Study Data Reviewer's Guide

Clinical

22nd Century Group, Inc.

Study CEG-P9-153

Study Data Reviewer's Guide

Contents

1. Introduction

1.1 Purpose

This document provides context for tabulation datasets and terminology that benefit from additional explanation beyond the Data Definitions document (define.xml). In addition, this document provides a summary of SDTM conformance findings.

1.2 Acronyms

Acronym	Translation
IG	Implementation Guide
CRF	Case Report Form
WHO-DDE	World Health Organization Drug Dictionary Enhanced
ATC	Anatomic Therapeutic Classification

1.3 Study Data Standards and Dictionary Inventory

Standard or Dictionary	Versions Used
SDTM	•SDTM v1.4 •SDTM-IG v3.2
Controlled Terminology	CDISC SDTM Controlled Terminology, 2018-09-28
Data Definitions	Define-XML v2.0
Medications Dictionary	SNOMED 2018-09-01, UNII 2018-08-31, NDF-RT 2018-02-05
Medical Events Dictionary	MedDRA v21.0
Drug Dictionary	WHO DDE March 1, 2018

2. Protocol Description

2.1 Protocol Number and Title

Protocol Number: CEG-P9-153

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

Protocol Versions: Final Protocol No. 2.0, Amendment No. 1.

2.2 Protocol Design

This study was 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 enrolled generally healthy adult male and female self-affirmed smokers 22 - 65 years of age, inclusive, who fulfill the inclusion and exclusion criteria. Subjects were current exclusive smokers of combustible, non-menthol cigarettes. The study consisted 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) was completed during a clinic visit within 28 days of the Confined Assessment Phase and consisted of a standard medical screen.

