	X	X	X	X	X
		Mean	X.X	X.X	X.X	X.X	X.X	X.X
		SD	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
		CV%	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
		SEM	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
		Minimum	XX	XX	XX	XX	XX	XX
		Median	X.X	X.X	X.X	X.X	X.X	X.X
		Maximum	XX	XX	XX	XX	XX	XX

Note: *Subjects used their own usual brand cigarettes at Week -1.
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM

Programmer Note: Study Week 6 and Factor 2 will also be presented in the table.

Post-text Table 14.2.9.2.2 will be in the following format:

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Table 14.2.9.2.2 Statistical Comparison of QSU-Brief Factor Score at Weeks 2 and 6 Versus Week -1 by Study Product Group (PP Population)

Factor	Study Week	Product Group	Means: Test Week	Means: Baseline	Difference (Test Week – Baseline)	XX% Confidence Interval	p-value
Factor 1	Week 2	VLN Non-Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
		VLN Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
		VLN Combined	XXX	XXX	XXX	XXX – XXX	X.XXXX
		UB Non-Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
		UB Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
		UB Combined	XXX	XXX	XXX	XXX – XXX	X.XXXX
	Week 6	VLN Non-Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
		VLN Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
		VLN Combined	XXX	XXX	XXX	XXX – XXX	X.XXXX
		UB Non-Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
		UB Mentholated	XXX	XXX	XXX	XXX – XXX	X.XXXX
		UB Combined	XXX	XXX	XXX	XXX – XXX	X.XXXX

Note: Baseline = Week -1
Subjects used their own usual brand cigarettes at Week -1.
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes
Paired t-test method is used to perform the analysis.

Program: /CAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM

Programmer Note: Factor 2 will also be presented in the table.

Post-text Table 14.2.9.2.3 will be in the following format:

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Table 14.2.9.2.3 Statistical Comparison of QSU-Brief Factor Score Among Study Product Groups at Weeks 2 and 6 (PP Population)

Factor	Study Week	Comparison	LSMeans Test (n)	LSMeans Reference (n)	LSMean Difference (Test – Reference)	XX% Confidence Interval	p-value
Factor 1	Week 2	VLN Non-mentholated vs UB Non-mentholated	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX
		VLN Mentholated vs UB Mentholated	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX
		VLN Combined vs UB Combined	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX
	Week 6	VLN Non-mentholated vs UB Non-mentholated	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX
		VLN Mentholated vs UB Mentholated	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX
		VLN Combined vs UB Combined	X.XX (X)	X.XX (X)	XXX.XX	XX.XX – XXX.XX	X.XXXX

Note: LSMeans, LSmean difference, CI and p-values are from the ANOVA.
n = Number of observation used in the analysis

Test = The first product in the comparison
Reference = The second product in the comparison

VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM

Programmer Note: Factor 2 will also be presented in the table.

Post-text Table 14.3.1.1 will be in the following format:

Table 14.3.1.1 Product-Use-Emergent Adverse Event Frequency–
Number of Subjects Reporting the Event (% of Subjects (% of Subject Used Study Product) (Safety Population)

Adverse Event*	Baseline	VLN Non-Mentholated	VLN Mentholated	UBN non-Mentholated	UB Mentholated	Overall#
Number of Subjects Use Study Product	XX (XXX%)	XX (XXX%)	XX (XXX%)	XX (XXX%)	XX (XXX%)	XX(XXX%)
Number of Subjects With PUEAEs^	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Number of Subjects Without PUEAEs^	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Eye disorders	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Vision blurred	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Gastrointestinal disorders	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Dyspepsia	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Nausea	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Musculoskeletal and connective tissue disorders	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Back pain	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Muscle cramps	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Musculoskeletal pain	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Nervous system disorders	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Headache NOS	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)

Note: *Adverse events are classified according to MedDRA Version 20.0. ^ = Product-use-emergent adverse events
Subject used their usual brand at Baseline (Week -1).
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes
Overall includes AEs after the start of Week1 product use.

