Altasciences
CLINICAL RESEARCH
ALGORITHME PHARMA

STATISTICAL ANALYSIS PLAN

For:

22nd Century Group, Inc.

RESEARCH PROTOCOL No. CEG-P9-153

Evaluation of the Abuse Liability of Very Low Nicotine (VLN) Cigarettes with Characterization of Nicotine Exposure Profiles in Adult Smokers

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Version: FINAL 2.0 Amendment 01

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STATISTICAL ANALYSIS PLAN APPROVAL

We have carefully read this Statistical Analysis Plan and agree it contains the necessary information required to handle the statistical analysis of study data.

(b) (6)

2018/08/16
Date

Senior Biostatistician
Algorithme Pharma

Émilie Simard, M.Sc.
Principal Scientist PK/PD
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Date

On behalf of the Sponsor:

(b) (6)

Date

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Justine Zehr
Senior Biostatistician
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2018/08/22
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8/16/18
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VERSION CONTROL

Version Number	Version Date	Author	Description of Significant Changes from Previous Approved Version
DRAFT 0.1	2018/06/13	(b) (6) [redacted] / Émilie Simard	Not Applicable – First Version
DRAFT 0.2	2018/07/03	(b) (6) [redacted] / Émilie Simard	Updates made following first round of comments and shells added
FINAL 1.0	2018/07/19	(b) (6) [redacted] / Émilie Simard	Final version
DRAFT 1.1	2018/08/14	(b) (6) [redacted] / Émilie Simard	Two listings shells added and minor updates in the body text.
FINAL 2.0	2018/08/15	(b) (6) [redacted] / Émilie Simard	Final version Amendment 01

CONTENTS

ABBREVIATIONS

AE	Adverse Event
ANOVA	Analysis of Variance
ATC	Anatomical/Therapeutic/Chemical
BMI	Body Mass Index
CI	Confidence Interval
CS	Clinically Significant
CV	Coefficient of Variation
CSR	Clinical Study Report
ECG	Electrocardiogram
ICF	Informed Consent Form
LSM	Least Square Mean
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Not Clinically Significant
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
SPUEAE	Study Pruduct Use-Emergent Adverse Event
TFLs	Tables, Figures, and Listings
VAS	Visual Analog Scale
VLN	Very Low Nicotine
WHO DDE	World Health Organization Druge Dictionary - Extended

1. INTRODUCTION

This statistical analysis plan (SAP) provides a detailed description of the statistical methods and procedures to be implemented for the analyses of data from Protocol No. 2.0, Amendment No. 1. The analyses described in the SAP are based upon the final amended protocol dated 2018/04/11.

2. STUDY OBJECTIVES

Primary Objective

The primary objective of the study is:

- To evaluate the abuse liability of VLN cigarettes (0.4 mg nicotine/gram of tobacco) relative to own-brand cigarettes and nicotine polacrilex gum under controlled use and uncontrolled use conditions.

Secondary Objective(s)

The secondary objectives of the study are:

- To compare the nicotine pharmacokinetic (PK) profiles of VLN cigarettes relative to own-brand cigarettes and nicotine polacrilex gum under controlled use and uncontrolled use conditions.
- To characterize product use behavior of VLN cigarettes, own-brand cigarettes, and nicotine polacrilex gum.

3. STUDY DESIGN

General Description

This study will be a randomized, two-part, 3-way crossover designed to evaluate the abuse liability, PK, and product use behavior associated with study products, including VLN cigarettes, subjects' own-brand cigarettes, and nicotine polacrilex gum in healthy adult male and female exclusive smokers. The study will enroll generally healthy adult male and female self-affirmed smokers 22 - 65 years of age, inclusive, who fulfill the inclusion and exclusion criteria. Subjects will be current exclusive smokers of combustible, non-menthol cigarettes. The study will consist of 3 phases: Screening, a Confined Assessment Phase consisting of product training session, Part A, and Part B, and an End of Study Phase.

The Screening Phase (Visit 1) will be completed during a clinic visit within 28 days of the Confined Assessment Phase and will consist of a standard medical screen.

Subjects who successfully complete the Screening Phase will return to the clinical unit on Day -1 for check-in and to complete a product trial session. Subjects will engage in a 10-minute product training session with the nicotine polacrilex gum in order to familiarize themselves with the "chew and park" method, which requires subjects to chew the gum until they experience a tingling sensation, park the gum between the cheek and gum until the tingling subsides, and then begin chewing again. On Day -1, subjects will also complete a training session on the pharmacodynamic questionnaires. Subjects will be required to abstain from using nicotine- and tobacco-containing products for approximately 20 hours prior to each product use session in Part A.

Part A will begin on Day 1. Subjects will be randomized to one of three product sequence groups in Part A, which will consist of an ad libitum product use session of each of the 3 study products for 4 hours in a randomized crossover manner (one product per day).

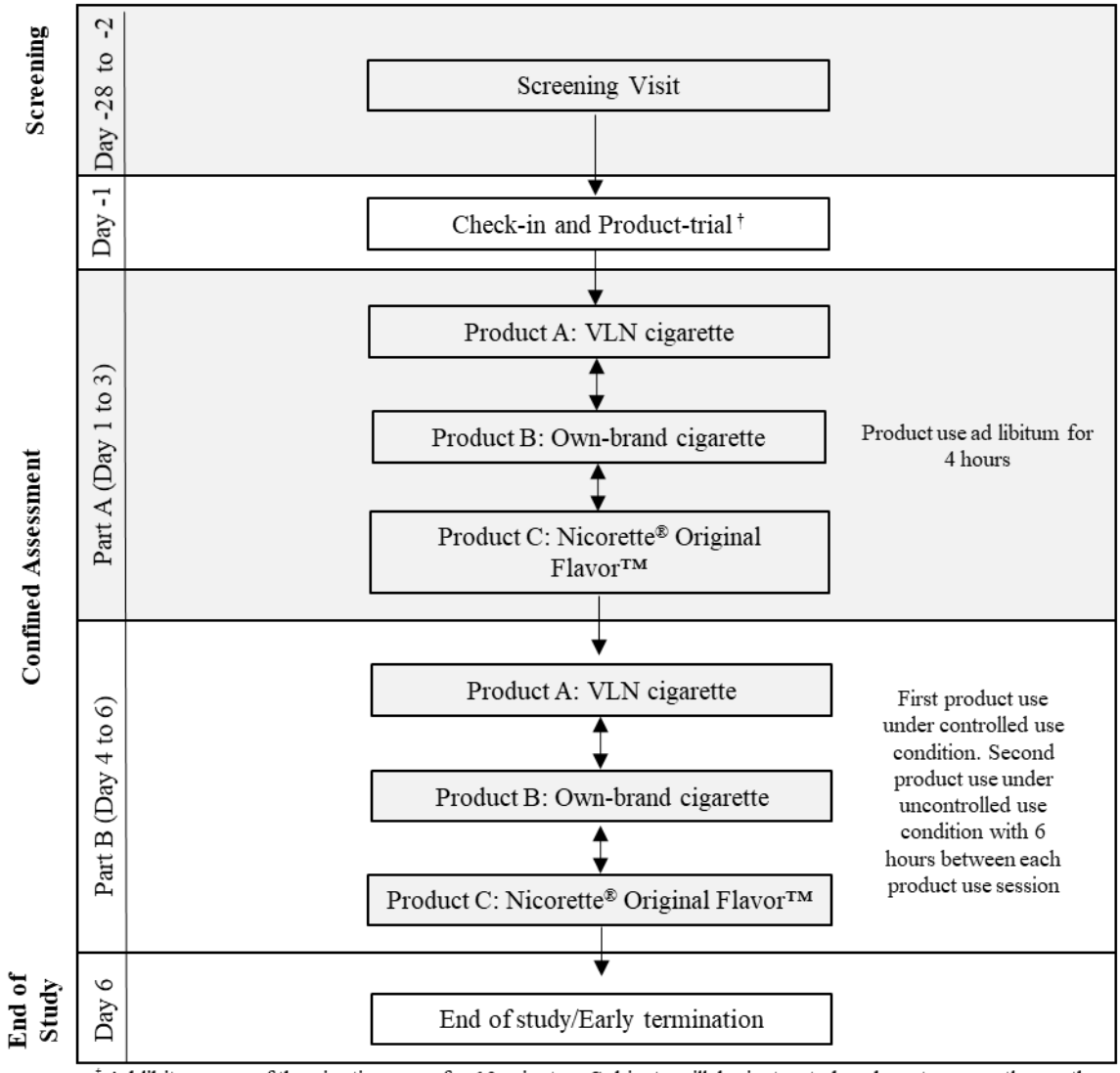
A pharmacodynamic measure ("use product again" visual analog scale [VAS]) will be administered at the end of each ad libitum product use period and product use behaviors (i.e., number of units consumed, duration of gum in mouth) will be collected throughout each ad libitum product use period.

Part B will begin upon completion of Part A. Subjects will be randomized to one of three product sequence groups in Part B, which will consist of 3 study days (Days 4 to 6), with one product per day. Each study day will consist of: 1) Controlled Product Use Session (10 puffs from their own-brand cigarette or VLN cigarette [maximum 3 ± 2 seconds per puff] at approximately 30 ± 5-second interpuff intervals, or chew the nicotine polacrilex gum using the "chew and park" method for 10 minutes); and 2) Uncontrolled Product Use Session (use of one unit of a product ad libitum for 10 minutes). The Controlled Product Use Session and Uncontrolled Product Use Session will be separated by approximately 6 hours. During Part B, pharmacodynamic measures, PK samples, and product use behavior (Uncontrolled Product Use Session only) will be collected at various time points each day.

Safety assessments, including AEs, physical examinations, vital signs (respiratory rate, pulse rate, blood pressure, and oral temperature), electrocardiogram (ECG), clinical laboratory tests (clinical chemistry, hematology, urinalysis, and serology), urine drug screen, and alcohol test will be collected at designated time points throughout the study.

Subjects will be discharged from the clinic on Day 6 once all procedures are completed (or at Early Termination).

Figure 1: Overview of Study Design



† Ad libitum use of the nicotine gum for 10 minutes. Subjects will be instructed on how to correctly use the nicotine gum using the "chew and park" method.

Treatments

Test Product:

- Product A: VLN cigarettes (0.4 mg nicotine/gram of tobacco)

Reference Products:

- Product B: Own-brand non-menthol-flavored combustible cigarettes
- Product C: Nicorette® Original Flavor™ nicotine polacrilex gum (4 mg)

Study procedures

For complete details on the study assessments to be performed for each study period, refer to Appendix A.

Randomization and Unblinding Procedures

Randomization:

Each potential subject will be assigned a unique number in the screening process (subject number). This number will be used to identify the subject throughout the study. Algorithme Pharma Inc. has prepared the randomization schedule with a computer program according to the study design, the number of subjects and the sequence of product use.

On Day 1, subjects will be randomized to one of three sequence groups (ABC, BCA, CAB, where A = VLN cigarette, B=subject's own-brand cigarette; and C= nicotine polacrilex gum), with approximately the same number of subjects per sequence group. On Day 4, subjects will be re-randomized into one of three sequence groups (ABC, BCA, CAB), with approximately the same number of subjects per sequence group.

Blinding:

The study design is not blinded since subjects will know if the product is a VLN cigarette, their own cigarette or a nicotine polacrilex gum. The study product codes will be open to all study staff and to the Sponsor. The randomization code will not be available to the personnel of the bioanalytical facility until the bioanalytical tables have been finalized and audited by the Quality Assurance department.

4. STUDY ENDPOINTS

Pharmacodynamic Parameters

The primary endpoints of this study are the Primary Pharmacodynamic Parameters:

$E_{max\_urge(controlled)}$ and $E_{max\_plst(controlled)}$

Secondary Pharmacodynamic Parameters:

- Ad libitum Product Use (Part A)
  - Use the Product Again VAS score
  - Product use behavior (number of units consumed, time spent per unit, number of inhalations per cigarette, duration of gum in mouth)
- Controlled and Uncontrolled Product Use (Part B)
  - Tobacco/Nicotine Withdrawal Questionnaire
    - $E_{max\_item(controlled)}$ and $E_{max\_item(uncontrolled)}$
  - Direct Effects of Product Questionnaire
    - $E_{max\_item(controlled)}$ and $E_{max\_item(uncontrolled)}$
  - Product use behavior (Uncontrolled Use Sessions; number of inhalations, duration of inhalations [per puff], duration of gum in mouth).

Pharmacokinetic Parameters

$C_{max(controlled)}$, $C_{max(uncontrolled)}$, $AUC_{(controlled)}$, $AUC_{(uncontrolled)}$, $T_{max(controlled)}$, $T_{max(uncontrolled)}$, $Kel_{(controlled)}$, $Kel_{(uncontrolled)}$, $T½_{(controlled)}$ and $T½_{(uncontrolled)}$.

Safety Endpoints

- AEs (incidence, frequency, severity and relationship to product), SAEs, and AEs leading to discontinuation;
- Vital signs (heart rate, blood pressure, respiratory rate, oral temperature);
- 12-lead ECG;
- Clinical laboratory tests (clinical chemistry, hematology, urinalysis);
- Physical examination (complete and brief) findings;
- Concomitant medications.

The details of the safety endpoints' assessment are presented in Section 10.