Subjects who successfully completed the Screening Phase returned to the clinical unit on Day -1 for check-in and to complete a product trial session. Subjects engaged in a 10-minute product training session with the nicotine polacrilex gum in order to familiarize themselves with the "chew and park" method, which required subjects to chew the gum until they experienced a tingling sensation, park the gum between the cheek and gum until the tingling subsides, and then began chewing again. On Day -1, subjects also completed a training session on the pharmacodynamic questionnaires. Subjects were required to abstain from using nicotine- and tobacco-containing products for approximately 20 hours prior to each product use session in Part A.
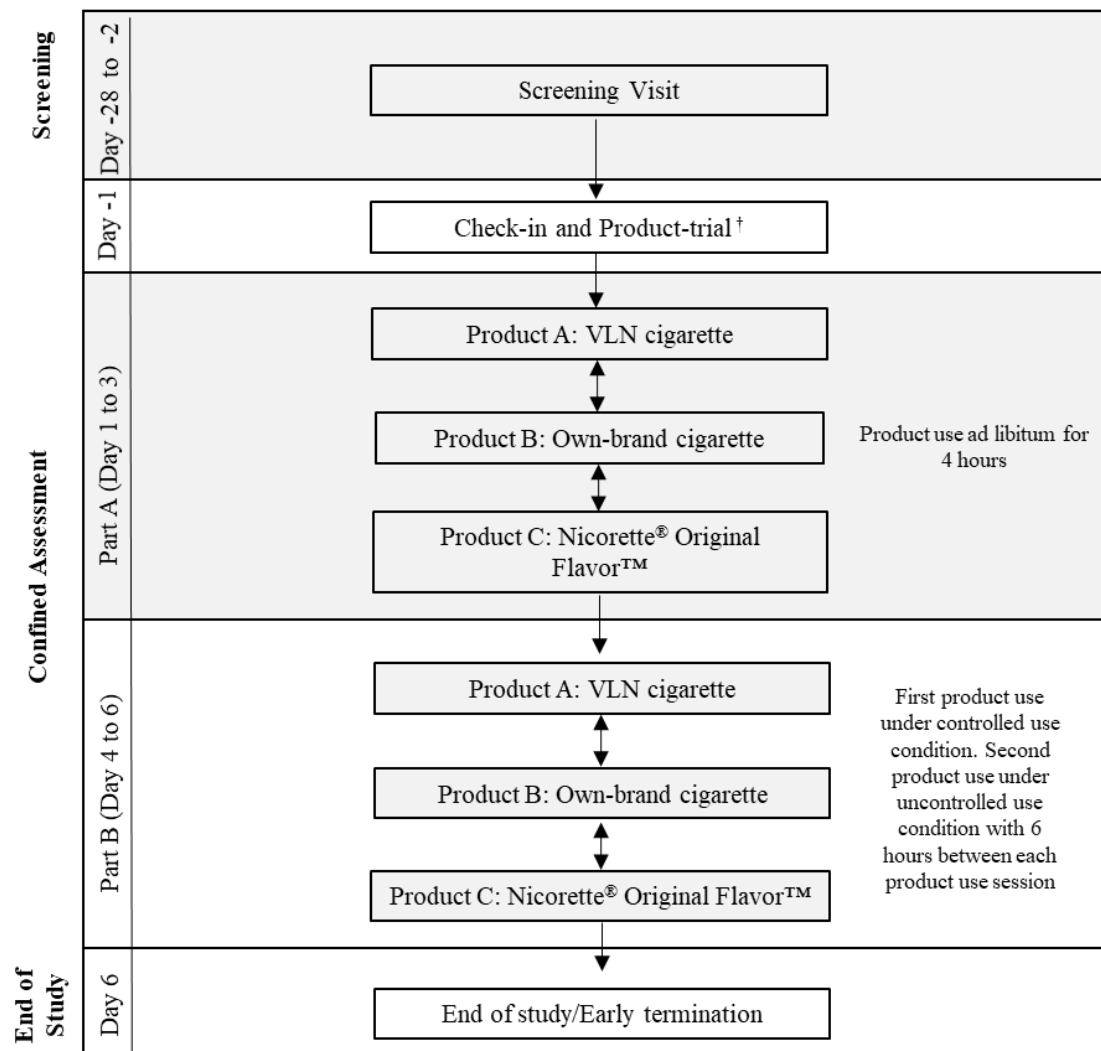
Part A began on Day 1. Subjects were randomized to one of three product sequence groups in Part A, which consisted of an ad libitum product use session of each of the 3 study products for 4 hours in a randomized crossover manner (one product per day).

A pharmacodynamic measure ("use product again" visual analog scale [VAS]) was 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) were collected throughout each ad libitum product use period.

Part B began upon completion of Part A. Subjects were randomized to one of three product sequence groups in Part B, which consisted of 3 study days (Days 4 to 6), with one product per day. Each study day consisted 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 were separated by approximately 6 hours. During Part B, pharmacodynamic measures, PK samples, and product use behavior (Uncontrolled Product Use Session only) were 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 were collected at designated time points throughout the study.

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

† 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.

2.3 Trial Design Datasets

Are Trial Design datasets included in the submission? - **Yes**

(If no, delete the remainder of this section. If yes, refer to SDRG Completion Guidelines Section 2.3 and provide additional information below.)

Dataset	Dataset Label
TA	Trial Arms
TE	Trial Elements
TV	Trial Visits

Dataset	Dataset Label
TI	Trial Inclusion/Exclusion Criteria
TS	Trial Summary

2.3.1 TE - Trial Elements

The study has the following elements:

- Screening – evaluation of a patient prior to taking of study drug
- Product A in Part A – administration of Product A in Part A
- Product A in Part B – administration of Product A in Part B
- Product B in Part A – administration of Product B in Part A
- Product B in Part B – administration of Product B in Part B
- Product C in Part A – administration of Product C in Part A
- Product C in Part B – administration of Product C in Part B
- Follow-up - evaluation of a patient after the end of product use

2.3.2 TV - Trial Visits

Dataset contains information about all planned visits.