Program: /CAXXXXX/ECR/sas_prg/stsas/tab progrname.sas DDMMMYYYY HH:MM

Post-text Table 14.3.1.2 will be in the following format:

Table 14.3.1.2 Product-Use-Emergent Adverse Event Frequency –
Number of Adverse Events (% of Total Adverse Events) (Safety Population)

Adverse Event*	Baseline	VLN Non-Mentholated	VLN Mentholated	UB non-Mentholated	UB Mentholated	Overall#
Number of PUEAEs	XX (XXX%)	XX (XXX%)	XX (XXX%)	XX (XXX%)	XX (XXX%)	XX(XXX%)
Eye disorders	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Vision blurred	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Gastrointestinal disorders	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Dyspepsia	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Nausea	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Musculoskeletal and connective tissue disorders	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Back pain	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Muscle cramps	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Musculoskeletal pain	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Nervous system disorders	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Headache NOS	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)

Note: *Adverse events are classified according to MedDRA Version 20.0. ^ = Product-use-emergent adverse events
Subject used their usual brand at Baseline (Week -1).
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes
Overall includes AEs after the start of Week1 product use.

Program: /CAXXXXX/ECR/sas_prg/stsas/tab progrname.sas DDMMMYYYY HH:MM

Post-text Table 14.3.1.3 will be in the following format:

Table 14.3.1.3 Product-Use-Emergent Adverse Event Frequency by Severity and Relationship to Study Product - Number of Subjects Reporting Adverse Events (Safety Population)

Adverse Event*	Number of Subjects With PUEAEs	Number of PUEAEs	Severity			Relationship to Study product				
			Mild	Moderate	Severe	Unrelated	Unlikely	Possibly	Probably	Likely
Abdominal pain	X	X	X	X	X	X	X	X	X	X
Constipation	X	X	X	X	X	X	X	X	X	X
Dry throat	X	X	X	X	X	X	X	X	X	X
Dysmenorrhoea	X	X	X	X	X	X	X	X	X	X
Dyspepsia	X	X	X	X	X	X	X	X	X	X
Baseline	X	X	X	X	X	X	X	X	X	X
UB Non-mentholated	X	X	X	X	X	X	X	X	X	X
UB mentholated	X	X	X	X	X	X	X	X	X	X
VLN Non-mentholated	X	X	X	X	X	X	X	X	X	X
VLN mentholated	X	X	X	X	X	X	X	X	X	X
Overall#	X	X	X	X	X	X	X	X	X	X

Note: * Adverse events are classified according to MedDRA Version 20.0. PUEAEs = Product-use-emergent adverse events
When a subject experienced the same AE at more than one level of severity, only the most severe one was counted.
When a subject experienced the same AE at more than one level of product relationship, only the one most closely related to study product was counted.
Subject used their usual brand at Baseline (Week -1).
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB Non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes
Overall includes AEs after the start of Week1 product use.
Program: /CAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM

Post-text Table 14.3.2 will be in the following format:

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Table 14.3.2 Serious Adverse Events (Safety Population)

Will match 16.2.7

Or contain statement as follows:

"There were no serious adverse events recorded during the study."

Program: /CAXXXXX/ECR/sas_prg/stsas/programname.sas DDMMMYYYY HH:MM

Post-text Tables 14.3.4.1, 14.3.4.2, and 14.3.4.3 will be in the following format:

Table 14.3.4.1 Out-of-Range Values and Recheck Results - Serum Chemistry (Safety Population)

Subject Number	Age/ Gender	Visit Name	Visit Date	Product Group	Parameter1 <Range1> <Unit1>	Parameter2 <Range2> <Unit2>	Parameter3 <Range3> <Unit3>	Parameter4 <Range4> <Unit4>	Parameter5 <Range5> <Unit5>	Parameter6 <Range6> <Unit6>
XXXXXX	XX/X	Screening	DDMMMYYYY	XX	XX HN				XX HN	

Note: F = Female, M = Male
H = Above Reference Range, L = Below Reference Range
N = Not Clinically Significant

VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Programmer Notes: Replace Parameter1, 2 etc. with actual lab tests in the study. Sort unscheduled assessment and early termination chronologically with other scheduled assessments and rechecks. Recheck should be sorted with the scheduled time point the recheck is for.

Programmer Notes: Clinically significant lab values generally will be captured as AEs, some of which the PI may indicate in Appendix 16.2.8.1.5 lab comments (as per GPG.03.0028 sections 2.9 and 2.10). Derive an additional CS flag for PI flag (+) based on positive comments (i.e. CS/Clinically Significant). Present this derived 4th column in all tables, and list only subjects/tests which are PI-determined clinically significant lab values in Table 14.3.4.4.