Sample Size Determination

Sample size estimation was performed on both pharmacodynamic endpoints.

Using a 2-sided Type I error rate at α=0.05 and assuming a mean difference in $E_{max\_urge(controlled)}$ between own-brand cigarette and nicotine polacrilex gum of 15.85 points and standard deviation (SD) of 28.44, 54 completed subjects will be required to detect a significant difference between own-brand cigarette and nicotine polacrilex gum with greater than 80% power. Using a 2-sided Type I error rate at α=0.05 and assuming a mean difference in $E_{max\_plst(controlled)}$ between own-brand cigarette and nicotine polacrilex gum of 35.21 points and SD of 31.82, estimate based on data obtained from the study site, 16 completed subjects will be adequate to detect a significant difference between own-brand cigarette and nicotine polacrilex gum with greater than 80% power.

An appropriate number of subjects will be randomized on Day 1 (Part A) to ensure that a minimum of 54 subjects complete the study. Replacement subjects may be enrolled to ensure that the minimum number of subjects complete the study.

5. ANALYSIS POPULATIONS

The study analysis populations will consist of:

Randomized Population (Part A):

All subjects who are randomized into Part A.

Randomized Population (Part B):

All subjects who are randomized into Part B.

Safety Population:

All randomized subjects who use at least one of the study products after the randomization. The Safety Population will be used for the summary of subject demographics, baseline characteristics, safety information and AEs.

Pharmacodynamic Population:

All subjects who use any study product and have pre-use (Tobacco/Nicotine Withdrawal questionnaire) and at least one post-use (for Tobacco/Nicotine Withdrawal and Direct Effects of Product) VAS score for the Controlled Use Session of Part B. This population will be used for statistical analyses of the pharmacodynamic measures.

Pharmacokinetic Population:

All subjects who use any study product and have pre- and at least one post-use plasma concentration value for the Controlled Use Session of Part B. The PK Population will be used for statistical analyses of the PK parameters.

Completer Population:

All randomized subjects who complete all product use sessions and have pharmacodynamic and PK data in the Controlled Use Session of Part B. Therefore, a subject to be counted as a Completer, he must meet the following three conditions for the controlled product use of Part B: 1) used the three products from all three periods, 2) has PK parameters from all three periods, and 3) had PD data from all three periods. This dataset will be used for analyses of the two primary pharmacodynamic endpoints as a sensitivity analyses to the primary analyses.

6. STATISTICAL METHODOLOGY

All analyses will be conducted using the SAS software, version 9.4.

Adverse events and medical history will be classified using standard MedDRA terminology Version 21.0 or higher.

Prior and concomitant medications will be coded with the WHO-DDE dictionary version Mar 1, 2018 or later.

Summary tables will be presented by product sequence and overall.

In general, the data listings will include all enrolled subjects up to the point of study completion or discontinuation; exceptions will be listings pertaining to a subset of subjects only (e.g., subjects with protocol deviations) or a subset of records/events (e.g., abnormal laboratory values). In all data listings, subject ID will be presented.

Categorical variables will be summarized using the PROC FREQ procedure. Continuous variables will be summarized using the PROC UNIVARIATE procedure – n, mean, standard deviation, median, Q1, Q3, min, max will be presented. For ln-transformed endpoints, geometric mean, geometric standard deviation, and coefficient of variation will also be presented.

The following general comments also apply to all statistical analyses and data presentations:

- Duration variables will be calculated using the general formula: (end date - start date) +1.
- If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table (e.g., a character string is reported for a parameter of the numerical type), a coded value must be appropriately determined and used in the statistical analyses. In general, a value or lower and upper limit of normal range such as '<10' or '≤5' will be treated as '10' or '5' respectively, and a value such as '>100' will be treated as '100'. However, the actual values as reported in the database will be presented in data listings.
- Individual subject listings of all data represented on the CRFs will be provided to facilitate the investigation of tabulated values and to allow for the clinical review of all efficacy and safety parameters.
- When assessments are repeated for a given time point, only the result which is the closest to the dosing time will be included in summary tables

The analyses described in this plan are considered a priori, in that they have been defined prior to database lock. Any analyses performed subsequent to database lock will be considered post hoc and exploratory. Post hoc analyses will be labeled as such in the corresponding statistical output and identified in the CSR.

Analysis Timepoints

Unless otherwise specified, the baseline value will be defined as the last non-missing evaluation prior to the first dose of study medication.

Methods for Handling Missing Data

No imputation of values for missing data will be performed. All data recorded on the case report form will be included in the listings that will accompany the clinical study report. Missing pharmacodynamic data, including reasons for the missing data, will be listed by subject and examined on a case-by-case basis to determine if these affect subject allocation.

7. STUDY SUBJECTS

Unless otherwise specified, summary tables for disposition, major protocol deviations, and demographics and other baseline characteristics will be presented for the Safety Population.

Disposition

Subject disposition will be summarized for all subjects enrolled in this study and for each analysis population, including:

- The number of subjects enrolled;
- The number of subjects randomized;
- The number and percentage of subjects who received study product at each study day;
- The number and percentage of subjects who completed each study part;
- The number and percentage of subjects discontinued from the study by primary reason for discontinuation;
- The number and percentage of subjects included in each of the study populations.

The percentages will be calculated using the number of subjects randomized as denominator.

A listing of subject's disposition will be provided. A listing of subjects included in each of the analysis populations will also be provided.

A listing presenting the subject ID and the corresponding randomization numbers will be provided as well.

Protocol Deviations

A listing of all protocol deviations will be provided. A separate listing will be generated for blood sampling time deviations.

The time of blood sample collection will be calculated according to the product administration schedule. For postdose samples, all deviations from the scheduled sampling time of more than 1 minute for the first 30 minutes and more than 5 minutes for the remaining samples will be reported in the final report. Actual elapsed time from dose administration will be used for evaluation of plasma PK parameters.

Subjects with inclusion/exclusion criteria violation will be presented in a separate listing.

8. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic and Baseline Characteristics

Demographic data and baseline characteristics will be presented in a data listing and summarized in a table by study population. Quantitative assessments to be summarized are age, height, body weight at screening and body mass index (BMI). Subject demographics include sex, age, ethnicity, and race. Age will be calculated from the date of birth to the date that the informed consent form was signed if it is not collected on the CRF. In addition, number of tobacco product used per day as well as the duration of tobacco use (derived as the interval between tobacco use start date and end date) will be summarized by type of tobacco use as well. Responses for smoking history and number of tobacco products used per day will be listed by type of tobacco use in the substance usage listing.

Medical History

Any medical history findings will be recorded and presented in a listing. The listing will include the MedDRA 21.0 coding terms (e.g., SOC and preferred terms).

Medication History

All medications, including prescription, over-the-counter, or herbal therapies used by the subjects will be documented for the 30 days prior to Screening will be recorded and presented as prior medication in a listing. The listing will include the WHO DDE (March 1, 2018) coding terms (e.g., ATC and Preferred Term).

Childbearing Potential and Contraceptive Method

Childbearing potential and, if applicable, contraceptive method will be recorded and presented in a listing for all female subjects.

9. PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Pharmacodynamic

VAS Scores

Responses to Tobacco/Nicotine Withdrawal and Direct Effects of the Product Questionnaires recorded as VAS scores will be treated as continuous variables. Data listings of VAS scores for each questionnaire item will be provided for each subject.

For the Tobacco/Nicotine Withdrawal questionnaire, the reduction in VAS score will be calculated using the difference between pre-use and post-use values at each time point for each treatment (i.e. $VAS_{pre\text{-}use1} - VAS_{post\text{-}use1}$).

Responses to each Tobacco/Nicotine Withdrawal Questionnaire and Direct Effects of Product Questionnaire item, as well as the Tobacco/Nicotine Withdrawal reduction from pre-use, will be summarized by time point for each study product, and product use condition using the following descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, maximum, CV%). Individual and mean figures for the responses to Tobacco/Nicotine Withdrawal Questionnaire (unadjusted and baseline adjusted) and Direct Effects of Product Questionnaire item will be presented using linear scale.

PD Parameters

The following subjective effect parameters will be calculated for each subject and treatment:

Questionnaire	PD Parameter	Definition
Tobacco/Nicotine Withdrawal Questionnaire	$E_{max\_item(controlled)}$	The maximum reduction in VAS score for each item during the first product use in Part B
	$E_{max\_item(uncontrolled)}$	The maximum reduction in VAS score for each item during the second product use in Part B
Direct Effects of Product Questionnaire	$E_{max\_item(controlled)}$	The largest VAS score recorded for the response to each item during the first product use in Part B
	$E_{max\_item(uncontrolled)}$	The largest VAS score recorded for the response to each item during the second product use in Part B

The definition of the different item in each questionnaire is detailed in the table below.

Questionnaire	Item	Question
Tobacco/Nicotine Withdrawal Questionnaire	$E_{max\_urge(controlled)}$ $E_{max\_urge(uncontrolled)}$	Urges to smoke
	$E_{max\_anx(controlled)}$ $E_{max\_anx(uncontrolled)}$	Anxious
	$E_{max\_diffct(controlled)}$ $E_{max\_diffct(uncontrolled)}$	Difficulty Concentrating
	$E_{max\_impat(controlled)}$ $E_{max\_impat(uncontrolled)}$	Impatient
	$E_{max\_crav(controlled)}$ $E_{max\_crav(uncontrolled)}$	Craving a Cigarette

Direct Effect of Product	$E_{max\_plst(controlled)}$ $E_{max\_plst(uncontrolled)}$	Is the product ‘’Pleasant’’ right now?
	$E_{max\_stf(controlled)}$ $E_{max\_stf(uncontrolled)}$	Is the product “Satisfying” right now?
	$E_{max\_calm(controlled)}$ $E_{max\_calm(uncontrolled)}$	Is the product making you feel “Calm” right now?
	$E_{max\_conc(controlled)}$ $E_{max\_conc(uncontrolled)}$	Is the product helping you “Concentrate” right now?
	$E_{max\_awake(controlled)}$ $E_{max\_awake(uncontrolled)}$	Is the product making you feel more “Awake” right now?
	$E_{max\_sick(controlled)}$ $E_{max\_sick(uncontrolled)}$	Is the product making you feel “Sick” right now?
	$E_{max\_hunger(controlled)}$ $E_{max\_hunger(uncontrolled)}$	Is the product reducing your “Hunger” for food right now?
	$E_{max\_more(controlled)}$ $E_{max\_more(uncontrolled)}$	Would you like “More” of the product right now?

The items $E_{max\_urge(controlled)}$ and $E_{max\_plst(controlled)}$ will be the primary endpoints of the study while the remaining items will be secondary endpoints.

Statistical Analysis of Subjective Effect Parameters

A linear mixed effects model for analysis of variance/covariance (Proc Mixed) will be performed on $E_{max\_urge(controlled)}$ and $E_{max\_plst(controlled)}$. The model will include E_{max} as the response variable, sequence, study product, and period as fixed model effects, baseline score as a covariate, and subject nested-within sequence as a random effect. Sequence will be tested using subject nested-within-sequence as the error term. Least square mean (LSM) and 95% confidence interval (CI) for each study product group will be provided. Comparisons will be made for Product A vs. B, A vs. C and B vs. C. The comparison between Product A and Product C will be used as a comparison for internal validity. The LSM difference, p-value and 95% CI of the difference will be provided.

The SAS code for the statistical modeling is:

```
Proc MIXED data=test;
        class subject sequence period product;
        model  Emax = sequence period product baseline / ddfm=KR;
        random subject (sequence) / type=UN
        estimate “Product A vs Product B” product 1 0 -1 /cl alpha=0.05;
        estimate “Product A vs Product C” product 1 0 -1 /cl alpha=0.05;
        estimate “Product B vs Product C” product 0 1 -1 /cl alpha=0.05;
        lsmeans product/cl alpha=0.05;
run;
```

The same model will be used for $E_{max\_urge(uncontrolled)}$ and $E_{max\_plst(uncontrolled)}$, and all E_{max} of other questions in the Tobacco/Nicotine Withdrawal Questionnaire and Direct Effects of Product Questionnaire for the controlled and uncontrolled product uses in Part B. Baseline (pre-use) score will be included as a covariate for all pharmacodynamics measures for which a pre-use score is collected.

The analysis on $E_{max\_urge(controlled)}$ and $E_{max\_plst(controlled)}$ will be based on the pharmacodynamic and the completer populations separately.

Use the Product Again

Responses to Use the Product Again VAS will be summarized by study product using descriptive statistics.

Pharmacokinetic

Concentration Data

Nicotine plasma concentrations produced by the administration of the study products will be determined to establish the PK profile of each treatment.

Concentrations that are below the limit of quantitation (BLQ) will be treated as zero for descriptive statistics.

Nicotine baseline adjusted concentration will be calculated as follows: post-use concentration – pre-use concentration.

Descriptive statistics will be calculated at each individual time point. Plasma concentration data (both unadjusted and baseline-adjusted) will be summarized by treatment using the following descriptive statistics: number of non-missing values (N), minimum (min), arithmetic mean, median, maximum (max), standard deviation (SD) and coefficient of variation (CV%).

The individual plasma concentration/time profiles will be presented using the actual sampling times whereas the mean plasma concentration/time profiles (±SD) will be presented using the nominal sampling times. Concentration profiles will be presented on both linear and semi-log scales.