2.3.3 TI - Trial Inclusion/Exclusion Criteria

The trial inclusion/exclusion criteria are not fully described in the TI domain. Please refer to Appendix I for the full text of the criteria.

3. Subject Data Description

3.1 Overview

Are the submitted data taken from an ongoing study?   No

Were the SDTM datasets used as sources for the analysis datasets?   Yes

Do the submission datasets include screen failures?   No

Were any domains planned, but not submitted because no data were collected?   Yes

If yes, list domains not submitted:

IE – All subjects met inclusion/exclusion criteria.

Are the submitted data a subset of collected data?   No

3.2 Annotated CRFs

Collected fields that have not been tabulated have been annotated as "Not Submitted". Altasciences Clinical Research collects certain data elements to facilitate certain operational processes including data cleaning and dynamically creating additional forms in the electronic data capture system. The document acrf.pdf includes the final version of the annotated CRF.

3.3 SDTM Subject Domains

Dataset - Dataset Label	Efficacy	PK	Safety	Other	SUPP--	Related Using RELREC	Observation Class
AE - Adverse Events			X		X	CM	EVENTS
CM - Concomitant Medications			X		X	AE, MH	INTERVENTIONS
CO - Comments				X			SPECIAL PURPOSE
DA - Drug Accountability				X			FINDINGS
DM - Demographics				X	X		SPECIAL PURPOSE
DS - Disposition				X	X		EVENTS
DV - Protocol Deviations				X			EVENTS
EG - ECG Test Results			X				FINDINGS
EX - Exposure				X	X		INTERVENTIONS
LB - Laboratory Test Results			X		X		FINDINGS
MH - Medical History			X		X	CM	EVENTS
PC - Pharmacokinetics Concentrations		X			X		FINDINGS
PE - Physical Examination			X		X		FINDINGS
PP - Pharmacokinetics Parameters		X			X		FINDINGS
QS - Questionnaires	X				X		FINDINGS
RP - Reproductive System Findings				X	X		FINDINGS
SE - Subject Elements				X			SPECIAL PURPOSE
SU - Substance Use				X			INTERVENTIONS

Dataset - Dataset Label	Efficacy	PK	Safety	Other	SUPP--	Related Using RELREC	Observation Class
SV - Subject Visits				X			SPECIAL PURPOSE
VS - Vital Signs			X		X		FINDINGS

3.3.1 AE - Adverse Events

A relationship has been defined in RELREC between the adverse events and concomitant medications used to treat the AE. The observations are related by AESPID and CMSPID.

QNAM	Description
AEDIS	Withdrawn From Study Due To AE
AEMEDERR	AE Due to Study Medication Error

3.3.2 CM - Concomitant Medications

A relationship has been defined in RELREC between the adverse events and concomitant medications used to treat the AE. The observations are related by AESPID and CMSPID. The Anatomic Therapeutic Classification (ATC) coding hierarchy is located in SUPPCM.

QNAM	Description
ATC01ID	Medication Therapy Name parent ID 01
ATC02ID	Medication Therapy Name parent ID 02
ATC04ID	Medication Therapy Name parent ID 04
CMAENO	AE Number
CMATC01	Medication Therapy Name parent term 01
CMATC02	Medication Therapy Name parent term 02
CMATC04	Medication Therapy Name parent term 04
CMDOFMOT	If Other Formulation, Please specify
CMDOSOTH	If Other Unit, Please specify
CMFRQOT	If Other Frequency, Please specify
CMINDOT	If Other Indication, Please specify
CMMHNO	MH Number

QNAM	Description
CMQUANT	Quantity
CMTOTUN	If Other Total Unit, Please specify
DRUGRECN	Medication/Therapy Name drug record nb
PREFERRE	Medication/Therapy Name term id

3.3.3 DM - Demographics

QNAM	Description
RANDANO	Randomization Number in Part A
RANDBNO	Randomization Number in Part B