Program: /CAXXXXX/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

Post-text Table 14.3.4.4 will be in the following format:

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Table 14.3.4.4 Clinically Significant Laboratory and Corresponding Results (Safety Population)

Subject Number	Age/ Sex	Visit Name	Visit Date	Product Group	Date	Time	Department	Test	Result	Reference Range	Unit
XXXXXX	XX/X	Screening	DDMMMYYYY	XX	02DEC2016	8:34	Serum Chemistry	Cholesterol	XXX	X – X	mg/dL

Programmer Note: All time points for a subject/test with at least one value deemed as CS by the PI will be presented in this table.

Note: F = Female, M = Male
H = Above Reference Range, L = Below Reference Range
N = Not Clinically Significant

VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

If no event meet this criteria then include a statement as follows:

"There were no clinical laboratory results documented as clinically significant by the PI."

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Post-text Tables 14.3.5.1, 14.3.5.2, and 14.3.5.3 will be in the following format:

Page 1 of X

Table 14.3.5.1 Clinical Laboratory Summary – Serum Chemistry (Safety Population)

Laboratory Test (unit)	Reference Range	Statistics	Time Point: Screening	Time Point: End of Study
XXXXXXXXX	XX –XX	n	X	X
		Mean	X.X	X.X
		SD	X.XX	X.XX
		Minimum	XX	XX
		Median	X.X	X.X
		Maximum	XX	XX
XXXXXXXXX	XX –XX#	n	X	X
		Mean	X.X	X.X
		SD	X.XX	X.XX
		Minimum	XX	XX
		Median	X.X	X.X
		Maximum	XX	XX

Note: # = Lowest of the lower ranges and highest of the higher ranges are used. Refer to Appendix 16.1.10.1 for the breakdown.

Program: /CAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM

Programmer Note: All laboratory tests will also be presented in the table.

Post-text Table 14.3.5.4 will be in the following format:

Page 1 of X

Table 14.3.5.4 Vital Sign Summary (Safety Population)

			Study Product Group			
Measurement (unit)	Study Week	Statistics	UB Non-Mentholated	UB Mentholated	VLN Non-Mentholated	VLN Mentholated
Systolic BP (mmHg)	Screening	n	X	X	X	X
		Mean	X.X	X.X	X.X	X.X
		SD	X.XX	X.XX	X.XX	X.XX
		Minimum	XX	XX	XX	XX
		Median	X.X	X.X	X.X	X.X
		Maximum	XX	XX	XX	XX
	Week -1	n	X	X	X	X
		Mean	X.X	X.X	X.X	X.X
		SD	X.XX	X.XX	X.XX	X.XX
		Minimum	XX	XX	XX	XX
		Median	X.X	X.X	X.X	X.X
		Maximum	XX	XX	XX	XX

Note: VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM

Programmer Note: Study Weeks 2, 4, 6 and other measuremetns will also be presented in the table.

15. LISTING SHELLS

The following listing shells provide a framework for the display of data from this study. The shells may change due to unforeseen circumstances. These shells may not be reflective of every aspect of this study, but are intended to show the general layout of the listings that will be presented and included in the final report. These listings will be generated from the Celerion SDTM 3.2 All listings will be presented in Courier New size font 9.

Appendix 16.1.10.1 Clinical Laboratory Reference Ranges

Laboratory Group	Test Name	Gender	Age Category	Normal Range	Unit
Serum Chemistry	Test Name	<>	<>	XX – XX	units
	Test Name	<>	<>	XX – XX	units
	Test Name	<>	<>	XX – XX	units
	Test Name	<>	<>	XX – XX	units
	Test Name	<>	<>	XX – XX	units
	Test Name	<>	<>	XX – XX	units
Hematology	Test Name	<>	<>	XX – XX	units
	Test Name	<>	<>	XX – XX	units
	Test Name	<>	<>	XX – XX	units
	Test Name	<>	<>	XX – XX	units
	Test Name	<>	<>	XX – XX	units

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Programmer Note: Similar for remaining Laboratory Groups and Test Names.