Pharmacokinetic Parameters

PK parameters will be derived from the plasma nicotine baseline-adjusted concentrations versus time profiles using a NCA, with Phoenix WinNonlin 6.3 (Model 200-202, extravascular). The following PK parameters will be calculated for controlled and uncontrolled use:

PK Parameter	Definition
$C_{max(controlled)}$	Maximum measured plasma nicotine concentration during the Controlled Use Session
$C_{max(uncontrolled)}$	Maximum measured plasma nicotine concentration during the Uncontrolled Use Session
$AUC_{(controlled)}$	Area under the nicotine concentration-time curve calculated using linear trapezoidal summation from time zero (defined as the start of controlled use) to 180 minutes (or the last quantifiable concentration during that interval)
$AUC_{(uncontrolled)}$	Area under the nicotine concentration-time curve calculated using linear trapezoidal summation from time 360 (defined as the start of uncontrolled use) to 540 minutes (or the last quantifiable concentration during that interval)
$T_{max(controlled)}$	Time of the maximum measured plasma nicotine concentration during the Controlled Use Session
$T_{max(uncontrolled)}$	Time of the maximum measured plasma nicotine concentration during the Uncontrolled Use Session
$K_{el(controlled)}$	Apparent first-order terminal nicotine elimination rate constant calculated from a semi-log plot of the plasma concentration-time curve of the Controlled Use Session
$K_{el(uncontrolled)}$	Apparent first-order terminal nicotine elimination rate constant calculated from a semi-log plot of the Uncontrolled Use Session

$T_{½(controlled)}$	Apparent first-order terminal nicotine elimination half-life calculated as 0.693/Kel of the plasma concentration-time curve from time zero (defined as the start of controlled use) to 180 minutes
$T_{½(uncontrolled)}$	Apparent first-order terminal nicotine elimination half-life calculated as 0.693/Kel of the plasma concentration-time curve from time 360 (defined as the start of uncontrolled use) to 540 minutes

Actual sampling times (relative to the corresponding administration time), will be used for calculation of PK parameters. In the case where less than 3 consecutive measurable concentrations are observed, AUC will not be estimated for that profile.

The trapezoidal rule (linear trapezoidal linear interpolation) will be used to estimate the area under the curve, and the terminal phase will be estimated by maximizing the coefficient of determination estimated from the log-linear regression model. However, t½ and K_{el} will not be estimated for individual concentration-time profiles where the terminal log-linear phase cannot be reliably characterized (log linear terminal phase with R^2 of at least 0.8 and using minimum of three data points not including C_{max}).

Plasma nicotine PK parameters will be summarized by treatment using the following descriptive statistics N, min, arithmetic mean, median, max, SD and CV%.

Data Presentation and Precision

Individual raw PD VAS scores and PK concentrations will be displayed with the same precision as received as per lab data.

Precision for individual PD and PK parameters will be displayed as follow:

- E_{max}, C_{max} and AUCs with the same precision as the raw data
- PK parameters associated with time (e.g. T_{max}, and $T_{1/2}$) with 2 decimal places
- R2 and K_{el} with 4 decimal places

Summary statistics for VAS scores, PD parameters, PK concentration and parameters will be displayed with the same precision as the individual values, with the exception of CV% which will be presented with 1 decimal place and N with 0 decimal place.

Statistical Analysis of PK Parameters

A linear mixed model for analysis of variance (Proc Mixed) will be performed on the baseline-adjusted log transformed nicotine PK parameters in Part B ($C_{max(controlled)}$, $C_{max(uncontrolled)}$, $AUC_{(controlled)}$ and $AUC_{(controlled)}$). The model will include sequence, study product, and period as fixed effects and subject nested-within sequence as a random effect. Sequence will be tested using subject nested-within sequence as the error term. From each model, the geometric LSM and 95% confidence intervals will be calculated for each study product. Separate analyses will be performed on the parameters calculated for the Controlled and Uncontrolled Use sessions. Geometric mean ratios for each pair comparison, 95% confidence interval and p value will be provided.

The SAS codes for the model will be as follows:

```
Proc MIXED data=test;
      class subject sequence period product;
      model  log(Cmax0-180) = sequence period product / ddfm=KR;
      random  subject (sequence) / type=UN;
      estimate “Product A vs Product B”  product 1 -1 0 /cl alpha=0.05;
      estimate “Product A vs Product C”  product 1 0 -1 /cl alpha=0.05;
      estimate “Product B vs Product C”  product 0 1 -1 /cl alpha=0.05;
      lsmeans product/cl alpha=0.05;
run;
```

The Hodges-Lehmann’s method will be used to estimate the median differences and the 95% confidence interval of T_{max} and T½ between the products for controlled and uncontrolled use.

10. SAFETY

Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation subject administered aproduct and may not necessarily have a causal relationship with the administered treatment. An AE can, therefore, be any unfavorable and unintended sign (including a clinically significant laboratory abnormality), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

A study product use-emergent adverse event (SPUEAE is defined as an AE that is starting or worsening at the time of or after study product administration (excluding product trial). An AE that occurs during the washout period between study products is considered study product use emergent to the last study product given.

SPUEAEs will be assigned to a product based on the time of occurrence in relation to the last product used prior to the onset of the SPUAE. SPUAEs will be assigned using the following rules:

- SPUAE will be assigned to the last product used by the subject where the date and time of the last product use is on or before of the start date and time of the event. Such assignment will be performed irrespective of any washout period between the start and stop dates of the SPUEAE.
- Any SPUEAE started after the discharge and during the follow-up period will be assigned to the last product that the subject has used during last cycle.

As an overall summary of AEs, the following will be presented by product use and overall in each part and by product use and overall regardlees the study part:

- Number of reported AEs;
- Number and percentage of subjects experiencing AEs;
- Number of reported SPUEAEs;
- Number and percentage of subjects experiencing SPUEAEs;
- Number and percentage of SPUEAEs by relationship to study product;
- Number and percentage of SPUEAEs by severity;
- Number of reported study product use-emergent serious adverse events (SPUSAEs);
- Number and percentage of subjects experiencing SPUSAEs;
- Number and percentage of subjects experiencing SPUEAEs leading to discontinuation; and
- SPUEAEs with an outcome of death.

Frequencies of subjects with study product use-emergent AEs and incidence of those events, regardless of relationship to study product will be summarized by study product and sorted by system organ class. Frequencies of subjects with study product use-emergent serious adverse events and incidence of events will be likewise summarized. Frequencies of study product use-emergent adverse events will be summarized by severity and by relationship in separate tables.

Subject listings of all AEs including verbatim term, preferred term, study product, severity and relationship to study product will be provided. AEs leading to withdrawal and SAEs will also be presented in separate listings.

Concomitant Medications

Medications intake during the study will be recorded and presented in a listing. The medication name, dose, units, route, indication or reason taken, code, date and time taken will be presented. The listing will include the WHO DDE coded terms (e.g., ATC and preferred terms).

Extent of Exposure

Study product use will be presented in separate listings for each study part and for part B, for each session.

Date, start and end time as well as duration of time a product is used (time spent per cigarette and duration of gum in mouth) will be presented for all entries.

For part A, number of products dispensed and returned will be presented.

For part B uncontrolled usual brand or VLN cigarettes, number dispensed and returned, start and stop times for inhalation, and duration of inhalation will be presented. For part B controlled usual brand or VLN cigarettes, start and stop time for inhalation, inhalation duration, and missed inhalations (and reason for miss) will be presented. For Part B nicotine polacrilex gum, only date, start and end timewill be presented.

Duration of time a product is used, number of inhalations (puffs), and duration of inhalation (per puff) per cigarette for own-brand and VLN cigarettes will also be summarized.

Clinical Laboratory Evaluations

Planned laboratory analyses include:

Clinical Laboratory Test	Parameters/Details
General biochemistry:	Sodium, potassium, glucose (random), creatinine, total protein, blood urea nitrogen (BUN), albumin, total bilirubin, alanine transferase, aspartate transferase, lactic dehydrogenase, gamma glutamyl transferase, alkaline phosphatase, creatine phosphokinase, FSH [a]
Hematology:	Hematocrit, hemoglobin, red blood cell count, total and differential (absolute) white blood cell count, platelets
Serology (screening visit only):	Hepatitis B surface antigen (HbsAg), anti-hepatitis C antibodies (HCVAb), human immunodeficiency virus (HIV)
Urinalysis:	Color, pH, snpecific gravity, ketones, protein, glucose, bilirubin, nitrite, urobilinogen, occult blood, microscopic examination of sediment, *only if urinalysis dipstick results are abnormal*
Urine drug screen:	Tetrahydrocannabinol (THC), opioids (morphine, codeine, heroin, hydrocodone, hydromorphone, and oxycodone), amphetamines, cocaine, and benzodiazepines.

[a] Postmenopausal women at Screening only.

Separate listings of all individual data for general biochemistry, hematology, urinalysis, serology and urine drug screen will be presented. Abnormal findings will be flagged in the listings.

Biochemistry, hematology and urinalysis results will be summarized by laboratory test and visit.

Subject listings of abnormal on-study laboratory values will be provided. Similarly, clinically significant on-study laboratory data will be presented in a second listing.

Vital Signs

Vital signs measurements consist of blood pressure, pulse rate, body temperature, and respiratory rate and will be presented in listings.

Descriptive summaries of vital signs will be presented by vital sign test and visit.

Subject listing of abnormal on-study vital signs values (Out-of-Range – NCS or CS) will be provided. Similarly, CS on-study vital signs values (Out-of-Range – CS) will be presented in a second listing.

Physical Examination Findings

The complete physical examination includes a review of the following: general appearance, head, eyes, ears, nose, throat (HEENT), neck, cardiovascular, respiratory, gastrointestinal, neurological, musculoskeletal/extremities, and skin. The brief physical examination includes a review of general appearance, respiratory, cardiovascular, and gastrointestinal systems. Results of complete and brief physical examinations will be presented in a listing.

Subject listing of abnormal on-study physical examination assessments (Abnormal – not clinically significant [NCS] or clinically significant [CS]) will be provided. Similarly, clinically significant on-study physical examination assessments (Abnormal – CS) will be presented in a second listing.

Electrocardiogram

Electrocardiograms (ECGs) parameters (heart rate, PR interval, QRS duration, QT interval and QTcF interval) as well as overall assessments (Normal, Abnormal– NCS or Abnormal – CS) will be listed.

ECGs parameters will also be summarized by parameter and visit.

Subject listing of abnormal on-study ECG overall assessment (Abnormal – NCS or CS) will be provided. Similarly, CS on-study ECG overall assessment values (Abnormal – CS) will be presented in a second listing.

11. INTERIM ANALYSES AND DATA SAFETY MONITORING

There is no interim analysis or safety data monitoring planned for this study.

12. CHANGES TO PROTOCOL-SPECIFIED ANALYSES

There are no changes to protocol or to specified analyses for this study.

13. GENERAL INFORMATION RELATED TO DATA PRESENTATIONS

All programs used to generate statistical analyses will be validated according to Algorithme Pharma's standard operating procedures.

TFLs will be displayed on letter size paper, 8 ½ inches by 11 inches, using the Courier New font.

In general, summary statistics for raw variables (i.e., variables measured at the study site or central laboratory) will be displayed as follows: minima and maxima will be displayed to the same number of decimal places as the raw data. Means, medians, and quartiles will be displayed to one additional decimal place and standard deviations will be displayed to two additional decimal places.

Percentages will be displayed to one decimal place. Percentages between 0 and 0.1 (exclusive) will be displayed as '<0.1'. P-values will be displayed to 3 decimal places. P-values that are less than 0.001 will be displayed as '<0.001'.

The numbers of decimal places for summary statistics of derived variables (i.e., variables that are not measured by the study site but are calculated for analysis based on other measured variables) will be determined on a case by case basis. In general, minima and maxima will be displayed to the commonly used unit of precision for the parameter. Means, medians, quartiles, and confidence limits will be displayed to one additional decimal place and standard deviations will be displayed to two additional decimal places.

The formats and layouts of TFLs are provided in subsequent sections. Actual formats and layouts may be altered slightly from those presented in the templates as necessary to accommodate actual data or statistics. Minor format changes will not require updates to the SAP.

The tables and listings listed below are common data displays. Their numbering and general content follow the ICH E3 guidelines.