3.3.4 DS - Disposition

QNAM	Description
DSDTCMED	Last Dose of Study Medication
ICFVRDTC	ICF Version Date
ICFVRN	ICF Version

3.3.5 EX - Exposure

QNAM	Description
EXBEV	Did the subject consume any beverages

3.3.6 LB - Laboratory Test Results

QNAM	Description
LBCLSIG	Clinical Significance

3.3.7 MH - Medical History

A relationship has been defined in RELREC between the adverse events and concomitant medications used to treat the MH. The observations are related by MHSPID and CMSPID.

QNAM	Description
MHCLSIG	Clinical Significance
MHOTHSP	If other MHTERM, please specify
MHRECUSE	History of Recreational Drug Use
MHSMK	Desire to Smoke Within 30mins of Walking

3.3.8 PC - Pharmacokinetics Concentrations

QNAM	Description
COND	Condition
PCDESC	Conc data used descriptive statistic
PCDESCBA	Concentration data used for DESCNBA
PCNCA	Concentration data for NCA
PCNCABA	Conc data used for NCA baseline adjusted
PKPOP	PK Population
USE	Use session

3.3.9 PE - Physical Examination

QNAM	Description
PETESTOT	If Other, please specify

3.3.10 PP - Pharmacokinetics Parameters

QNAM	Description
COND	Condition
PKPOP	PK Population

QNAM	Description
USE	Use session

3.3.11 QS - Questionnaires

QNAM	Description
QSENDTC	Stop Date/Time of Finding

3.3.12 RP - Reproductive System Findings

QNAM	Description
BCMSTDTC	Contraceptive Start date
SCPRODT1	Procedure date
SCPRODT2	Procedure date
SCSUR1	Non-childbearing potential
SCSUR2	Non-childbearing potential

3.3.13 VS - Vital Signs

QNAM	Description
TIMESPOS	Position Start Time
VSCLSIG	MD Safety Review

4. Data Conformance Summary

4.1 Conformance Inputs

Was Pinnacle21 used to evaluate conformance?	**Yes**
If yes, specify the versions of Pinnacle21 and the Pinnacle21 validation rules:	**Pinnacle 21 Enterprise version 3.4.3**
Were sponsor-defined validation rules used to evaluate conformance?	**No**
Were the SDTM datasets evaluated in relation to define.xml?	**Yes**
Was define.xml evaluated?	**Yes**

4.2 Issues Summary

Dataset	Diagnostic Message	Severity	Count (Issue Rate)	Explanation
AE	EPOCH value not found in 'Epoch' extensible codelist	Warning	63 (78.75%)	Extensible codelist; sponsor defined terminology
CM	CMDOSFRQ value not found in 'Frequency' extensible codelist	Warning	2 (4.55%)	Extensible codelist; sponsor defined terminology
CM	CMDOSU value not found in 'Unit' extensible codelist	Warning	12 (27.27%)	Extensible codelist; sponsor defined terminology
CM	EPOCH value not found in 'Epoch' extensible codelist	Warning	15 (34.09%)	Extensible codelist; sponsor defined terminology
CM	CMDOSFRM value not found in 'Pharmaceutical Dosage Form' extensible codelist	Warning	4 (9.09%)	Extensible codelist; sponsor defined terminology
DA	DAORRESU value not found in 'Unit' extensible codelist	Warning	2087 (100.00%)	Extensible codelist; sponsor defined terminology