Appendix 16.2.1.1 Subject Discontinuation (Safety Population)

Site	Subject Number	Randomization Number	Randomization Date	Product	Completion/ Discontinuation Date	Completed Study?	Reason for Discontinuation	Specify
XXX	XXXXXX	XXX	DDMMMYYYY	XX	DDMMMYYYY	Yes		
	XXXXXX	XXX	DDMMMYYYY	XX	DDMMMYYYY	Yes		
	XXXXXX	XXX	DDMMMYYYY	XX	DDMMMYYYY	Yes		
	XXXXXX	XXX	DDMMMYYYY	XX	DDMMMYYYY	Yes		
	XXXXXX	XXX	DDMMMYYYY	XX	DDMMMYYYY	No	Personal Reason	
	XXXXXX	XXX	DDMMMYYYY	XX	DDMMMYYYY	Yes		
	XXXXXX	XXX	DDMMMYYYY	XX	DDMMMYYYY	Yes		
	XXXXXX	XXX	DDMMMYYYY	XX	DDMMMYYYY	Yes		

Note: VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

<also need site footnotes>

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.1.2 Subject Discontinuation (Screen Failures)

Site	Subject Number	Discontinuation Date	Reason for Discontinuation	Specify
XXX	XXXXXX	DDMMMYYYY	XXXXXXXXXX	
	XXXXXX	DDMMMYYYY	XXXXXXXXXX	

Note: <also need site footnotes>

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.4.1 Demographics (Safety Population)

Site	Subject Number	Product Group	Age (yrs)	Gender	Race	Ethnicity	Reproductive Status	Height (cm)	Weight (kg)	BMI (kg/m^2)	Informed Consent Date	Informed Re-Consent Date
XXX	XXXXXX	XX	XX	XXXX	XXXXXXXXX	XXXXXXXXXXX	XXXXXXXXXXX	XX.X	XXX.X	XX.XX	DDMMMYYYY	DDMMMYYYY
	XXXXXX	XX	XX	XXXX	XXXXXXXXX	XXXXXXXXXXX	XXXXXXXXXXX	XX.X	XXX.X	XX.XX	DDMMMYYYY	DDMMMYYYY
	XXXXXX	XX	XX	XXXX	XXXXXXXXX	XXXXXXXXXXX	XXXXXXXXXXX	XX.X	XXX.X	XX.XX	DDMMMYYYY	DDMMMYYYY
	XXXXXX	XX	XX	XXXX	XXXXXXXXX	XXXXXXXXXXX	XXXXXXXXXXX	XX.X	XXX.X	XX.XX	DDMMMYYYY	DDMMMYYYY
	XXXXXX	XX	XX	XXXX	XXXXXXXXX	XXXXXXXXXXX	XXXXXXXXXXX	XX.X	XXX.X	XX.XX	DDMMMYYYY	DDMMMYYYY
	XXXXXX	XX	XX	XXXX	XXXXXXXXX	XXXXXXXXXXX	XXXXXXXXXXX	XX.X	XXX.X	XX.XX	DDMMMYYYY	DDMMMYYYY

Note: BMI = Body Mass Index

VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

<also need site footnotes>

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.4.2 Physical Examination (Safety Population)

Subject Number	Visit Name	Visit Date	Product Group	Was PE Done?	Reason for Not Done	System	Result	Comment	Clinical Significance
XXXXXX	Screening	DDMMMYYYY	XX	XXX		XXXXXXX	XXXXXXX		
						XXXXXXX	XXXXXXX	XXXXXXX	NCS
						XXXXXXX	XXXXXXX		
						XXXXXXX	XXXXXXX		

Note: NCS = Not clinically significant, CS = Clinically significant

VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.4.3 Medical History (Safety Population)

Subject Number	Any History?	Visit Name	Visit Date	Product Group	MH Number	Reported Term		Date Start	Date End	Ongoing?
XXXXXX	XXX	Screening	DDMMMYYYY	XX	XX	XXXXXX	XXXXX	MMYYYY		YES
					XX	XXXXXX	XXXXX	MMYYYY	MMYYYY	NO
XXXXXX	XXX	Screening	DDMMMYYYY	XX	XX	XXXXXX	XXXXX	MMYYYY	MMYYYY	YES

Note: UNK = Unknown

VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.4.4 Tobacco/Nicotine Use History (Safety Population)