PLANNED FIGURES

Pharmacokinetic Data

Section 14.2.1	Summary of Plasma Concentration and PK Parameters
Section 14.2.1.1	Summary of Concentration Data
Figure 14.2.1.1.1	Mean (±SD) Unadjusted Plasma Nicotine Concentration Following Administration of Product A, B and C – Controlled Use (Linear Scale)
Figure 14.2.1.1.2	Mean (±SD) Unadjusted Plasma Nicotine Concentration Following Administration of Product A, B and C – Controlled Use (Semi-Log Scale)
Figure 14.2.1.1.3	Mean (±SD) Unadjusted Plasma Nicotine Concentration Following Administration of Product A, B and C – Uncontrolled Use (Linear Scale)
Figure 14.2.1.1.4	Mean (±SD) Unadjusted Plasma Nicotine Concentration Following Administration of Product A, B and C – Uncontrolled Use (Semi-Log Scale)
Figure 14.2.1.1.5	Mean (±SD) Baseline-Adjusted Plasma Nicotine Concentration Following Administration of Product A, B and C – Controlled Use (Linear Scale)
Figure 14.2.1.1.6	Mean (±SD) Baseline-Adjusted Plasma Nicotine Concentration Following Administration of Product A, B and C – Controlled Use (Semi-Log Scale)
Figure 14.2.1.1.7	Mean (±SD) Baseline-Adjusted Plasma Nicotine Concentration Following Administration of Product A, B and C – Uncontrolled Use (Linear Scale)
Figure 14.2.1.1.8	Mean (±SD) Baseline-Adjusted Plasma Nicotine Concentration Following Administration of Product A, B and C – Uncontrolled Use (Semi-Log Scale)

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Figure 14.2.3.1.1	Mean Tobacco/Nicotine Withdrawal Questionnaire Responses Following Administration of Product A, B and C – Controlled Use (Linear Scale)
Figure 14.2.3.1.2	Mean Tobacco/Nicotine Withdrawal Questionnaire Responses Following Administration of Product A, B and C – Uncontrolled Use (Linear Scale)
Figure 14.2.3.1.3	Mean Tobacco/Nicotine Withdrawal Questionnaire Reduction in VAS score Following Administration of Product A, B and C – Controlled Use (Linear Scale)
Figure 14.2.3.1.4	Mean Tobacco/Nicotine Withdrawal Questionnaire Reduction in VAS score Following Administration of Product A, B and C – Uncontrolled Use (Linear Scale)
Figure 14.2.3.1.5	Mean Direct Effects of Product Questionnaire Responses Following Administration of Product A, B and C – Controlled Use (Linear Scale)
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Table 14.1.1.3	Subject Disposition (Randomized Population [Part B])
Table 14.1.1.4	Subject Disposition Characteristics (Safety Population)
Table 14.1.1.5	Subject Disposition (Pharmacodynamic Population)
Table 14.1.1.6	Subject Disposition (Pharmacokinetic Population)

Table 14.1.1.7	Subject Disposition (Completer Population)
Table 14.1.2.1	Summary of Demographic Characteristics (Randomized Population [Part A])
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Table 14.1.2.3	Summary of Demographic Characteristics (Safety Population)
Table 14.1.2.4	Summary of Demographic Characteristics (Pharmacodynamic Population)
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Table 14.1.2.6	Summary of Demographic Characteristics (Completer Population)
Table 14.1.3	Summary of Tobacco Use History (Safety Population)
Table 14.1.4.1	Summary of Product Use Part A (Safety Population)
Table 14.1.4.2	Summary of Second Product Use Part B (Safety Population)

Pharmacokinetic Data

Tables in this section are based on the pharmacokinetic population unless otherwise stated.

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Table 14.2.1.1.1	Summary of Unadjusted Plasma Nicotine Concentration Following Administration of Product A – Controlled Use
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Pharmacodynamic Data

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Safety Data

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Table 14.3.1.4.3	Summary of Study Product Use-Emergent Adverse Events by System Organ Class, MedDRA Preferred Term and Severity – Overall
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Listing 16.2.2.1	Listing of Blood Sampling Time Deviations
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APPENDIX A

STUDY SCHEDULE

	Screening	Check-in	Part A	Part B																End of Study/ET
Day:	**-28 to –2**	**-1**	**1 to 3**	**4 to 6 (Daily controlled use and uncontrolled use sessions)**																**6**
Assessment				**Assessment timepoints (minutes[a])**																
Informed consent	X																			
Demographics	X																			
Medical history	X																			
Review of eligibility	X	X																		
Physical examination	X	X[b]																		X[b]
Height, weight, BMI	X																			
HIV, Hepatitis B/C	X																			
Pregnancy test	X[c]	X[d]																		

NOTE: Pre-use assessments (not including PK) may be conducted up to 60 minutes prior to product use. When assessments coincide at any given timepoint during a product use session, the order of assessments should be pharmacodynamics assessments followed by PK. The pharmacodynamic assessments should be conducted at the nominal timepoint (±2 minutes up to 30 minutes postdose and ±5 minutes postdose thereafter). AE=adverse event; BMI=body mass index; ECG=electrocardiogram; ET=early termination; FSH=follicle stimulating hormone; HIV=human immunodeficiency virus; pre=pre-use

[a] All listed timepoints are minutes after the start of product use
[b] Abbreviated (symptom-directed) physical examination performed at the investigator's discretion
[c] Serum pregnancy test
[d] Urine pregnancy test

	Screening	Check-in	Part A	Part B																End of Study/ET
Day:	**-28 to –2**	**-1**	**1 to 3**	**4 to 6 (Daily controlled use and uncontrolled use sessions)**																**6**
Assessment				**Assessment timepoints (minutes[a])**																
FSH (post-menopausal women)	X																			
Vital signs[e]	X	X																		X
Oral temperature	X	X																		X
12-lead ECG	X																			X
Urine cotinine screen	X																			
Urine drug and alcohol test	X	X																		
Clinical laboratory tests[f]	X																			X
Concomitant medications	X	X	X	<--------- Recorded throughout --------->																X
AE Monitoring[g]	X	X	X	<--------- Recorded throughout --------->																X
Randomization			pre[h]	pre[i]																

[e] Vital signs include respiratory rate, pulse rate and blood pressure
[f] Clinical laboratory assessments include hematology, biochemistry, and urinalysis
[g] Spontaneous AE reporting is continuous throughout the study, beginning with the time the subject gives informed consent; however, at regular intervals, AE checks will be performed using a non-leading question.
[h] Day 1 only
[i] Day 4 only

	Screening	Check-in	Part A	Part B																End of Study/ET
Day:	**-28 to –2**	**-1**	**1 to 3**	**4 to 6 (Daily controlled use and uncontrolled use sessions)**																**6**
Assessment				**Assessment timepoints (minutes[a])**																
Product use		X[j]	X[k]		<0[l]	-	-	-	>											
PK sampling[m]				pre		2	5	7	10	12	15	20	30	45	60	90	120	150	180	
Pharmacodynamic Training/practice[n]		X																		
Tobacco/Nicotine Withdrawal Questionnaire[o]				pre			5				15		30		60	90				
Direct Effects of Product Questionnaire[o]				pre			5				15		30		60	90				
Use the product again VAS			X[p]													90[o]				

[j] Trial of 4 mg nicotine polacrilex gum for 10 minutes
[k] Product use under ad libitum condition for 4 hours on each day
[l] First product under controlled use condition manner (10 puffs [maximum 3 ± 2 seconds per puff] with approximately 30-second inter-puff-intervals for cigarettes and 10 minutes “chew and park” for nicotine polacrilex gum) and second product under uncontrolled use condition for approximately 10 minutes (ad libitum) with approximately 6 hours in between 1st and 2nd use sessions
[m] Blood samples collected at same time points following the start of the 1st and 2nd product use sessions. Pre-product use samples should be collected within approximately 5 minutes prior to the start of product use, all other time points should be taken within ± 1 minute for the first 30 minutes and ±5 minutes from the nominal time for all other time points (except when coinciding with PD testing). Actual time of blood draw will be recorded.
[n] Additional PD training sessions may be performed throughout the study, as necessary.
[o] Administered at same time points following the start of the 1st and 2nd product use sessions
[p] Questionnaire administered at end of each product use session, within 10 minutes of completing the product use session (i.e., 4 hours ± 10 minutes)

	Screening	Check-in	Part A	Part B																End of Study/ET
Day:	**-28 to –2**	**-1**	**1 to 3**	**4 to 6 (Daily controlled use and uncontrolled use sessions)**																**6**
Assessment				**Assessment timepoints (minutes[a])**																
Amount of product used			X[q]		<[r]	-	-	-	>											
Tobacco cessation information																				X
Admission		X																		
Discharge																				X

[q] Number of units consumed and duration of gum in mouth
[r] Uncontrolled Product Use Sessions only; number of inhalations per cigarette, duration of inhalations [per puff], duration of gum in mouth

APPENDIX B

TABLE SHELLS

Table 14.1.1.1
Summary of Subject Disposition
(All Subjects)

			Sequence 1	Etc	Overall
Subjects Enrolled [N]					xx
Subjects Randomized [N]			xx	xx	xx
Subjects Who Received Study Product [n(%)]	Study Day 1	Yes	xx (xx.x)	xx (xx.x)	
		No	xx (xx.x)	xx (xx.x)	
	Etc.	Yes	xx (xx.x)	xx (xx.x)	
		No	xx (xx.x)	xx (xx.x)	
	Study Day 6	Yes	xx (xx.x)	xx (xx.x)	
		No	xx (xx.x)	xx (xx.x)	
Subjects Who Completed the Study [n(%)]		Yes	xx (xx.x)	xx (xx.x)	xx (xx.x)
		No	xx (xx.x)	xx (xx.x)	xx (xx.x)
If No, Reason for Early Withdrawal [n(%)]		Reason 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Reason 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Etc.	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects Included in Randomized Population (Part A) [n(%)]			xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects Included in Randomized Population (Part B) [n(%)]			xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects Included in Safety Population [n(%)]			xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects Included in Pharmacodynamic Population [n(%)]			xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects Included in Pharmacokinetic Population [n(%)]			xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects Included in Completer Population [n(%)]			xx (xx.x)	xx (xx.x)	xx (xx.x)

Note(s): The percentages are based on the number of randomized subjects;

Date: VERSION - YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

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Similar Tables:
Table 14.1.1.2    Summary of Subject Disposition (Randomized Population [Part A])
Table 14.1.1.3    Summary of Subject Disposition (Randomized Population [Part B])
Table 14.1.1.4    Summary of Subject Disposition (Safety Population)
Table 14.1.1.5    Summary of Subject Disposition (Pharmacodynamic Population)
Table 14.1.1.6    Summary of Subject Disposition (Pharmacokinetic Population)
Table 14.1.1.7    Summary of Subject Disposition (Completer Population)
```

Table 14.1.2.1
Summary of Demographic Characteristics
(Randomized Population [Part A])

		Sequence 1 (N=XX)	Etc (N=XX)	Overall (N=XX)
Age (years)	N	xx	xx	xx
	Mean (SD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Median	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx
Gender [n(%)]	MALE	xx (xx.x)	xx (xx.x)	xx (xx.x)
	FEMALE	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ethnicity [n(%)]	HISPANIC/LATINO	xx (xx.x)	xx (xx.x)	xx (xx.x)
	NOT HISPANIC/NOT LATINO	xx (xx.x)	xx (xx.x)	xx (xx.x)
Race [n(%)]	RACE1	xx (xx.x)	xx (xx.x)	xx (xx.x)
	RACE2	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Etc.	xx (xx.x)	xx (xx.x)	xx (xx.x)
	MULTIPLE RACE	xx (xx.x)	xx (xx.x)	xx (xx.x)
Weight (kg)	N	xx	xx	xx
	Mean (SD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Median	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx
Height (cm)	N	xx	xx	xx
	Mean (SD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Median	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx
Body Mass Index (kg/m^2)	N	xx	xx	xx
	Mean (SD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Median	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

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Similar Tables:
Table 14.1.2.2    Summary of Demographic Characteristics (Randomized Population [Part B])
Table 14.1.2.3    Summary of Demographic Characteristics (Safety Population)
Table 14.1.2.4    Summary of Demographic Characteristics (Pharmacodynamic Population)
Table 14.1.2.5    Summary of Demographic Characteristics (Pharmacokinetic Population)
Table 14.1.2.6    Summary of Demographic Characteristics (Completer Population)
```

Table 14.1.3
Summary of Tobacco Use History
(Safety Population)

	Tobacco Product		Product Trial (N=XX)	Overall (N=XX)
Number of Tobacco Product Used Per Day	Cigarette	N	xx	xx
		Mean (SD)	xx (xx.x)	xx (xx.x)
		Median	xx.x	xx.x
		Min, Max	xx, xx	xx, xx
	Etc…	N	xx	xx
		Mean (SD)	xx (xx.x)	xx (xx.x)
		Median	xx.x	xx.x
		Min, Max	xx, xx	xx, xx
Duration of Tobacco Product Using (years)	Cigarette	N	xx	xx
		Mean (SD)	xx (xx.x)	xx (xx.x)
		Median	xx.x	xx.x
		Min, Max	xx, xx	xx, xx
	Etc…	N	xx	xx
		Mean (SD)	xx (xx.x)	xx (xx.x)
		Median	xx.x	xx.x
		Min, Max	xx, xx	xx, xx

Programming Note: Duration of Tobacco Product Using = number of years between tobacco use start date and end date.

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Table 14.1.4.1
Summary of Product Use Part A
(Safety Population)

		Study Product A	Study Product B	Study Product C
Number of Product Used	N	xx	xx	xx
	Mean (SD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Median	xx.x	xx.x	xx.x
	Q1, Q3	xx, xx	xx, xx	xx, xx
	Min, Max	xx, xx	xx, xx	xx, xx
Duration of Product Use	N	xx	xx	xx
	Mean (SD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Median	xx.x	xx.x	xx.x
	Q1, Q3	xx, xx	xx, xx	xx, xx
	Min, Max	xx, xx	xx, xx	xx, xx

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Table 14.1.4.2
Summary of Second Product Use Part B
(Safety Population)

		Study Product A	Study Product B	Study Product C
Total Number of Inhalations per Subject	N	xx	xx	
	Mean (SD)	xx (xx.x)	xx (xx.x)	
	Median	xx.x	xx.x	
	Q1, Q3	xx, xx	xx, xx	
	Min, Max	xx, xx	xx, xx	
Duration of Inhalations	N	xx	xx	
	Mean (SD)	xx (xx.x)	xx (xx.x)	
	Median	xx.x	xx.x	
	Q1, Q3	xx, xx	xx, xx	
	Min, Max	xx, xx	xx, xx	
Average Duration of Inhalations per Subject	N	xx	xx	
	Mean (SD)	xx (xx.x)	xx (xx.x)	
	Median	xx.x	xx.x	
	Q1, Q3	xx, xx	xx, xx	
	Min, Max	xx, xx	xx, xx	
Total Duration of Inhalations per Subject	N	xx	xx	
	Mean (SD)	xx (xx.x)	xx (xx.x)	
	Median	xx.x	xx.x	
	Q1, Q3	xx, xx	xx, xx	
	Min, Max	xx, xx	xx, xx	
Duration of Gum Product Use	N			xx
	Mean (SD)			xx (xx.x)
	Median			xx.x
	Q1, Q3			xx, xx
	Min, Max			xx, xx

Programming Note: The N for Duration of Inhalations = Total puff count of the product group.
N for Average and Total Duration of Inhalations per Subject = Number of subjects in each product group.

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Table 14.3.1.1.1
Summary of Adverse Events – Part A
(Safety Population)

Parameter	Study Product A (N=XX)	Study Product B (N=XX)	Study Product C (N=XX)	Part A Overall (N=XX)
Adverse Events Reported [n]				
Subjects With At Least One AE [n(%)] [1]				
Study Product Use-Emergent Adverse Events (SPUEAEs) Reported [n]	xx	xx	xx	xx
Subjects With At Least One SPUEAE [n(%)] [1]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
SPUEAEs Relationship [2]				
Not Related [n(%)]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Unlikely [n(%)]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Possible [n(%)]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Likely [n(%)]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Definitely [n(%)]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
SPUEAEs Severity/Intensity [2]				
Mild [n(%)]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate [n(%)]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe [n(%)]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Study Product Use-Emergent Serious Adverse Events (SPUESAEs) Reported [n] [2]	xx	xx	xx	xx
Subjects With At Least One SPUESAE [n(%)][1]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
SPUEAEs Leading To Study Discontinuation Reported [n] [2]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
SPUEAEs Leading To Death Reported [n] [2]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

[1] Percentages are based on the number of subjects in the Safety Population in each Study Product group.
[2] Percentages are based on the total number of Study Product Use-Emergent adverse events reported in each Study Product group.
Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Table 14.3.1.1.2
Summary of Adverse Events – Part B
(Safety Population)

Parameter	Study Product A (N=XX)	Study Product B (N=XX)	Study Product C (N=XX)	Part B Overall (N=XX)
Study Product Use-Emergent Adverse Events (SPUEAEs) Reported [n]	xx	xx	xx	xx
Subjects With At Least One SPUEAE [n(%)] [1]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
SPUEAEs Relationship [2]				
Not Related [n(%)]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Unlikely [n(%)]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Possible [n(%)]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Likely [n(%)]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Definitely [n(%)]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
SPUEAEs Severity/Intensity [2]				
Mild [n(%)]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate [n(%)]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe [n(%)]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Study Product Use-Emergent Serious Adverse Events (SPUESAEs) Reported [n] [2]	xx	xx	xx	xx
Subjects With At Least One SPUESAE [n(%)][1]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
SPUEAEs Leading To Study Discontinuation Reported [n] [2]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
SPUEAEs Leading To Death Reported [n] [2]	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

[1] Percentages are based on the number of subjects in the Safety Population in each Study Product group.
[2] Percentages are based on the total number of Study Product Use-Emergent adverse events reported in each Study Product group.
Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Similar Table:
Table 14.3.1.1.3 Summary of Adverse Events – Overall

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Table 14.3.1.2.1
Summary of Study Product Use-Emergent Adverse Events by System Organ Class and MedDRA Preferred Term – Part A
(Safety Population)

System Organ Class MedDRA Preferred Term	Study Product A (N=XX)		Study Product B (N=XX)		Study Product C (N=XX)	
	Subjects [n(%)]	Events [n]	Subjects [n(%)]	Events [n]	Subjects [n(%)]	Events [n]
Any SPUEAE	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
System Organ Class 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
MedDRA Term 11	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
MedDRA Term 12	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
MedDRA Term 13	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
System Organ Class 2	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
MedDRA Term 21	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
MedDRA Term 22	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
MedDRA Term 23	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Etc.	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx

Note(s): For the subject counts, each Study Product Use-Emergent adverse event is counted only once for each subject within each System Organ Class and MedDRA Preferred Term.

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Similar Tables:
Table 14.3.1.2.2 Summary of Study Product Use-Emergent Adverse Events by System Organ Class and MedDRA Preferred Term – Part B
Table 14.3.1.2.3 Summary of Study Product Use-Emergent Adverse Events by System Organ Class and MedDRA Preferred Term – Overall

Table 14.3.1.3.1
Summary of Serious Study Product Use-Emergent Adverse Events by System Organ Class and MedDRA Preferred Term
(Safety Population)

System Organ Class MedDRA Preferred Term	Study Product A (N=XX)		Study Product B (N=XX)		Study Product C (N=XX)	
	Subjects [n(%)]	Events [n]	Subjects [n(%)]	Events [n]	Subjects [n(%)]	Events [n]
Any Serious SPUEAE	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
System Organ Class 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
MedDRA Term 11	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
MedDRA Term 12	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
MedDRA Term 13	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
System Organ Class 2	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
MedDRA Term 21	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
MedDRA Term 22	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
MedDRA Term 23	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Etc.	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx

Note(s): For the subject counts, each Study Product Use-Emergent adverse event is counted only once for each subject within each System Organ Class and MedDRA Preferred Term.

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Similar Tables:
Table 14.3.1.3.2 Summary of Serious Study Product Use-Emergent Adverse Events by System Organ Class and MedDRA Preferred Term – Part B
Table 14.3.1.3.3 Summary of Serious Study Product Use-Emergent Adverse Events by System Organ Class and MedDRA Preferred Term – Overall

Table 14.3.1.4.1
Summary of Study Product Use-Emergent Adverse Events by System Organ Class, MedDRA Preferred Term and Severity
(Safety Population)

System Organ Class MedDRA Preferred Term	Study Product A (N=XX)			Study Product B (N=XX)			Study Product C (N=XX)		
	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe
Any SPUEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
System Organ Class 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
MedDRA Term 11	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
MedDRA Term 12	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
MedDRA Term 13	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
System Organ Class 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
MedDRA Term 21	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
MedDRA Term 22	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
MedDRA Term 23	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Etc.	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note(s): For the subject counts, each Study Product Use-Emergent adverse event is counted only once for each subject within each System Organ Class and MedDRA Preferred Term.

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Similar Tables:

Table 14.3.1.4.2	Summary of Study Product Use-Emergent Adverse Events by System Organ Class, MedDRA Preferred Term and Severity – Part B
Table 14.3.1.4.3	Summary of Study Product Use-Emergent Adverse Events by System Organ Class, MedDRA Preferred Term and Severity – Overall

Table 14.3.1.5.1
Summary of Study Product Use-Emergent Adverse Events by System Organ Class, MedDRA Preferred Term and Relationship
(Safety Population)

System Organ Class MedDRA Preferred Term	Study Product A (N=XX)					Etc… (N=XX)				
	Not Related	Unlikely	Possible	Likely	Definitely	Not Related	Unlikely	Possible	Likely	Definitely
Any SPUEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
System Organ Class 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
MedDRA Term 11	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
MedDRA Term 12	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
MedDRA Term 13	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
System Organ Class 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
MedDRA Term 21	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
MedDRA Term 22	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
MedDRA Term 23	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Etc.	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Programming Note: SPUEAE will also be summarized for Study Product B and Study Product C.

Note(s): For the subject counts, each Study Product Use-Emergent adverse event is counted only once for each subject within each System Organ Class and MedDRA Preferred Term.

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Similar Tables:

Table 14.3.1.5.2	Summary of Study Product Use-Emergent Adverse Events by System Organ Class, MedDRA Preferred Term and Relationship – Part B
Table 14.3.1.5.3	Summary of Study Product Use-Emergent Adverse Events by System Organ Class, MedDRA Preferred Term and Relationship – Overall

Table 14.3.2.1
Listing of Deaths, Other Serious and Significant Adverse Events
(Safety Population)

Subject Id	Study Part/Day/ Study Product/ AE #	SOC MedDRA Preferred Term Description of AE	Onset Date/Time (Time since Last Dose)	Resolution Date/Time (Duration)	S: Severity R: Relationship to Study Product F: Frequency	O: Outcome S: Serious AE D: AE Lead To Discontinuation	Action Taken With Product Use / Was this AE a result of Study Medication error?	Was a concomitant treatment given because of the occurrence of the event? / CM #
Xxx	xxxxx xxxxx xx	xxxxxxxxxxxx xxxxxxxxxxxx xxxxxxxxxxxx	YYYY-MM-DD/ HH:MM (DD:HH:MM)	YYYY-MM-DD/ HH:MM (DD:HH:MM)	xxxxxx	xxxxx	xxxxxx	xxxxxx

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Similar Table:
Table 14.3.2.2 Listing of Adverse Events Leading To Study Discontinuation

Table 14.3.4.1
Summary of General Biochemistry
(Safety Population)

Parameter (unit)	Visit			Overall (N=XX)
Lab Test 1				
	Screening	Value	N	xx
			Mean (SD)	xx (xx.x)
			Median	xx.x
			Min, Max	xx, xx
Etc.	Etc.			

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Similar Tables:

Table 14.3.4.2	Summary of Hematology (Safety Population)
Table 14.3.4.3	Summary of Urinalysis (Safety Population)

Table 14.3.4.4
Listing of Abnormal On-Study Laboratory Values

Category/ Parameter (Unit)	Reference Range	Subject ID	Visit	Date / Time	Value	Flag	Assessment [1]

Note: Abnormal values are determined by applying the reference ranges to the results as reported by the external laboratory analysis.

[1] NCS: Not Clinically Significant / CS: Clinically Significant / TBC: To Be Controlled / RPT: Repeated.

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Similar Table:

Table 14.3.4.5 Listing of Clinically Significant On-Study Laboratory Values (Safety Population)

Table 14.3.5.1
Summary of Vital Signs
(Clinical Safety Set)

Parameter (unit)	Visit			Overall (N=XX)
Vital Sign 1	xx	Value	N	xx
			Mean (SD)	xx (xx.x)
			Median	xx.x
			Min, Max	xx, xx
	xx	Value	N	xx
			Mean (SD)	xx (xx.x)
			Median	xx.x
			Min, Max	xx, xx
Etc.	Etc.			

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Table 14.3.5.2
Listing of Abnormal On-Study Vital Signs Values

Parameter (Units)	Subject ID	Visit	Date/Time	Time	Value	MD Safety Review [1]

[1] NCS: Not Clinically Significant / CS: Clinically Significant

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Similar Table:

Table 14.3.5.3 Listing of Clinically Significant On-Study Vital Signs Values (Safety Population)

Table 14.3.6.1
Summary of ECG Parameters
(Clinical Safety Set)

Parameter (unit)	Visit			Overall (N=XX)
XXX				
	Screening	Value	N	xx
			Mean (SD)	xx (xx.x)
			Median	xx.x
			Min, Max	xx, xx
Etc.	Etc.			

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Table 14.3.6.2
Listing of Abnormal On-Study ECG Assessments
(Safety Population)

Subject ID	Visit	Date/Time	Position	MD Safety Review [1]	Parameter (Unit)	Value

[1] NCS: Not Clinically Significant / CS: Clinically Significant

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Similar Table:

Table 14.3.6.3 Listing of Clinically Significant On-Study ECG Assessments (Safety Population)

Table 14.3.7.1
Listing of Abnormal On-Study Physical Examination

Body System Examined	Subject ID	Visit	Date/Time	Result (Abnormal Findings)

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Similar Table:

Table 14.3.7.2 Listing of Clinically Significant On-Study Physical Examination (Safety Population)

APPENDIX C

SUMMARY OF PK ANALYSIS

STATISTICAL ANALYSIS

Section 14.2.2 Statistical analysis of Plasma Pharmacokinetic Parameters

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Table 14.2.2.1.1
Pharmacokinetic Statistical Analysis – Product A vs Product B
(Pharmacokinetic Population)

Parameter	Geometric Lsmeans [1]		P value of Product Effect	Ratio Product A/ Product B	95% Confidence Interval	
	Product A	Product B			Lower Bound	Upper Bound
$C_{max(controlled)}$	xxxxxx	xxxxxx	xxx	xxx	xxx	xxx
$C_{max(uncontrolled)}$	xxxxxx	xxxxxx	xxx	xxx	xxx	xxx
$AUC_{(controlled)}$	xxxxxx	xxxxxx	xxx	xxx	xxx	xxx
$AUC_{(uncontrolled)}$	xxxxxx	xxxxxx	xxx	xxx	xxx	xxx

[1]: Units are xxx for Cmax, xxx for AUC.
Note(s): An analysis of variance (ANOVA) was performed on the ln-transformed parameters with the following fixed factors: sequence, period, Product, and the following random factor: subject nested-within sequence. The ratio and 95% confidence interval (CI) were obtained by exponentiating the resulting difference in Product least-squares means and its corresponding 95% CI.