Dataset	Diagnostic Message	Severity	Count (Issue Rate)	Explanation
DA	DASTRESU value not found in 'Unit' extensible codelist	Warning	2087 (100.00%)	Extensible codelist; sponsor defined terminology
DA	EPOCH value not found in 'Epoch' extensible codelist	Warning	2086 (99.95%)	Extensible codelist; sponsor defined terminology
DS	EPOCH value not found in 'Epoch' extensible codelist	Warning	61 (21.79%)	Extensible codelist; sponsor defined terminology
DV	EPOCH value not found in 'Epoch' extensible codelist	Warning	173 (96.65%)	Extensible codelist; sponsor defined terminology
EX	EPOCH value not found in 'Epoch' extensible codelist	Warning	3649 (100.00%)	Extensible codelist; sponsor defined terminology
EX	EXDOSU value not found in 'Unit' extensible codelist	Warning	857 (23.49%)	Extensible codelist; sponsor defined terminology
LB	EPOCH value not found in 'Epoch' extensible codelist	Warning	581 (10.09%)	Extensible codelist; sponsor defined terminology
LB	LBSTRESU value not found in 'Unit' extensible codelist	Warning	1285 (22.31%)	Extensible codelist; sponsor defined terminology
LB	LBORRESU value not found in 'Unit' extensible codelist	Warning	1285 (22.31%)	Extensible codelist; sponsor defined terminology
PC	PCSTRESU value not found in 'Unit' extensible codelist	Warning	5250 (100.00%)	Extensible codelist; sponsor defined terminology
PC	PCORRESU value not found in 'Unit' extensible codelist	Warning	5250 (100.00%)	Extensible codelist; sponsor defined terminology

Dataset	Diagnostic Message	Severity	Count (Issue Rate)	Explanation
PC	EPOCH value not found in 'Epoch' extensible codelist	Warning	4474 (85.22%)	Extensible codelist; sponsor defined terminology
PE	EPOCH value not found in 'Epoch' extensible codelist	Warning	50 (6.90%)	Extensible codelist; sponsor defined terminology
PP	EPOCH value not found in 'Epoch' extensible codelist	Warning	3042 (100.00%)	Extensible codelist; sponsor defined terminology
PP	PPSTRESU value not found in 'PK Units of Measure' extensible codelist	Warning	246 (8.09%)	Extensible codelist; sponsor defined terminology
PP	PPORRESU value not found in 'PK Units of Measure' extensible codelist	Warning	246 (8.09%)	Extensible codelist; sponsor defined terminology
QS	EPOCH value not found in 'Epoch' extensible codelist	Warning	31895 (97.18%)	Extensible codelist; sponsor defined terminology
QS	QSCAT value not found in 'Category of Questionnaire' extensible codelist	Warning	32819 (100.00%)	Extensible codelist; sponsor defined terminology
SE	EPOCH value not found in 'Epoch' extensible codelist	Warning	370 (73.71%)	Extensible codelist; sponsor defined terminology
SU	SUDOSU value not found in 'Unit' extensible codelist	Warning	73 (82.95%)	Extensible codelist; sponsor defined terminology
SV	EPOCH value not found in 'Epoch' extensible codelist	Warning	380 (71.16%)	Extensible codelist; sponsor defined terminology
TA	EPOCH value not found in 'Epoch' extensible codelist	Warning	63 (72.41%)	Extensible codelist; sponsor defined terminology

Dataset	Diagnostic Message	Severity	Count (Issue Rate)	Explanation
VS	EPOCH value not found in 'Epoch' extensible codelist	Warning	5 (0.42%)	Extensible codelist; sponsor defined terminology
DS	DSDECOD value not found in 'Completion/Reason for Non-Completion' extensible codelist when DSCAT == 'DISPOSITION EVENT'	Warning	11 (16.67%)	Extensible codelist; sponsor defined terminology
SU	Missing End Time-Point value	Warning	73 (82.95%)	The end date and time was not collected for some substance use habits
DV	Missing Start Time-Point value	Warning	1 (0.56%)	The start date and time was not collected for a deviation for subject 01-015
PP	Missing value for PPORRESU, when PPORRES is provided	Warning	492 (19.80%)	PK parameters LAMZ, LAMZHL, LAMZLL, LAMZNPT, LAMZUL and R2 do not have units
RP	Missing value for RPORRESU, when RPORRES is provided	Warning	8 (100.00%)	Reproductive findings do not have units
PP	Missing value for PPSTRESU, when PPSTRESC is provided	Warning	492 (19.80%)	PK parameters LAMZ, LAMZHL, LAMZLL, LAMZNPT, LAMZUL and R2 do not have units
RP	Missing value for RPSTRESU, when RPSTRESC is provided	Warning	8 (100.00%)	Reproductive findings do not have units