Subject Number	Visit Name	Visit Date	Product Group	Not Done?	Reason for Not Done	Duration of Cigarette Use (unit)	Typical Number of CPD	Cigarette Brand	Cigarette Flavor	Cigarette Size	Other Cigarette Brand	Other Cigarette Flavor	Other Cigarette Size
X	Screening	DDMMMYYYY	XX	XX		XX years	XX	XXX	XXX	XX	XXX	XXX	XX

Note: CPD = Cigarette smoked per day
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.1 Inclusion / Exclusion Criteria Not Met (Safety Population)

Subject Number	Visit Name	Visit Date	Product Group	Met All Eligibility Criteria?	Inclusion/ Exclusion Category	Criterion Identifier	Criterion
X	Screening	DDMMMYYYY	XX	No	XX	XXXX	XXXXXXXXXXXXXXXX

Note: VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.2.1 VLN Product Trial (Safety Population)

Subject Number	Visit Name	Visit Date	Visit Day	Product Group	Number of cigarettes smoked
X	XXXX	DDMMMYYYY	X	XX	X

Note: VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.2.2.1 Product Dispensed (Safety Population)

Subject Number	Visit Name	Visit Date	Visit Day	Product Group	Product Dispensed	If Usual Brand, Specify	Date Dispensed	Number of Cigarettes Dispensed
X	XXXX	DDMMMYYYY	X	XX	XXX		DDMMMYYYY	XXX

Note: VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.2.2.2.1 Product Returned (I of II) (Safety Population)

Subject Number	Visit Name	Visit Date	Visit Day	Product Group	Product Name	If Usual Brand, Specify	Date Returned	Number of Cigarettes Returned	Cigarette Butts Returned	Number of Non VLN Butts Returned
X	XXXX	DDMMMYYYY	X	XX	XXX		DDMMYYYY	XXX	XXX	XX

Note: VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.2.2.2.2 Product Returned (II of II) (Safety Population)

	Visit				Any Tobacco Products Other than e-diary			Additional Information*	
Subject Number	Name	Date	Day	Product Group	Answer	When	Amount	Answer	Specify
X	XXXX	DDMMMYYYY	X	XX	XX			XX	XXXXXXXX

Note: * any additional information to provide about the difference between reported cigarette use and number of cigarettes and butts returned?
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.2.2.3 Puff Topography (Safety Population)

Subject Number	Visit Name	Visit Date	Product Group	Date Collection	Did Subject Smoke?	Number of Cigarettes Smoked*	Topography: Puff Duration (unit)	Topography: Puff Volume (unit)	Topography: Puff Flow Rate (unit)	Topography: Average Flow Rate (unit)	Topography: Inter-Puff Interval (unit)
X	XXXX	DDMMMYYYY	XX	DDMMMYYYY	XX	XX	XX	XX	XX	XX	XX

Note: * How many cigarettes did the subject smoke during the 1 hour topography session?
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.3.1 Plasma/Blood Sampling (Safety Population)

Subject Number	Visit Name	Visit Date	Visit Day	Product Group	Not Done?	If Not Done, Specify	Assay	Collection Date	Collection Time
X	XXXX	DDMMMYYYY	X	XX			XXX	DDMMMYYYY	HH:MM

Note: VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.3.2 24-Hour Urine Collection (Safety Population)

Subject Number	Visit Name	Visit Date	Product Group	Planned Timepoint	Was the sample Collected?	Reason for Not Done	Start Date	Start Time	Stop Date	Stop Time	Total Weight (g)	Lost or Discard	Comment for Lost/ Discard
XXXXXX	XXXXXX	DDMMMYYYY	XX	XXXXXXXXX	YES		DDMMYYYY	HH:MM	DDMMYYYY	HH:MM	XXX	XX	
				XXXXXXXXX	YES		DDMMYYYY	HH:MM	DDMMYYYY	HH:MM	XXX	XX	

Note: VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.4 Prior and Concomitant Medications (Safety Population)

Subject Number	Study Product	Any Med?	Medication (WHO* Term)	Indication	Primary MH Number	Primary AE Number	Dosage	Route	Start Date	Stop Date	Frequency	Ongoing?	Prior to Study?
XXXXXX	X	XXX	ACETAMINOPHEN (XXXXXXXXX)	Toothache		XX	620 mg	ORAL	DDMMMYYYY	DDMMMYYYY	Once	No	X

Note: *Concomitant medications are coded with WHO Drug Dictionary Version 01SEP2018.

VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.6.1 Number of Cigarettes Smoked and Number of Cigarette Butts Collected per Week (Safety Population)

Subject Number	Product Group	Study Week	Number of Cigarettes Smoked	Number of Cigarette Butts Collected
X	XX	-1	XXX	XXX

Note: Subjects used their own usual brand cigarettes at Week -1.
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.6.2 Puff Topography Parameters (Safety Population)

Subject Number	Product Group	Study Week	Puff Duration (unit)	Puff Volume (unit)	Puff Flow Rate (unit)	Average Flow Rate (unit)	Inter-Puff Interval (unit)
X	XX	-1	XXX	XXX	XXX	XXX	XXX

Note: Subjects used their own usual brand cigarettes at Week -1.
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Programmer Note: Replace parameters and units with actual parameter names and units.

Appendices 16.2.6.3, 16.2.6.4, 16.2.6.5, 16.2.6.6, 16.2.6.7, and 16.2.6.8.2 will have following format.

Appendix 16.2.6.3 Urinary Total NNAL (Safety Population)

Subject Number	Product Group	Study Week	Biomarker Concentration (unit)	Urine Volume (unit)	24-Hour Amount Excreted			Creatinine Concentration (unit)	Creatinine Adjusted Values		
					Amount (unit)	CFB (unit)	PCFB (%)		Amount (unit)	CFB (unit)	PCFB (%)
X	XX	-1	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX

Note: Baseline = Week -1
CFB = Change from baseline, PCFB = Percent change from baseline
Subjects used their own usual brand cigarettes at Week -1.
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.6.8.1 Urine Nicotine and Metabolites (I of II) (Safety Population)

Subject Number	Product Group	Study Week	Volume (mL)	Nicotine (ng/mL)	Nicotine (mg/24 hours)	Nicotine Glucuronide (ng/mL)	Nicotine Glucuronide (mg/24 hours)	Cotinine (ng/mL)	Cotinine (mg/24 hours)
X	XX	-1	XXX	XXX	XXX	XXXX	XXX	XXX	XXX

Note: Subjects used their own usual brand cigarettes at Week -1.
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Programmer Note: 16.2.6.8.2 will present the concentration and amount excreted of 'Cotinine Glucuronide', 'Trans-3-hydroxy Cotinine', and 'Trans-3-hydroxy Cotinine Glucuronide'.

Appendix 16.2.6.9 Blood COHb (Safety Population)

Subject Number	Product Group	Study Week	Biomarker Concentration (unit)	CFB (unit)	PCFB (%)
X	XX	-1	XXX	XXX	XXX

Note: Baseline = Week -1
CFB = Change from baseline, PCFB = Percent change from baseline
Subjects used their own usual brand cigarettes at Week -1.
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.6.10 Plasma Cotinine (Safety Population)

Subject Number	Product Group	Study Week	Biomarker Concentration (unit)
X	XX	-1	XXX

Note: Subjects used their own usual brand cigarettes at Week -1.
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.6.12 FTCD Response and Score (Safety Population)

Subject Number	Product Group	Study Week	Date	Question* 1	2	3	4	5	6	Total Score
X	XX	-1	DDMMMYYYY	XXX	XXX	XXX	XXX	XXX	XXX	XXX

Note: *1. How soon after you wake up do you smoke your first cigarette?
2. Do you find it difficult to refrain from smoking in places where it is forbidden (e.g., in church, at the library, in the cinema, etc.)?
3. Which cigarette would you hate most to give up?
4. How many cigarettes per day do you smoke?
5. Do you smoke more frequently during the first hours after waking than during the rest of the day?
6. Do you smoke if you are so ill that you are in bed most of the day?
Subjects used their own usual brand cigarettes at Week -1.
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.6.13 QSU-Brief Response and Factor Score (Safety Population) (Safety Population)

Subject Number	Product Group	Study Week	Date	Question* 1	2	3	4	5	6	7	8	9	10	Factor 1 Score	Factor 2 Score
X	XX	-1	DDMMMYYYY	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX

Note: *1. I have a desire to smoke right now. 2. Nothing would be better than smoking right now.
3. If it were possible, I probably would smoke right now. 4. I could control things better right now if I could smoke.
5. All I want right now is a cigarette. 6. I have an urge for a cigarette.
7. A cigarette would taste good now. 8. I would do almost anything for a cigarette now.
9. Smoking would make me less depressed. 10. I am going to smoke as soon as possible.
Factor 1 (anticipation of pleasure from smoking) calculated as the average of the response scores from Questions 1, 3, 6, 7, and 10;
Factor 2 (relief of nicotine withdrawal) calculated as the average of the response scores from Questions 2, 4, 5, 8, and 9).
Scale: 1 = Strongly disagree, 7 = Strongly agree
Subjects used their own usual brand cigarettes at Week -1.
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.6.14 MNWS-R Response and Total Score (Safety Population)

Subject Number	Product Group	Study Week	Date	Question* 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Total Score
X	XX	-1	DDMMMYYYY	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	

Note: *1. Angry, irritable, frustrated; 2. Anxious, nervous; 3. Depressed mood, sad; 4. Desire or craving to smoke
5. Difficulty concentrating; 6. Increased appetite, hungry, weight gain; 7. Insomnia, sleep problems, awakening at night;
8. Restless; 9. Impatient; 10. Constipation; 11. Dizziness; 12. Coughing; 13. Dreaming or nightmares; 14. Nausea; 15. Sore throat
Scale: 0 = none, 1 = slight, 2 = mild, 3 = moderate, 4 = severe
Subjects used their own usual brand cigarettes at Week -1.
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.6.15 Perceived Health Risk Scale (Safety Population)

Subject Number	Product Group	Study Week	Date	Perceived Health Risk Scale*
X	XX	-1	DDMMMYYYY	XXX

Note: * Indicate your perception of the risk of becoming addicted to the cigarette you are currently using.
Scale: 1 = Very low risk, 10 = Very high risk
Subjects used their own usual brand cigarettes at Week -1.
VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.7.1 Adverse Events (Safety Population)

Subject Number	Study Product	UE?^	System Organ Class >Preferred Term* >>Adverse Event	Time From Last Product Use (DD:HH:MM)	Onset Date Time/ Resolved Date Time	Frequency	Severity	Serious	Outcome	Relationship to Study Product	Action
XXXXXX	X	XXX	XXXXXXXXXXXXX >XXXXXXXXX >>XXXXXXXXXXXXXXXX	XX:XX:XX	DDMMMYYYY HH:MM/ DDMMMYYYY HH:MM	XXXXXXX	XXXXX	XXXX	XXXXXX	XXXXXXXX	XXXXX

Note: ^ = Abbreviation for study product use-emergent (UE), UE is assigned to last product used prior to AE start.
* = Adverse events are classified according to the MedDRA Version 21.0.

VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Programmer Note: Other action will also be listed if there is any.

Appendices 16.2.8.1.1 through 16.2.8.1.3 will have the following format.

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Appendix 16.2.8.1.1 Clinical Laboratory Report - Serum Chemistry (Safety Population)

Subject Number	Age/ gender	Visit Name	Visit Date	Product Group	Parameter1 <Range1> <Unit1>	Parameter2 <Range2> <Unit2>	Parameter3 <Range3> <Unit3>	Parameter4 <Range4> <Unit4>	Parameter5 <Range5> <Unit5>	Parameter6 <Range6> <Unit6>
XXXXXX	XX/X	Screening	DDMMMYYYY	XX	XX HN	XX	XX	XX	XX HN	XX

Note: F = Female, M = Male
H = Above Reference Range, L = Below Reference Range
N = Not Clinically Significant

VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Programmer Note: Replace Parameter1, 2 etc. with actual lab tests in the study.

Appendix 16.2.8.1.4 Clinical Laboratory Report – Comments (Safety Population)

Subject Number	Visit Name	Visit Date	Product Group	Lab Panel	Test	Result	Unit	Comment
XXXXXX	Screening	DDMMMYYYY	XX	Hematology	XXXXXXXX	XXX	mg/dL	Not significant in the context of this study.