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Similar table(s):

T14.2.2.1.2 Pharmacokinetic Statistical Analysis – Product A vs Product C
T14.2.2.1.3 Pharmacokinetic Statistical Analysis – Product B vs Product C

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Table 14.2.2.2.1
Between-Product Comparisons of Tmax and T1/2 – Non-Parametric Analysis (First Product Use of Part B)
(Pharmacokinetic Population)

Pair wise Comparisons	PK Parameter	n	Median of Difference	95% CI	P value
Product A –Product B	xxx	X	XX.X (XX.XX)	XX.X – XX.X	xxxx
Product A –Product C	xxx	X	XX.X (XX.XX)	XX.X – XX.X	xxxx
Product B –Product C	xxx	X	XX.X (XX.XX)	XX.X – XX.X	xxxx

Notes: Median differences between Products and associated 95% CI are estimated using the method of Hodges-Lehmann.

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Similar table:

Table 14.2.2.2.2 Between-Product Comparisons of Tmax and T1/2 – Non-Parametric Analysis (Second Product Use of Part B)

Section 14.2.3.1 Summary of Questionnaires Responses

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Table 14.2.3.1.1
Use the Product Again – Descriptive Statistics
(Pharmacodynamic Population)

Visit	Product Use Session	Time Point		Product A (N=XX)	Product B (N=XX)	Product C (N=XX)
xxx	xxxx	xxxx	N	xx	xx	xx
			Mean (SD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
			% CV			
			Min	xx	xx	xx
			Q1			
			Median	xx	xx	xx
			Q3			
			Max	xx	xx	xx
			N	xx	xx	xx
			Mean (SD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
			% CV			
			Min	xx	xx	xx
			Q1			
			Median	xx	xx	xx
			Q3			
			Max	xx	xx	xx
	Etc.					

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Table 14.2.3.1.2
Tobacco/Nicotine Withdrawal – Descriptive Statistics
(Pharmacodynamic Population)

Item	Visit	Product Use Session	Time Point			Product A (N=XX)	Etc. (N=XX)
xxx	xxx	xxxx	xxxx	Value	N	xx	xx
					Mean (SD)	xx (xx.x)	xx (xx.x)
					% CV		
					Min	xx	xx
					Q1		
					Median	xx	xx
					Q3		
					Max	xx	xx
				Change From Baseline	N	xx	xx
					Mean (SD)	xx (xx.x)	xx (xx.x)
					% CV		
					Min	xx	xx
					Q1		
					Median	xx	xx
					Q3		
					Max	xx	xx
			Etc.				
		Etc.					
Etc.							

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Similar table:

Table 14.2.3.1.3 Direct Effect of Product Questionnaire – Descriptive Statistics

Section 14.2.3.2 Summary of Subjective Effect Parameters

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Table 14.2.3.2.1
Summary of Subjective Effect Parameters for Tobacco/Nicotine Withdrawal
(Pharmacodynamic Population)

Subjective Effect Parameter	Product Use Session			Product A (N=XX)	Product B (N=XX)	Product C (N=XX)
xxxx	xxx	Value	N	xx	xx	xx
			Mean (SD)	xx (xx.x)	xx (xx.x)	xx (xx.x)
			% CV			
			Min	xx	xx	xx
			Q1			
			Median	xx	xx	xx
			Q3			
			Max	xx	xx	xx
Etc.						

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Similar table(s):

Table 14.2.3.2.2 Summary of Subjective Effect Parameters for Direct Effect of Product Questionnaire

Section 14.2.3.3 Statistical Analysis of Subjective Effect Parameters

22ND CENTURY GROUP, INC. Algorithme Pharma
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Table 14.2.3.3.1.1
Statistical Analysis of Subjective Effect Parameters for Tobacco/Nicotine Withdrawal – Product A vs Product B
(Pharmacodynamic Population)

		Lsmeans [1]				95% Confidence Interval	
Subjective Effect Parameter	Product Use Session	Product A	Product B	Difference A – B (SD)	P value of Product Effect	Lower Bound	Upper Bound
XXX	Controlled Use	xxxxxx	xxxxxx	xxxxxx (xx.x)	xxx	xxx	xxx
	Uncontrolled Use	xxxxxx	xxxxxx	xxxxxx (xx.x)	xxx	xxx	xxx

Note(s): The Analysis of Variance (ANOVA) model included the Emax as the response variable, sequence, study product, and period as fixed model effects, baseline score as a covariate and subject nested-within sequence as a random effect.

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Similar table(s):

T14.2.3.3.1.2	Statistical Analysis of Subjective Effect Parameters for Tobacco/Nicotine Withdrawal – Product A vs Product C
T14.2.3.3.1.3	Statistical Analysis of Subjective Effect Parameters for Tobacco/Nicotine Withdrawal – Product B vs Product C
T14.2.3.3.2.1	Statistical Analysis of Subjective Effect Parameters for Direct Effect of Product Questionnaire – Product A vs Product B
T14.2.3.3.2.2	Statistical Analysis of Subjective Effect Parameters for Direct Effect of Product Questionnaire – Product A vs Product C
T14.2.3.3.2.3	Statistical Analysis of Subjective Effect Parameters for Direct Effect of Product Questionnaire – Product B vs Product C

Table 14.2.3.3.1.4
Statistical Analysis of Subjective Effect Parameters for Tobacco/Nicotine Withdrawal
(Completer Population)

			Lsmeans [1]				95% Confidence Interval	
Subjective Effect Parameter	Product Use Session	Comparison	Product	vs Product	Difference (SD)	P value of Product Effect	Lower Bound	Upper Bound
Emax_urge	Controlled Use	Product A vs Product D	xxxxxx	xxxxxx	Xxxxxx (xx.x)	xxx	xxx	xxx
		Product B vs Product D	xxxxxx	xxxxxx	Xxxxxx (xx.x)	xxx	xxx	xxx
		Product C vs Product D	xxxxxx	xxxxxx	Xxxxxx (xx.x)	xxx	xxx	xxx
		Etc.						
	Ad libitum Use	Product A vs Product D	xxxxxx	xxxxxx	Xxxxxx (xx.x)	xxx	xxx	xxx
		Etc.						

Note(s): The Analysis of Variance (ANOVA) model included the Emax as the response variable, sequence, study product, and period as fixed model effects, baseline score as a covariate and subject nested-within sequence as a random effect.

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Similar table:

Table 14.2.3.3.2.4 Statistical Analysis of Subjective Effect Parameters for Direct Effect of Product Questionnaire (Completer Population)

CONCENTRATION FIGURES

APPENDIX D

LISTING SHELLS

Listing 16.1.7
Listing of Randomization

Subject Id	Date	Stage	Randomization Number	Sequence

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Listing 16.2.1
Listing of Study Disposition

Subject ID	Date of Completion or Discontinuation	Date of Last Dose of Study Medication	Study Completed	Primary Reason for Study Discontinuation	If other, Specify	Additional Comments

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Listing 16.2.2.1
Listing of Blood Sampling Time Deviations

Visit	Product Use Session	Elapsed Time (h)	Subject ID	Scheduled Collection Date/Time	Actual collection Date/Time	Deviations (min)	Comments

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Listing 16.2.2.2
Listing of Protocol Deviations

Subject Id	Description	Category	Comments	Start Date

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Listing 16.2.2.3
Listing of Inclusion/Exclusion Criteria Violation

Subject Id	Category	Criteria Number	Comment

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Listing 16.2.3
Listing of Analysis Populations

Subject ID	Randomized Population (Part A)	Randomized Population (Part B)	Safety Population	Pharmacodynamic Population	Pharmacokinetic Population	Completer Population

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Listing 16.2.4.1
Listing of Demographic Characteristics

Subject Id	Age	Gender	Ethnicity	Race	Other Race	Weight (kg)	Height (cm)	BMI (kg/m^2)

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Listing 16.2.4.2
Listing of Medical History

Subject ID	MH #	System Organ Class MedDRA Preferred Term Description of MH	Condition	Start Date	End Date	Safety Review

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Listing 16.2.4.3
Listing of Prior Medication

Subject ID	#CM	ATC / PT / Medication Name	Indication	Strength (unit)	Route	Frequency / Formulation	Total Dose	Start Date/Time	End Date/Time	AE # / MH #

Note(s): ATC=Anatomical/therapeutic/chemical classification; PT=Preferred term.

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Listing 16.2.4.4
Listing of Tobacco Use History

Subject Id	Type of Tobacco Used	Frequency	Start Date	End Date	Yearly Use (Units)	Monthly Use (Units)	Weekly Use (Units)	Daily Use (Units)

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Listing 16.2.4.5
Listing of Contraceptive Methods (Female Only)

Subject ID	Childbearing Potential	Subject Considered Post-Menopausal	Last Menses	Contraceptive Method	Start Date	Non-Childbearing Potential Criteria	Procedure Date

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Listing 16.2.5.1.1
Listing of VLN Cigarette Product Use Part A

Subject ID	Visit	Date	Number Dispensed	Time Dispensed	Number of Butts Returned	Time Returned	Number of Product Used	Duration of Product Use

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Similar listing:

Listing 16.2.5.1.2 Listing of Usual Brand Cigarette Product Use Part A

Listing 16.2.5.1.3
Listing of Gum Product Use Part A

Subject ID	Visit	Date	Number Dispensed	Time Dispensed	Number of Pieces Returned	Time Returned/Discarded	Number of Product Used	Duration of Product Use

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Listing 16.2.5.2.1
Listing of First VLN Cigarette Product Use Part B

Subject ID	Visit	Date	Session Start Time	Puff #	Puff Begin Time	Puff End Time	Duration	Time Since Last Puff End Time	Reason if Missed Puff

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Similar listing:

Listing 16.2.5.2.2 Listing of First Usual Brand Cigarette Product Use Part B

Listing 16.2.5.2.3
Listing of First Gum Product Use Part B

Subject ID	Visit	Date	Session Start Time	Session End Time	Duration

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Listing 16.2.5.3.1
Listing of Second VLN Cigarette Product Use Part B

Subject ID	Visit	Date	Session Start Time	Session Start Time	Inhalation Begin Time	Inhalation End Time	Duration	Time Since Last Puff End Time	Session Total Inhalations

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Similar listing:

Listing 16.2.5.3.2 Listing of Second Usual Brand Cigarette Product Use Part B

Listing 16.2.5.3.3
Listing of Second Gum Product Use Part B

Subject ID	Visit	Date	Session Start Time	Session End Time	Duration

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

APPENDIX 16.2.6.1 Questionnaire Responses

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Listing 16.2.6.1.1
Listing of Use the Product Again Responses
(Pharmacodynamic Population)

Subject Id	Visit	Product Use Session	Time Point	Date/Time	VAS Score

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Listing 16.2.6.1.2
Listing of Tobacco/Nicotine Withdrawal Questionnaire Responses
(Pharmacodynamic Population)

Subject Id	Visit	Product Use Session	Time Point	Date/Time	Item	Result	Change From Pre-Use

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Listing 16.2.6.1.3
Listing of Direct Effect of Product Questionnaire Responses
(Pharmacodynamic Population)

Subject Id	Visit	Product Use Session	Time Point	Date/Time	Item	Result

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Listing 16.2.7
Listing of Adverse Events
(Safety Population)

Subject Id	Study Part/Day/ Study Product/ AE #	SOC MedDRA Preferred Term Description of AE	Onset Date/Time (Time since Last Dose)	Resolution Date/Time (Duration)	S: Severity R: Relationship to Study Product F: Frequency	O: Outcome S: Serious AE D: AE Lead To Discontinuation	Action Taken With Product Use / Was this AE a result of Study Medication error?	Was a concomitant treatment given because of the occurrence of the event? / CM #
Xxx	xxxxx xxxxx xx	xxxxxxxxxxxx xxxxxxxxxxxx xxxxxxxxxxxx	YYYY-MM-DD/ HH:MM (DD:HH:MM)	YYYY-MM-DD/ HH:MM (DD:HH:MM)	xxxxxx	xxxxx	xxxxxx	xxxxxx

Date: VERSION - YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Listing 16.2.8.1
Listing of General Biochemistry
(Safety Population)

Subject Id	Visit	Date/Time	Parameter (Unit)	Reference Range	Value	Flag	Assessment [1]

[1] NCS: Not Clinically Significant / CS: Clinically Significant

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Similar listing(s):

L16.2.8.2 Listing of Hematology
L16.2.8.3 Listing of Serology
L16.2.8.4 Listing of Urine Drug Screen
L16.2.8.5 Listing of Urinalysis
L16.2.8.6 Listing of Other Laboratory Tests (Endocrinology)

Listing 16.2.9.1
Listing of Concomitant Medication
(Safety Population)

Subject ID	#CM	ATC / PT / Medication Name	Indication	Strength (unit)	Route	Frequency / Formulation	Total Dose	Start Date/Time	End Date/Time	AE # / MH #

Note(s): ATC=Anatomical/therapeutic/chemical classification; PT=Preferred term.

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Listing 16.2.9.2
Listing of General Physical Examination
(Safety Population)

Subject Id	Visit	Date/Time	Body System Examined	Result (Abnormal Findings)

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Listing 16.2.9.3
Listing of Vital Signs
(Safety Population)

Subject ID	Visit	Date/ Time	Parameter (Units)	Value	MD Safety Review [1]

[1] NCS: Not Clinically Significant / CS: Clinically Significant

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

Listing 16.2.9.4
Listing of ECG Assessments
(Safety Population)

Subject ID	Visit	Date/Time	Position	MD Safety Review [1]	Parameter (Unit)	Value

[1] NCS: Not Clinically Significant / CS: Clinically Significant

Date: VERSION – YYYY-MM-DD Data Source: XXXX Program Source: XXXXX.sas

APPENDIX E

WinNoline Shells

Section 14.2.1 Summary of Plasma Concentration and PK Parameters
Section 14.2.1.1 Summary of Concentration Data

Table 14.2.1.1.1 Summary of Plasma Nicotine Concentration Following Administration of Product A – Controlled Use

			Time (unit)							
			0.00	2.00	5.00	7.00	10.00	12.00	...	180.00
Product	Condition		Unadjusted Concentration (Unit)							
Product A	Controlled Use	N								
		Mean								
		SD								
		Min								
		Median								
		Max								
		CV%								

Similar Tables:
Table 14.2.1.1.2 Summary of Unadjusted Plasma Nicotine Concentration Following Administration of Product A – Uncontrolled Use
Table 14.2.1.1.3 Summary of Unadjusted Plasma Nicotine Concentration Following Administration of Product B – Controlled Use
Table 14.2.1.1.4 Summary of Unadjusted Plasma Nicotine Concentration Following Administration of Product B – Uncontrolled Use
Table 14.2.1.1.5 Summary of Unadjusted Plasma Nicotine Concentration Following Administration of Product C – Controlled Use
Table 14.2.1.1.6 Summary of Unadjusted Plasma Nicotine Concentration Following Administration of Product C – Uncontrolled Use
Table 14.2.1.2.1 Summary of Baseline-Adjusted Plasma Nicotine Concentration Following Administration of Product A – Controlled Use
Table 14.2.1.2.2 Summary of Baseline-Adjusted Plasma Nicotine Concentration Following Administration of Product A – Uncontrolled Use
Table 14.2.1.2.3 Summary of Baseline-Adjusted Plasma Nicotine Concentration Following Administration of Product B – Controlled Use
Table 14.2.1.2.4 Summary of Baseline-Adjusted Plasma Nicotine Concentration Following Administration of Product B – Uncontrolled Use
Table 14.2.1.2.5 Summary of Baseline-Adjusted Plasma Nicotine Concentration Following Administration of Product C – Controlled Use
Table 14.2.1.2.6 Summary of Baseline-Adjusted Plasma Nicotine Concentration Following Administration of Product C – Uncontrolled Use

Section14.2.1.3 Summary of Pharmacokinetic Parameters

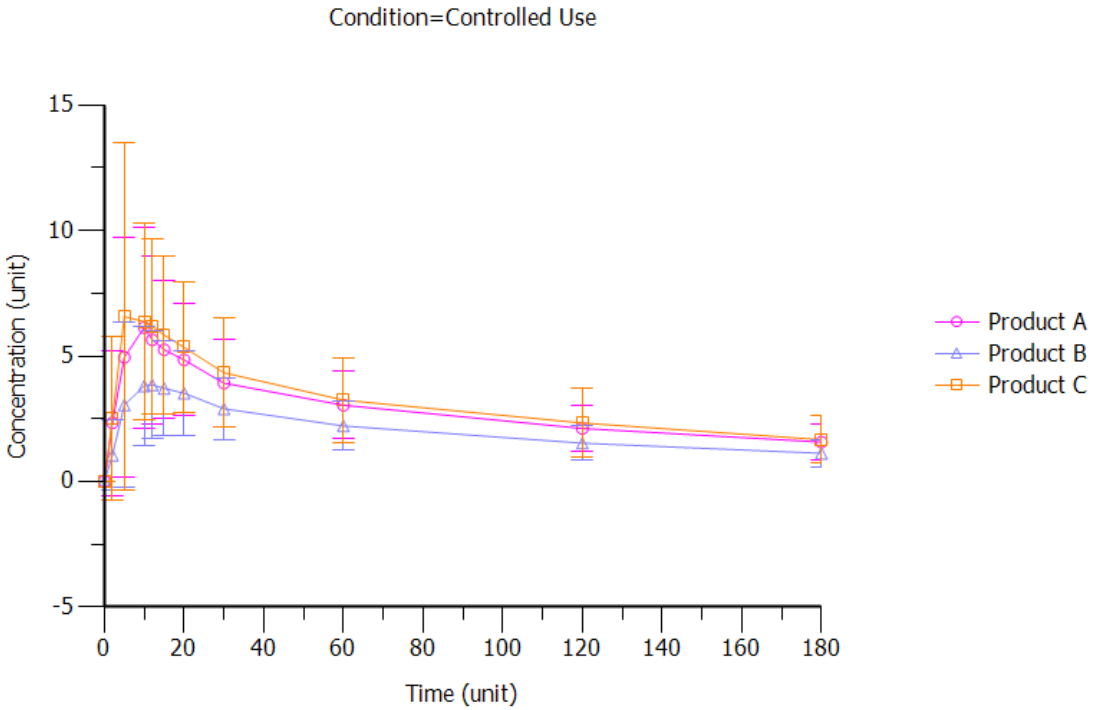
Table 14.2.1.3.1 Summary of Baseline-Adjusted Plasma Nicotine Pharmacokinetic Parameter Following Administration of Product A – Controlled Use

Product	Condition		$AUC_{(Controlled}$ (unit)	$C_{max(Controlled)}$ (unit)	$T_{max(Controlled)}$ (unit)	$T_{1/2(Controlled)}$ (unit)	$K_{el(Controlled)}$ (unit)
Product A	**Controlled Use**	**N**					
		Mean					
		SD					
		Min					
		Median					
		Max					
		CV%					

Table 14.2.1.3.2 Summary of Baseline-Adjusted Plasma Nicotine Pharmacokinetic Parameter Following Administration of Product A – Uncontrolled Use
Table 14.2.1.3.3 Summary of Baseline-Adjusted Plasma Nicotine Pharmacokinetic Parameter Following Administration of Product B – Controlled Use
Table 14.2.1.3.4 Summary of Baseline-Adjusted Plasma Nicotine Pharmacokinetic Parameter Following Administration of Product B – Uncontrolled Use
Table 14.2.1.3.5 Summary of Baseline-Adjusted Plasma Nicotine Pharmacokinetic Parameter Following Administration of Product C – Controlled Use
Table 14.2.1.3.6 Summary of Baseline-Adjusted Plasma Nicotine Pharmacokinetic Parameter Following Administration of Product C – Uncontrolled Use

PLANNED FIGURES

Figure 14.2.1.1.1 Mean (±SD) Unadjusted Plasma Nicotine Concentration Following Administration of Product A, B and C – Controlled Use (Linear Scale)



Note: The figure does not reflect the actual data of the study.

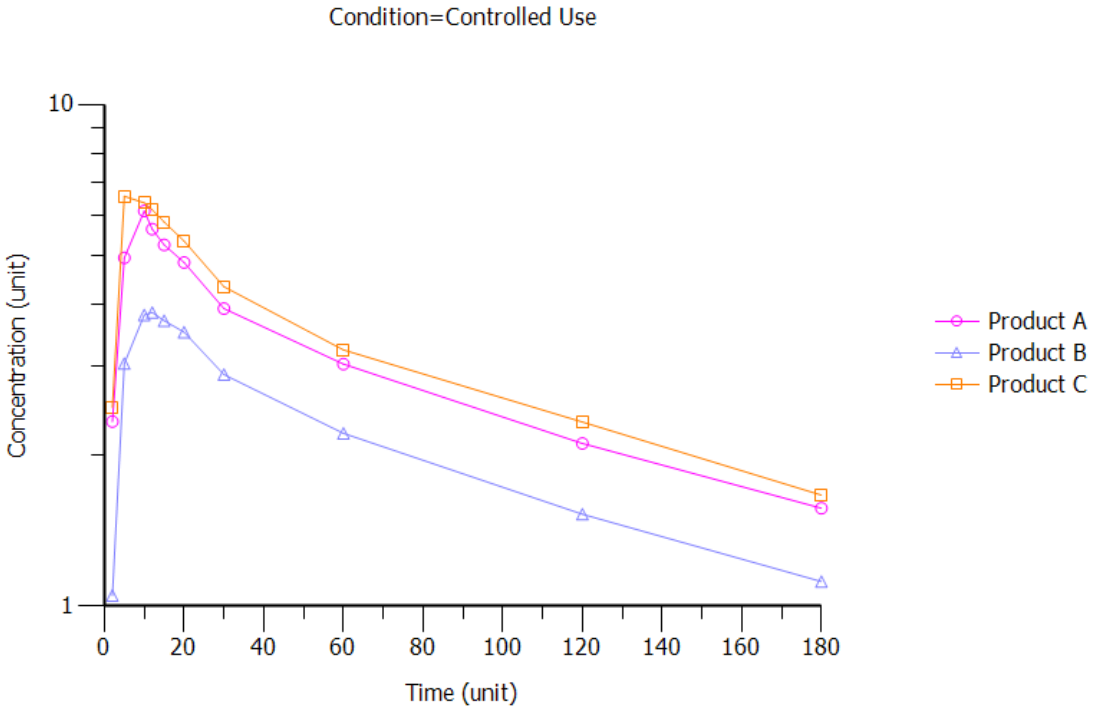
Similar Figures:

Figure 14.2.1.1.3 Mean (±SD) Unadjusted Plasma Nicotine Concentration Following Administration of Product A, B and C – Uncontrolled Use (Linear Scale)

Figure 14.2.1.1.5 Mean (±SD) Baseline-Adjusted Plasma Nicotine Concentration Following Administration of Product A, B and C – Controlled Use (Linear Scale)

Figure 14.2.1.1.7 Mean (±SD) Baseline-Adjusted Plasma Nicotine Concentration Following Administration of Product A, B and C – Uncontrolled Use (Linear Scale)

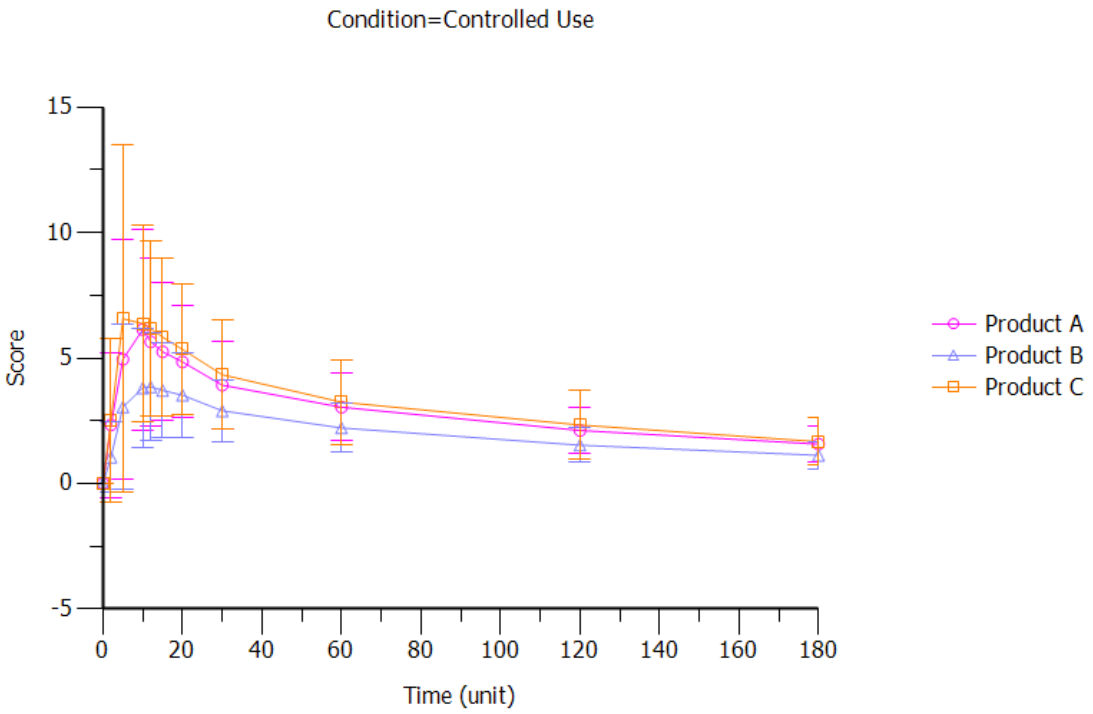
Figure 14.2.1.1.2 Mean (±SD) Unadjusted Plasma Nicotine Concentration Following Administration of Product A, B and C – Controlled Use (Semi-Log Scale)



Note: The figure does not reflect the actual data of the study.