Dataset	Diagnostic Message	Severity	Count (Issue Rate)	Explanation
AE	AE start date is after the latest Disposition date	Error	22 (27.50%)	Some AEs occurred on same date as disposition but the time is specified for the AE and not for the disposition event
EX	Exposure end date is after the latest Disposition date	Warning	841 (23.05%)	Exposure end date occurred on same date as disposition but the time is specified for the exposure record and not for the disposition event
SV	VISITNUM value does not match TV domain data	Warning	10 (1.94%)	VISITNUM=999 was not a planned visit in TV
EG	VISIT/VISITNUM values do not match TV domain data	Warning	70 (7.63%)	VISIT=EARLY TERM with corresponding VISITNUM=999 was not a planned visit in TV
LB	VISIT/VISITNUM values do not match TV domain data	Warning	350 (6.12%)	VISIT=EARLY TERM with corresponding VISITNUM=999 was not a planned visit in TV
PE	VISIT/VISITNUM values do not match TV domain data	Warning	5 (0.69%)	VISIT=EARLY TERM with corresponding VISITNUM=999 was not a planned visit in TV

Dataset	Diagnostic Message	Severity	Count (Issue Rate)	Explanation
VS	VISIT/VISITNUM values do not match TV domain data	Warning	50 (4.23%)	VISIT=EARLY TERM with corresponding VISITNUM=999 was not a planned visit in TV
EX	Variable not recommended for use	Warning	1 (25.00%)	EXSTAT is not used in the analysis
CO	Model permissible variable added into standard domain	Warning	1 (4.00%)	COVAL1 was added, this is a permissible variable
EX	Model permissible variable added into standard domain	Warning	2 (6.90%)	VISITNUM, VISIT were added, they are permissible variables
MH	Model permissible variable added into standard domain	Warning	12 (28.57%)	MHPTCD, MHLLT, MHHLTCD, MHSOCCD, MHBDSYCD, MHHLGT, VISITNUM, MHLLTCD, MHSOC, VISIT, MHHLT, MHHLGTCD were added, they are permissible variables
PE	Model permissible variable added into standard domain	Warning	1 (1.92%)	PEBLFL was added, this is a permissible variable
PP	Model permissible variable added into standard domain	Warning	2 (3.45%)	VISITNUM, VISIT were added, they are permissible variables

Dataset	Diagnostic Message	Severity	Count (Issue Rate)	Explanation
SU	Model permissible variable added into standard domain	Warning	2 (6.06%)	VISITNUM, VISIT were added, they are permissible variables
TS	Model permissible variable added into standard domain	Warning	1 (10.00%)	TSVAL1 was added, this is a permissible variable
VS	Permissible variable with missing value for all records	Warning	1 (33.33%)	VSSTAT was populated in case some vital signs were not done
AE	No Treatment Emergent info for Adverse Event	Warning	80 (100.00%)	The treatment emergent information was not collected so the flag is derived in ADAE only.
DA	Duplicate records	Warning	2 (< 0.1%)	For subject 01-016, Day 2, the time was not collected. For subject 01-160, Day 1, DATESTCD=DISPAMT: the subject took 2 products within one minute and since seconds are not recorded, it causes duplicates. DASEQ permits to differentiate records