Note: VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.8.1.5 Urine Drug Screens (Safety Population)

Subject Number	Visit Name	Visit Date	Product Group	Was the Urine Sample Collected?	Date of Collection	Test Name	Result
XXXXXX	Screening	DDMMMYYYY	XX	XXX	DDMMMYYYY	XXXXXXXXXXXXX	XXXXXX
						XXXXXXXXXXXXX	XXXXXX

Note: VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.8.1.6 Pregnancy Tests (Safety Population)

Subject Number	Visit Name	Visit Date	Product Group	Was the Pregnancy Test Done?	Reason for Not Done	Collection Date	Test Type	Test Result
XXXXXX	Screening	DDMMMYYYY	XX	XXX		DDMMMYYYY	XXXXXX	XXX
	XXXXXXXXX	DDMMMYYYY		XXX		DDMMMYYYY	XXXXXX	XXX

Note: VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.8.1.7 Serum FSH (Safety Population)

Subject Number	Visit Name	Visit Date	Product Group	Was Serum FSH Collected?	Reason for Not Done	Was Postmenopausal Status Confirmed?	Collection Date
XXXXXX	Screening	DDMMMYYYY	XX	XXX	XXXX	XXX	DDMMMYYYY

Note: VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.8.1.8 Urine Cotinine Screens (Safety Population)

Subject Number	Visit Name	Visit Date	Product Group	Was the Urine Cotinine Sample Collected?	Date of Collection	Is Result Positive* for Urine Cotinine?
XXXXXX	Screening	DDMMMYYYY	XX	XXX	DDMMMYYYY	XXX

Note: *Positive = greater than or equal to 500 ng/mL

VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.8.1.9 Serology Sample Collection (Safety Population)

Subject Number	Visit Name	Visit Date	Product Group	Was the Sample Collected?	Collection Date
XXXXXX	Screening	DDMMMYYYY	XX	XXX	DDMMMYYYY

Note: VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.8.1.10 Exhaled CO Measurement (Safety Population)

Subject Number	Visit Name	Visit Date	Product Group	Was Exhaled CO Measurements Performed?	Collection Date	Exhaled CO Measurement (ppm)
XXXXXX	Screening	DDMMMYYYY	XX	XXX	DDMMMYYYY	XX

Note: VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.8.2 Vital Signs (Safety Population)

Subject Number	Visit Name	Product Group	Date	Time	Not Done?	Reason for Not Done?	Blood Pressure (mmHg) Systolic/Diastolic	Pulse (bpm)	Respiration (rpm)	Temperature (°F)
XXXXXX	Screening	XX	DDMMMYYYY	HH:MM			XXX/ XX	XX	XX	XX.X
	XXXXXX		DDMMMYYYY	HH:MM			XXX/ XX NCS	XX	XX	XX.X
	XXXXXX		DDMMMYYYY	HH:MM			XXX/ XX	XX CS	XX	XX.X
	XXXX		DDMMMYYYY	HH:MM			XXX/ XX	XX	XX	XX.X

Note: NCS = Not clinically significant, CS = Clinically significant
mmHg = millimeter of mercury, bpm = beats per minute, rpm = respiration per minute

VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.8.3 12-Lead Electrocardiogram (Safety Population)

Subject Number	Visit Name	Product Group	Planned Timepoint?	Date	Time	Was ECG Performed?	Overall Result	Heart Rate (bpm)	PR (msec)	RR (msec)	QRS (msec)	QT (msec)	QTcB* (msec)	QTcF* (msec)	If Abnormal, Specify
XXXXXX	Screening	XX	XXX	DDMMMYYYY	HH:MM	Normal	Normal	XX	XXX	XXX	XX	XXX	XXX	XXX	

Note: QTcB* = QTc corrected using Bazett's correction, QTcF* = QTc corrected using Fridericia's correction,
ANCS = Abnormal, Not Clinically Significant
bpm = beats per minute, msec = millisecond

VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.8.4 Phone Call (Safety Population)

Subject Number	Visit Name	Visit Date	Product Group	Date of Call	Was Tobacco Cessation Information Provided?	Did Subject Need to Return to the Clinic for a Symptom Driven Physical Exam?
X	End of Study	DDMMMYYYY	XX	DDMMMYYYY	XXX	XXX

Note: VLN non-mentholated = Non-mentholated VLN cigarettes
VLN mentholated = Mentholated VLN cigarettes
UB non-mentholated = Subjects' UB non-mentholated filtered cigarettes
UB mentholated = Subjects' UB mentholated filtered cigarettes

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM