Study Data Reviewer's Guide

Clinical

22nd Century Group, Inc.

Study CEG-P1-078

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 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, 2018-12-21
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

2. Protocol Description

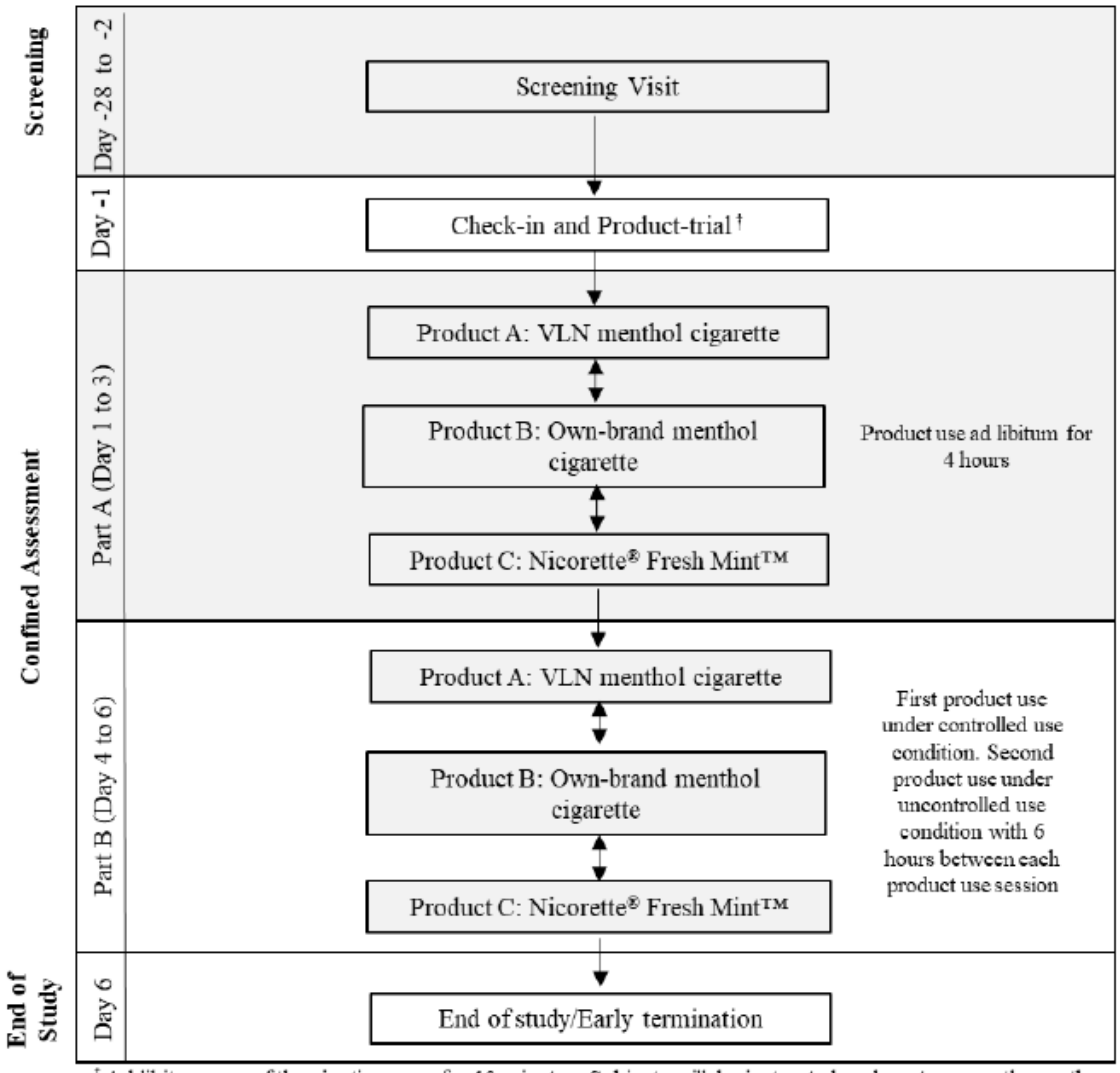
2.1 Protocol Number and Title

Protocol Number: CEG-P1-078

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

Protocol Versions: Version 1.0 / 2018-08-15

2.2 Protocol 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.

2.3 Trial Design Datasets

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

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 TI - Trial Inclusion/Exclusion Criteria

Complete text for all inclusion/exclusion criteria described in TI is provided in the Appendix I: Inclusion/Exclusion 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?	**No**
Are the submitted data a subset of collected data?	**No**

3.2 Annotated CRFs

Collected fields and pages that have not been tabulated have been annotated as "Not Submitted". 22nd Century Group, Inc. collects certain data elements to facilitate operational processes including data cleaning and dynamically creating additional forms in the electronic data capture system. All fields and pages that have been annotated as "Not Submitted" meet this criterion.

3.3 SDTM Subject Domains

Dataset - Dataset Label	PK/PD	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

Dataset - Dataset Label	PK/PD	Safety	Other	SUPP--	Related Using RELREC	Observation Class
SE - Subject Elements			X			SPECIAL PURPOSE
SU - Substance Use		X				INTERVENTIONS
SV - Subject Visits			X			SPECIAL PURPOSE
VS - Vital Signs		X		X		FINDINGS

3.3.1 AE - Adverse Events

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AEDIS	Withdrawn From Study Due To AE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

3.3.2 CM - Concomitant Medications

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
CMDOSUOT	If Other Dose Unit, Please specify
CMFRQOT	If Other Frequency, Please specify
CMINDOT	If Other Indication, Please specify
CMMHNO	MH Number

QNAM	Description
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

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
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 1
SCPRODT2	Procedure date 2
SCSUR1	Non-childbearing potential 1
SCSUR2	Non-childbearing potential 2

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 3.4.4**

Were sponsor-defined validation rules used to evaluate conformance? **No**

If yes, describe any significant sponsor-defined validation rules: **n/a**

Were the SDTM datasets evaluated in relation to define.xml? **Yes**

Was define.xml evaluated? **Yes**

Provide any additional compliance evaluation information:

4.2 Issues Summary

Check ID	Diagnostic Message	Severity	Dataset	Count (Issue Rate)	Explanation
CT2002	EPOCH value not found in 'Epoch' extensible codelist	Warning	AE	52 (83.87%)	Acceptable as the codelist is extensible.
CT2002	CMDOSU value not found in 'Unit' extensible codelist	Warning	CM	5 (11.90%)	Acceptable as the codelist is extensible.
CT2002	CMDOSFRQ value not found in 'Frequency' extensible codelist	Warning	CM	5 (11.90%)	Acceptable as the codelist is extensible.

Check ID	Diagnostic Message	Severity	Dataset	Count (Issue Rate)	Explanation
CT2002	CMDOSFRM value not found in 'Pharmaceutical Dosage Form' extensible codelist	Warning	CM	3 (7.14%)	Acceptable as the codelist is extensible.
CT2002	EPOCH value not found in 'Epoch' extensible codelist	Warning	CM	20 (47.62%)	Acceptable as the codelist is extensible.
CT2002	DASTRESU value not found in 'Unit' extensible codelist	Warning	DA	1630 (100.00%)	Acceptable as the codelist is extensible.
CT2002	DAORRESU value not found in 'Unit' extensible codelist	Warning	DA	1630 (100.00%)	Acceptable as the codelist is extensible.
CT2002	EPOCH value not found in 'Epoch' extensible codelist	Warning	DA	1630 (100.00%)	Acceptable as the codelist is extensible.
CT2002	EPOCH value not found in 'Epoch' extensible codelist	Warning	DS	59 (24.28%)	Acceptable as the codelist is extensible.
CT2002	EPOCH value not found in 'Epoch' extensible codelist	Warning	DV	152 (44.19%)	Acceptable as the codelist is extensible.

Check ID	Diagnostic Message	Severity	Dataset	Count (Issue Rate)	Explanation
CT2002	EXDOSU value not found in 'Unit' extensible codelist	Warning	EX	664 (19.39%)	Acceptable as the codelist is extensible.
CT2002	EPOCH value not found in 'Epoch' extensible codelist	Warning	EX	3425 (100.00%)	Acceptable as the codelist is extensible.
CT2002	EPOCH value not found in 'Epoch' extensible codelist	Warning	LB	588 (11.00%)	Acceptable as the codelist is extensible.
CT2002	LBORRESU value not found in 'Unit' extensible codelist	Warning	LB	1192 (22.30%)	Acceptable as the codelist is extensible.
CT2002	LBSTRESU value not found in 'Unit' extensible codelist	Warning	LB	1192 (22.30%)	Acceptable as the codelist is extensible.
CT2002	PCORRESU value not found in 'Unit' extensible codelist	Warning	PC	5130 (100.00%)	Acceptable as the codelist is extensible.
CT2002	PCSTRESU value not found in 'Unit' extensible codelist	Warning	PC	5130 (100.00%)	Acceptable as the codelist is extensible.

Check ID	Diagnostic Message	Severity	Dataset	Count (Issue Rate)	Explanation
CT2002	EPOCH value not found in 'Epoch' extensible codelist	Warning	PC	4307 (83.96%)	Acceptable as the codelist is extensible.
CT2002	EPOCH value not found in 'Epoch' extensible codelist	Warning	PE	25 (4.32%)	Acceptable as the codelist is extensible.
CT2002	EPOCH value not found in 'Epoch' extensible codelist	Warning	PP	1989 (66.17%)	Acceptable as the codelist is extensible.
CT2002	PPTEST value not found in 'PK Parameters' extensible codelist	Warning	PP	334 (11.11%)	Acceptable as the codelist is extensible.
CT2002	PPSTRESU value not found in 'PK Units of Measure' extensible codelist	Warning	PP	221 (7.35%)	Acceptable as the codelist is extensible.
CT2002	PPORRESU value not found in 'PK Units of Measure' extensible codelist	Warning	PP	221 (7.35%)	Acceptable as the codelist is extensible.
CT2002	EPOCH value not found in 'Epoch' extensible codelist	Warning	QS	31264 (97.34%)	Acceptable as the codelist is extensible.

Check ID	Diagnostic Message	Severity	Dataset	Count (Issue Rate)	Explanation
CT2002	QSCAT value not found in 'Category of Questionnaire' extensible codelist	Warning	QS	32118 (100.00%)	Acceptable as the codelist is extensible.
CT2002	EPOCH value not found in 'Epoch' extensible codelist	Warning	SE	352 (74.26%)	Acceptable as the codelist is extensible.
CT2002	SUDOSU value not found in 'Unit' extensible codelist	Warning	SU	70 (86.42%)	Acceptable as the codelist is extensible.
CT2002	EPOCH value not found in 'Epoch' extensible codelist	Warning	SV	358 (72.03%)	Acceptable as the codelist is extensible.
CT2002	EPOCH value not found in 'Epoch' extensible codelist	Warning	TA	63 (72.41%)	Acceptable as the codelist is extensible.
CT2003	PPTESTCD and PPTEST values do not have the same Code in CDISC CT	Error	PP	334 (11.11%)	CMAX is listed as Cmax in PPTEST.

Check ID	Diagnostic Message	Severity	Dataset	Count (Issue Rate)	Explanation
CT2005	DSDECOD value not found in 'Completion/Reason for Non-Completion' extensible codelist when DSCAT == 'DISPOSITION EVENT'	Warning	DS	6 (9.84%)	Acceptable as the codelist is extensible.
SD0021	Missing End Time-Point value	Warning	SU	70 (86.42%)	SUENRF is not collected in the CRF.
SD0026	Missing value for PPORRESU, when PPORRES is provided	Warning	PP	442 (19.08%)	No units provided for "Number of Points for Lambda Z".
SD0027	Missing value for DAORRES, when DAORRESU is provided	Warning	DA	2 (0.12%)	DAORRESU was assigned for all records irrespective of the amount of drug returned.
SD0029	Missing value for PPSTRESU, when PPSTRESC is provided	Warning	PP	442 (19.08%)	No units provided for "Number of Points for Lambda Z", "R Squared".
SD0030	Missing value for DASTRESC, when DASTRESU is provided	Warning	DA	2 (0.12%)	DASTRESU was assigned for all records irrespective of the amount of drug returned.

Check ID	Diagnostic Message	Severity	Dataset	Count (Issue Rate)	Explanation
SD0054	Variable in define.xml is not present in the dataset	Warning	LB	2 (7.14%)	LBSTAT, LBREASND are permissible variables with all missing values.
SD0054	Variable in define.xml is not present in the dataset	Warning	SU	1 (6.25%)	SUSTDY is permissible value with all missing values.
SD0054	Variable in define.xml is not present in the dataset	Warning	VS	1 (5.56%)	VSSTAT is a permissible value with all missing values.
SD0077	Invalid referenced record	Error	CO	1 (0.17%)	For patient number CEG-P1-078-02-139, comments identified by IDVARVAL values 4 and 5 refer to the same record in DS identified by DSSEQ = 5.
SD0080	AE start date is after the latest Disposition date	Error	AE	14 (22.58%)	Time is not collected as part of Disposition, hence all AEs occurring on the same date as the DSSTDTC are indicated as occurring post disposition date by Pinnacle 21.
SD0082	Exposure end date is after the latest Disposition date	Warning	EX	796 (23.24%)	Time is not collected as part of Disposition, hence all exposures occurring on the same date as the DSSTDTC are indicated as occurring post disposition date by Pinnacle 21.
SD1017	VISITNUM value does not match TV domain data	Warning	SV	6 (1.25%)	Early Termination (VSITINUM=999) is not identified as a planned visit in the TV domain.
SD1023	VISIT/VISITNUM values do not match TV domain data	Warning	EG	42 (4.92%)	Early Termination (VSITINUM=999) is not identified as a planned visit in the TV domain.

Check ID	Diagnostic Message	Severity	Dataset	Count (Issue Rate)	Explanation
SD1023	VISIT/VISITNUM values do not match TV domain data	Warning	LB	220 (4.13%)	Early Termination (VSITINUM=999) is not identified as a planned visit in the TV domain.
SD1023	VISIT/VISITNUM values do not match TV domain data	Warning	PE	5 (0.86%)	Early Termination (VSITINUM=999) is not identified as a planned visit in the TV domain.
SD1023	VISIT/VISITNUM values do not match TV domain data	Warning	VS	30 (2.73%)	Early Termination (VSITINUM=999) is not identified as a planned visit in the TV domain.
SD1075	Variable not recommended for use	Warning	EX	1 (25.00%)	EXSTAT has been included to determine if exposure to investigational drug occurred.
SD1076	Model permissible variable added into standard domain	Warning	CO	1 (4.00%)	COVAL1 captures characters in excess of 200 from COVAL.
SD1076	Model permissible variable added into standard domain	Warning	EX	2 (6.90%)	VISITNUM, VISIT added for traceability
SD1076	Model permissible variable added into standard domain	Warning	MH	10 (23.81%)	MHHLGT, MHHLTCD, MHSOCCD,MHPTCD, MHSOC, MHHLGTCD,MHLLT,MHHLT,MHLLTCD,MHBDSYCD are added as captured from the MedDRA dictionary.
SD1076	Model permissible variable added into standard domain	Warning	PP	2 (3.45%)	VISITNUM, VISIT are added for traceability.

Check ID	Diagnostic Message	Severity	Dataset	Count (Issue Rate)	Explanation
SD1076	Model permissible variable added into standard domain	Warning	SU	2 (6.06%)	VISITNUM, VISIT are added for traceability.
SD1076	Model permissible variable added into standard domain	Warning	TS	1 (10.00%)	TSVAL1 captures characters in excess of 200 from TSVAL.
SD1097	No Treatment Emergent info for Adverse Event	Warning	AE	62 (100.00%)	No Treatment Emergent information for AEs were collected in CRF
SD1117	Duplicate records	Warning	DA	1 (< 0.1%)	The records are not duplicates when considering DAREFID which captures the inhalation occurrence number.
SD1117	Duplicate records	Warning	PC	19 (0.37%)	These records are not duplicates as the timepoint of collection is different for each record.
SD1117	Duplicate records	Warning	PP	1485 (49.40%)	These records are not duplicates as the testing conditions differ as captured in SUPPPP.QVAL, when QNAM is COND.
SD1123	PCORRES value is populated, when PCSTAT is 'NOT DONE'	Warning	PC	124 (100.00%)	PCORRES is populated as NS for these records as no sample was collected.
SD1201	Duplicate records in DV domain	Warning	DV	4 (1.16%)	Mapped as reported by the clinic

Check ID	Diagnostic Message	Severity	Dataset	Count (Issue Rate)	Explanation
SD2002	Invalid value for ACTARMCD	Error	DM	5 (8.20%)	ACTARMCD reflects only the actual treatments administered to the patient and may not be the same as described in TA domain, as the patient may have dropped out of the study earlier than planned.
SD2003	Invalid value for ACTARM	Error	DM	5 (8.20%)	ACTARM reflects only the actual treatments administered to the patient and may not be the same as described in TA domain, as the patient may have dropped out of the study earlier than planned.
SD2236	ACTARMCD does not equal ARMCD	Warning	DM	6 (9.84%)	ACTARMCD reflects only the actual treatments administered to the patient and may not be the same as described in TA domain, as the patient may have dropped out of the study earlier than planned.
DD0039	Variable is in wrong order within Dataset 'SU'	Warning	DEFINE	1 (100.00%)	SUSTDY is permissible value with all missing values, hence dropped in the dataset but listed in the Define.

Appendix I: Inclusion/Exclusion Criteria

Protocol/ Amendment Version	Category	IETESTCD	Full Text of Criterion
CEG-P1-078	INCLUSION	INCL01	Must provide written informed consent prior to the initiation of any protocol-specific procedures.
CEG-P1-078	INCLUSION	INCL02	Male and female adults, between 22 to 65 years of age, inclusive.
CEG-P1-078	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).
CEG-P1-078	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.
CEG-P1-078	INCLUSION	INCL05	Smoking history of an average of at least 10 manufactured 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.
CEG-P1-078	INCLUSION	INCL06	Self-reporting of desire to smoke within approximately 30 minutes of waking.
CEG-P1-078	INCLUSION	INCL07	Positive urine cotinine (?500 ng/mL) at Screening.
CEG-P1-078	INCLUSION	INCL08	Negative pregnancy test at Screening and Day -1 (check-in) for all female subjects.

Protocol/ Amendment Version	Category	IETESTCD	Full Text of Criterion
CEG-P1-078	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).
CEG-P1-078	INCLUSION	INCL10	Able to speak, read, and understand English sufficiently to allow completion of all study assessments.
CEG-P1-078	INCLUSION	INCL11	Must be willing to comply with the requirements and restrictions of the study.
CEG-P1-078	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.
CEG-P1-078	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.
CEG-P1-078	EXCLUSION	EXCL03	History or presence of any type of malignant tumors.
CEG-P1-078	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.

Protocol/ Amendment Version	Category	IETESTCD	Full Text of Criterion
CEG-P1-078	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).
CEG-P1-078	EXCLUSION	EXCL06	An acute illness (e.g., upper respiratory infection, viral infection) requiring treatment within 2 weeks prior to Day -1 (check-in).
CEG-P1-078	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).
CEG-P1-078	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).
CEG-P1-078	EXCLUSION	EXCL09	Positive urine drug screen (UDS) or urine alcohol test at Screening or Day -1 (check-in).
CEG-P1-078	EXCLUSION	EXCL10	History or any current conditions that may interfere with drug absorption, distribution, metabolism, or excretion.
CEG-P1-078	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.
CEG-P1-078	EXCLUSION	EXCL12	Requires concomitant treatment with prescription or non-prescription products that contain pseudoephedrine (e.g., nasal/sinus decongestants).
CEG-P1-078	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.

Protocol/ Amendment Version	Category	IETESTCD	Full Text of Criterion
CEG-P1-078	EXCLUSION	EXCL14	Subject has unsuitable or difficult venous access or is unwilling or unable to undergo direct venipuncture or catheter insertion.
CEG-P1-078	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.
CEG-P1-078	EXCLUSION	EXCL16	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.
CEG-P1-078	EXCLUSION	EXCL17	Subject is lactating and or breast feeding.
CEG-P1-078	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.