Dataset	Diagnostic Message	Severity	Count (Issue Rate)	Explanation
PC	Duplicate records	Warning	35 (0.67%)	PCSEQ permits to differentiate records
PP	Duplicate records	Warning	1485 (48.82%)	Due to study design (two product use per day), each PK parameter are calculated twice each day. The product use session information is available in SUPPRP
RP	Missing value for RPSTRESN	Warning	8 (100.00%)	When RPSTRESC is a numeric, it is actually the year from a date and therefore RPSTRESN is not applicable.
PC	PCORRES value is populated, when PCSTAT is 'NOT DONE'	Warning	145 (100.00%)	When PCSTAT is NOT DONE, PCORRES is NS
DV	Duplicate records in DV domain	Warning	1 (0.56%)	The deviation was collected twice with different DVSPID.
DM	Invalid value for ACTARMCD	Error	9 (13.64%)	Some subjects didn't complete all product use sessions and therefore, products not taken were removed from ACTARMCD

Dataset	Diagnostic Message	Severity	Count (Issue Rate)	Explanation
DM	Invalid value for ACTARM	Error	9 (13.64%)	Some subjects didn't complete all product use sessions and therefore, products not taken were removed from ACTARM
DM	ACTARMCD does not equal ARMCD	Warning	10 (15.15%)	Some subjects didn't complete all product use sessions and therefore didn't receive all products as per ARMCD

Appendix I: Inclusion/Exclusion Criteria

Protocol/ Amendment Version	Category	IETESTCD	Full Text of Criterion
V1.0, 2.0	EXCLUSION	EXCL01	Inability to tolerate 4 mg nicotine polacrilex gum during product use trial on Day -1 (check-in) or dentition prevents subjects from chewing gum.
V1.0, 2.0	EXCLUSION	EXCL02	History or presence of any clinically significant cardiac, psychiatric, endocrine, hematologic, hepatic, immunologic, metabolic, urologic, pulmonary, neurologic, dermatologic, renal, or other major disease at Screening, which in the opinion of an investigator would jeopardize the safety of the subject or the validity of the study results.
V1.0, 2.0	EXCLUSION	EXCL03	History or presence of any type of malignant tumors.
V1.0, 2.0	EXCLUSION	EXCL04	Clinically significant abnormal findings on the vital signs, physical examination (including oral exam), medical history, or clinical laboratory results, in the opinion of an investigator.
V1.0, 2.0	EXCLUSION	EXCL05	Positive serology test results for human immunodeficiency virus (HIV)-1/HIV-2 Antibodies, hepatitis B surface antigen (HbsAg), or hepatitis C Antibody (HCVAb).
V1.0, 2.0	EXCLUSION	EXCL06	An acute illness (e.g., upper respiratory infection, viral infection) requiring treatment within 2 weeks prior to Day -1 (check-in).
V1.0, 2.0	EXCLUSION	EXCL07	Drug or alcohol abuse or dependence within the 24 months prior to Screening (except nicotine), as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th edition text revision (DSM-IV-TR), or any self-reported dependence or "addiction" within the subject's lifetime (except nicotine or caffeine).
V1.0, 2.0	EXCLUSION	EXCL08	Subjects who have ever been in treatment for substance use disorder(s) or who are currently seeking treatment for substance use disorder(s).
V1.0, 2.0	EXCLUSION	EXCL09	Positive urine drug screen (UDS) or urine alcohol test at Screening or Day -1 (check-in).
V1.0, 2.0	EXCLUSION	EXCL10	History or any current conditions that may interfere with drug absorption, distribution, metabolism, or excretion.