Similar Figures:
Figure 14.2.1.1.4 Mean (±SD) Unadjusted Plasma Nicotine Concentration Following Administration of Product A, B and C – Uncontrolled Use (Semi-Log Scale)
Figure 14.2.1.1.6 Mean (±SD) Baseline-Adjusted Plasma Nicotine Concentration Following Administration of Product A, B and C – Controlled Use (Semi-Log Scale)
Figure 14.2.1.1.8 Mean (±SD) Baseline-Adjusted Plasma Nicotine Concentration Following Administration of Product A, B and C – Uncontrolled Use (Semi-Log Scale)

Section 14.2.3.1 Summary of Questionnaires Responses
Figure 14.2.3.1.1 Mean Tobacco/Nicotine Withdrawal Questionnaire Responses Following Administration of Product A, B and C – Controlled Use (Linear Scale)



Note: The figure does not reflect the actual data of the study.

Similar Figures:
Figure 14.2.3.1.2 Mean Tobacco/Nicotine Withdrawal Questionnaire Responses Following Administration of Product A, B and C – Uncontrolled Use (Linear Scale)
Figure 14.2.3.1.3 Mean Tobacco/Nicotine Withdrawal Questionnaire Reduction in VAS score Following Administration of Product A, B and C – Controlled Use (Linear Scale)
Figure 14.2.3.1.4 Mean Tobacco/Nicotine Withdrawal Questionnaire Reduction in VAS score Following Administration of Product A, B and C – Uncontrolled Use (Linear Scale)
Figure 14.2.3.1.5 Mean Direct Effects of Product Questionnaire Responses Following Administration of Product A, B and C – Controlled Use (Linear Scale)
Figure 14.2.3.1.6 Mean Direct Effects of Product Questionnaire Responses Following Administration of Product A, B and C – Uncontrolled Use (Linear Scale)

LISTING

Listing 16.2.6.2.1 Listing of Tobacco/Nicotine Withdrawal Questionnaire Effect Parameters

Subject	Product	Condition	Emax_urge(controlled) (unit)	Emax_anx(controlled) (unit)	Emax_diffct(Controlled) (unit)	Emax_impat(controlled) (unit)	Emax_crav(controlled) (unit)
...							

Similar Listing:
Listing 16.2.6.2.2 Listing of Direct Effects of Product Questionnaire Effect Parameters

Listing 16.2.6.3.1.1 Listing of Unadjusted Plasma Nicotine Concentration (Controlled Use)

			Time (unit)							
			0.00	2.00	5.00	7.00	10.00	12.00	...	180.00
Subject	Product	Condition	Concentration (unit)							
	Product A	Controlled Use								

Listing 16.2.6.3.1.2 Listing of Unadjusted Plasma Nicotine Concentration (Uncontrolled Use)
Listing 16.2.6.3.2.1 Listing of Baseline-Adjusted Plasma Nicotine Concentration (Controlled Use)
Listing 16.2.6.3.2.2 Listing of Baseline-Adjusted Plasma Nicotine Concentration (Uncontrolled Use)

Listing 16.2.6.3.3 Listing of Baseline-Adjusted Plasma Nicotine Pharmacokinetic Parameters

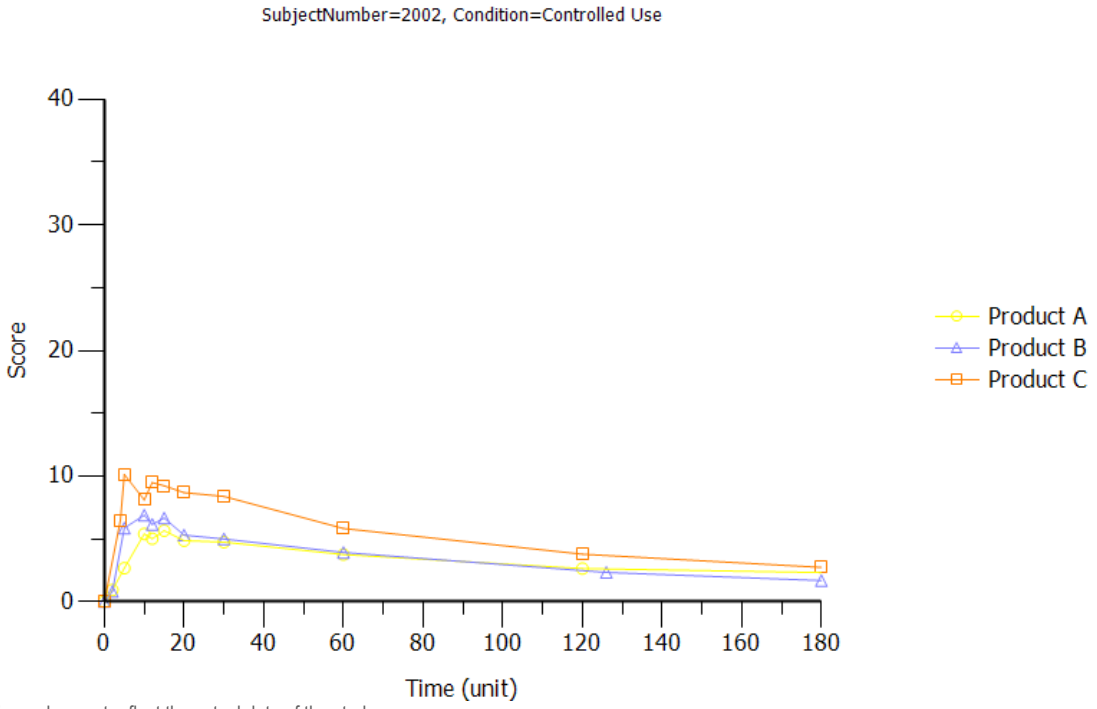
Subject	Product	Condition	$AUC_{(Controlled}$ (unit)	$C_{max(Controlled)}$ (unit)	$T_{max(Controlled)}$ (unit)	$T_{1/2(Controlled)}$ (unit)	$K_{el(Controlled)}$ (unit)
...							

Listing 16.2.6.3.4 Listing of Nicotine Actual Sampling Time

			Time (unit)							
			0.00	2.00	5.00	7.00	10.00	12.00	...	180.00
Subject	Product	Condition	Actual Time (unit)							
	Product A	Controlled Use								

Individual Figures:

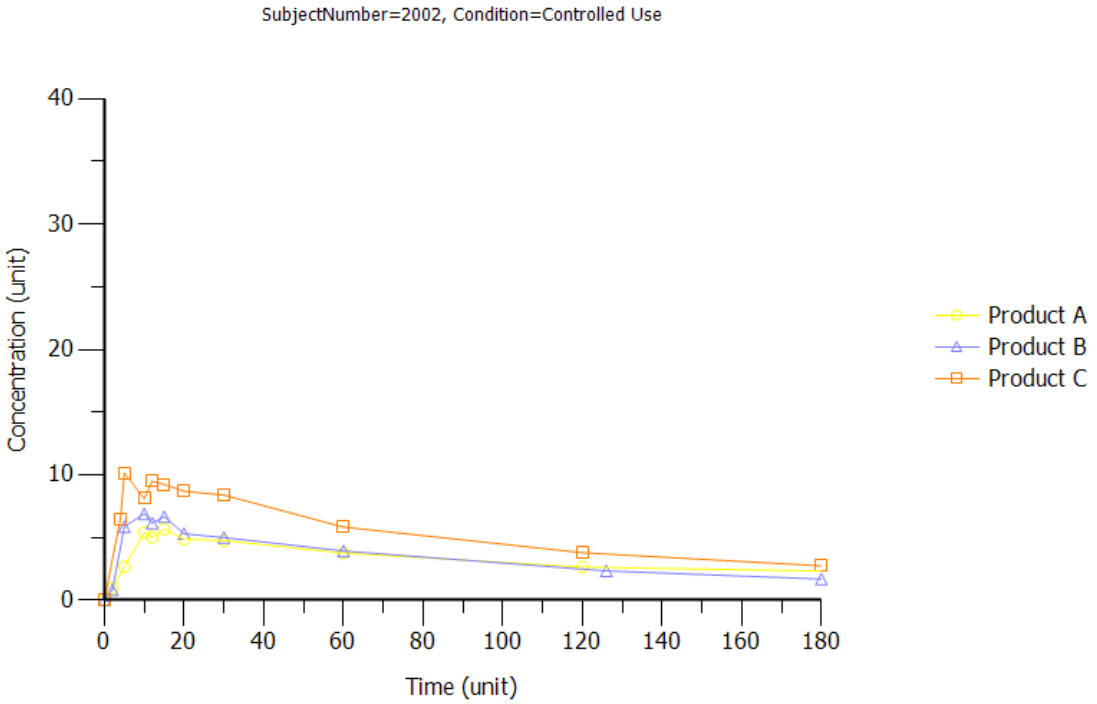
Listing 16.2.6.1.4 Individual Tobacco/Nicotine Withdrawal Questionnaire Response Profiles (Controlled Use) – Linear Scale



Note: The figure does not reflect the actual data of the study.

Similar Figures:
Listing 16.2.6.1.5 Individual Tobacco/Nicotine Withdrawal Questionnaire Response Profiles (Uncontrolled Use) – Linear Scale
Listing 16.2.6.1.6 Individual Tobacco/Nicotine Withdrawal Questionnaire Reduction in VAS Score Profiles (Controlled Use) – Linear Scale
Listing 16.2.6.1.7 Individual Tobacco/Nicotine Withdrawal Questionnaire Reduction in VAS Score Profiles (Uncontrolled Use) – Linear Scale
Listing 16.2.6.1.8 Individual Direct Effects of Product Questionnaire Response Profiles (Controlled Use) – Linear Scale
Listing 16.2.6.1.9 Individual Direct Effects of Product Questionnaire Response Profiles (Uncontrolled Use) – Linear Scale

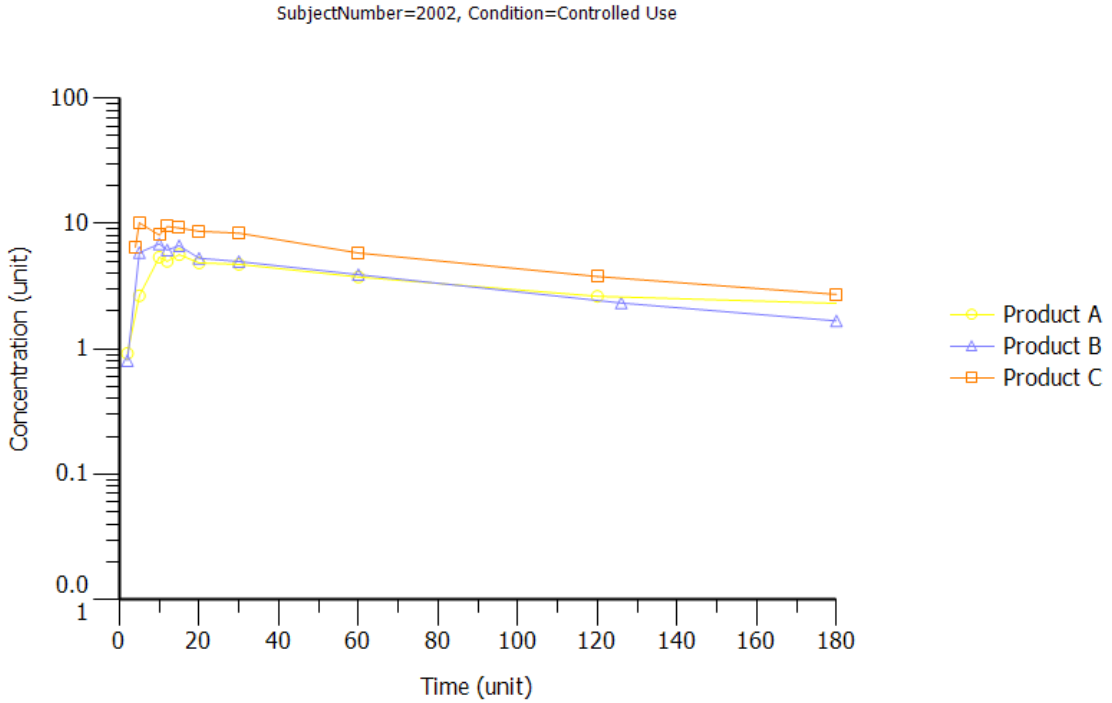
Listing 16.2.6.3.5 Individual Unadjusted Plasma Nicotine Concentration Profiles (Controlled Use) – Linear Scale



Note: The figure does not reflect the actual data of the study.

Similar Figures:
Listing 16.2.6.3.7 Individual Unadjusted Plasma Nicotine Concentration Profiles (Uncontrolled Use) – Linear Scale
Listing 16.2.6.3.9 Individual Baseline-Adjusted Plasma Nicotine Concentration Profiles (Controlled Use) – Linear Scale
Listing 16.2.6.3.11 Individual Baseline-Adjusted Plasma Nicotine Concentration Profiles (Uncontrolled Use) – Linear Scale

Listing 16.2.6.3.6 Individual Unadjusted Plasma Nicotine Concentration Profiles (Controlled Use) – Semi-Log Scale



Note: The figure does not reflect the actual data of the study.

Similar Figures:
Listing 16.2.6.3.8 Individual Unadjusted Plasma Nicotine Concentration Profiles (Uncontrolled Use) – Semi-Log Scale
Listing 16.2.6.3.10 Individual Baseline-Adjusted Plasma Nicotine Concentration Profiles (Controlled Use) – Semi-Log Scale
Listing 16.2.6.3.12 Individual Baseline-Adjusted Plasma Nicotine Concentration Profiles (Uncontrolled Use) – Semi-Log Scale

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