Protocol/ Amendment Version	Category	IETESTCD	Full Text of Criterion
V1.0, 2.0	EXCLUSION	EXCL11	History of severe allergic reaction (including anaphylaxis) to any substance, or previous status asthmaticus, or food allergies/intolerances/restrictions, or special dietary needs which, in the judgment of an investigator, contraindicates the subject's participation in the study.
V1.0, 2.0	EXCLUSION	EXCL12	Requires concomitant treatment with prescription or non-prescription products that contain pseudoephedrine (e.g., nasal/sinus decongestants).
V1.0, 2.0	EXCLUSION	EXCL13	Self-reported use of nicotine polacrilex gum, or other nicotine replacement therapy products in the 30 days prior to Day -1 (check-in). Isolated incidents within 30 days prior to Day -1 (check-in) may be permitted at the discretion of the investigator.
V1.0, 2.0	EXCLUSION	EXCL14	Subject has unsuitable or difficult venous access or is unwilling or unable to undergo direct venipuncture or catheter insertion.
V1.0, 2.0	EXCLUSION	EXCL15	Subject has donated or lost 100 to 499 mL whole blood within 30 days or more than 499 mL whole blood within 56 days preceding entry into the Confined Assessment Phase.
V1.0, 2.0	EXCLUSION	EXCL16	16. Subject is an employee of the sponsor or research site personnel directly affiliated with this study or their immediate family member defined as a spouse, parent, child or sibling, whether biological or legally adopted.
V1.0, 2.0	EXCLUSION	EXCL17	Subject is lactating and or breast feeding.
V1.0, 2.0	EXCLUSION	EXCL18	A subject who, in the opinion of an investigator, is considered unsuitable or unlikely to comply with the study protocol for any reason.
V1.0, 2.0	INCLUSION	INCL01	Must provide written informed consent prior to the initiation of any protocol-specific procedures.
V1.0, 2.0	INCLUSION	INCL02	Male and female adults, between 22 to 65 years of age, inclusive.
V1.0, 2.0	INCLUSION	INCL03	Body mass index (BMI) within 18.0 to 35.0 kg/m2, inclusive (minimum weight of at least 50.0 kg at Screening).

Protocol/ Amendment Version	Category	IETESTCD	Full Text of Criterion
V1.0, 2.0	INCLUSION	INCL04	Healthy, as determined by no clinically significant medical history, physical examination, 12-lead ECG, vital signs or laboratory (including hematology, clinical chemistry, urinalysis, and serology) findings at Screening, as judged by an investigator.
V1.0, 2.0	INCLUSION	INCL05	Smoking history of an average of at least 10 manufactured non-menthol flavored filtered standard (i.e., not slim) king size combustible cigarettes daily for at least 1 year prior to Screening. Brief periods (i.e., up to 7 consecutive days) of non-smoking during the 3 months prior to Screening (e.g., due to illness or participation in a study where smoking was prohibited) will be permitted.
V1.0, 2.0	INCLUSION	INCL06	Self-reporting of desire to smoke within approximately 30 minutes of waking.
V1.0, 2.0	INCLUSION	INCL07	Positive urine cotinine (≥500 ng/mL) at Screening.
V1.0, 2.0	INCLUSION	INCL08	Negative pregnancy test at Screening and Day -1 (check-in) for all female subjects.
V1.0, 2.0	INCLUSION	INCL09	Female subjects of non-childbearing potential must be surgically sterile or 1 year postmenopausal (as confirmed by serum Follicle Stimulating Hormone [FSH] > 35 U/L). A subject is considered to be surgically sterile if she has had a tubal ligation, hysterectomy, bilateral salpingo-oopherectomy or bilateral oopherectomy, or hysterectomy with bilateral salpingo-oopherectomy. If the subject is of childbearing potential, she must be using a medically accepted method of contraception and agree to continued use of this method for the duration of the study and for 30 days after completion of the study. Acceptable methods of contraception include abstinence, birth control pill, or an intrauterine device (known to have a failure rate of less than 1% per year) or double barrier method of contraception (e.g., male condom in addition to a diaphragm, contraceptive sponge or spermicide).
V1.0, 2.0	INCLUSION	INCL10	Able to speak, read, and understand English sufficiently to allow completion of all study assessments.
V1.0, 2.0	INCLUSION	INCL11	Must be willing to comply with the requirements and restrictions of the study.