Analysis Data Reviewer's Guide

22nd Century Group, Inc.

Study CEG-P9-153

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Contents

1. Introduction

1.1 Purpose

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

1.2 Acronyms

Acronym	Translation
IG	Implementation Guide
PD	Pharmacodynamics
PK	Pharmacokinetics

1.3 Study Data Standards and Dictionary Inventory

Standard or Dictionary	Versions Used
SDTM	•SDTM v1.4 •SDTM-IG v3.2
ADaM	•ADaM v2.1 •ADaM-IG v1.1
Controlled Terminology	CDISC ADaM Controlled Terminology, 2017-09-29
Data Definitions	Define-XML v2.0
Medical Events Dictionary	MedDRA v21.0

1.4 Source Data Used for Analysis Dataset Creation

The analysis files for this study were derived from the submitted SDTM files. SDTM files were prepared from CRF data according to version 3.2 of the SDTM IG.

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 in Relation to ADaM Concepts

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.

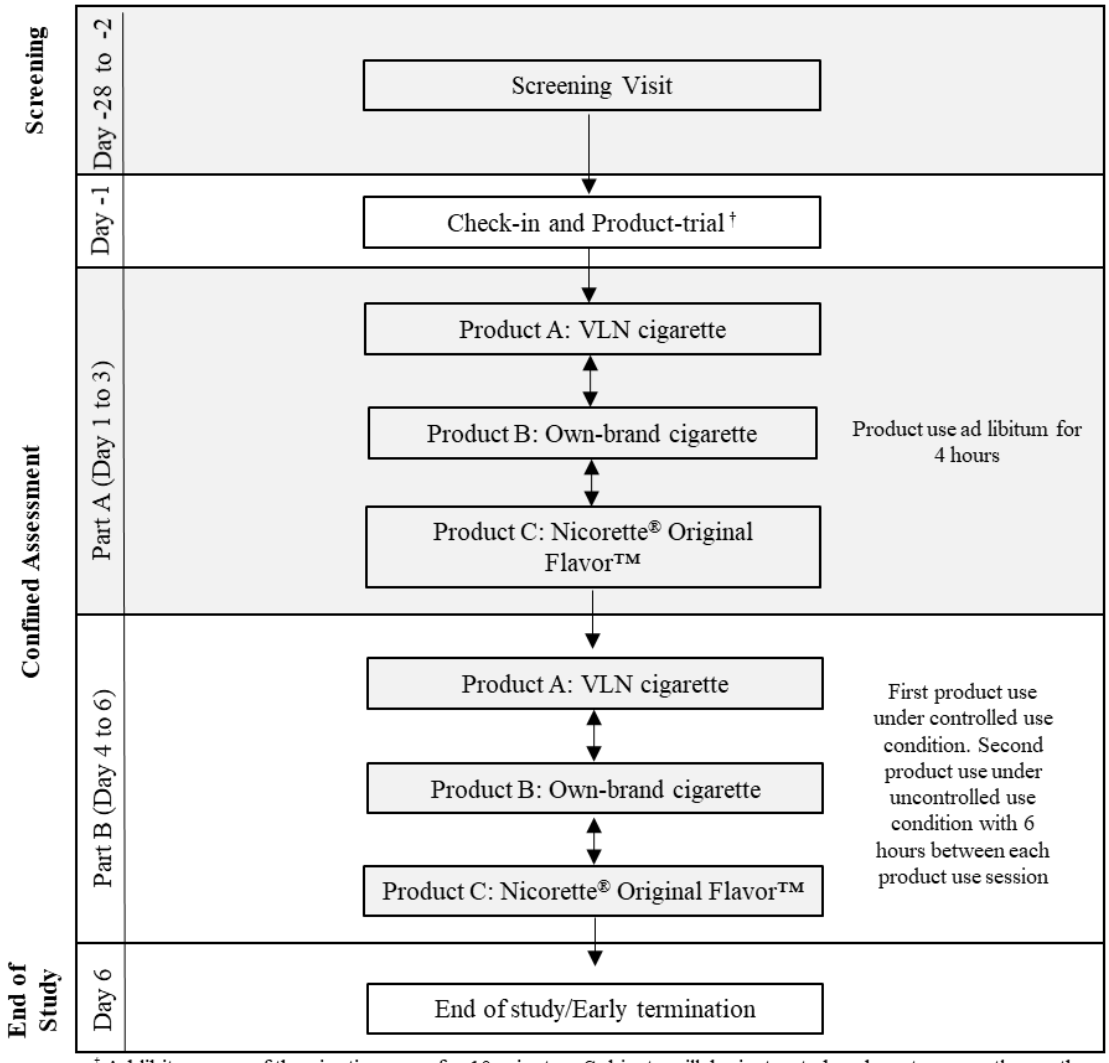
Part A began on Day 1. Subjects were randomized to one of three product sequence groups in Part A, which consisted of an ad libitum product use session of each of the 3 study products for 4 hours in a randomized crossover manner (one product per day).

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.

3. Analysis Considerations Related to Multiple Analysis Datasets

3.1 Comparison of SDTM and ADaM Content

- *Are data for screen failures, including data for run-in screening (for example, SDTM values of ARMCD='SCRNFAIL', or 'NOTASSGN') included in ADaM datasets?*

  No. Screen failure subjects were not included in SDTM.

- *Are data taken from an ongoing study?*

  No. This is a final locked database.

3.2 Core Variables

Core variables are those that are represented across all/most analysis datasets.

Variable Name	Variable Description
STUDYID	Study Identifier
USUBJID	Unique Subject Identifier
SUBJID	Subject Identifier for the Study
SITEID	Study Site Identifier
ENRLFL	Enrolled Population Flag
SAFFL	Safety Population Flag
RANDAFL	Randomized Population Flag in part A
RANDBFL	Randomized Population Flag in part B
PKFL	Pharmacokinetic Population Flag
PDFL	PD Population Flag
COMPLFL	Completers Population Flag
ARM	Description of Planned Arm
ARMCD	Planned Arm Code
ACTARM	Description of Actual Arm
ACTARMCD	Actual Arm Code
TRTSDT	Date of First Exposure to Treatment
TRTSDTM	Datetime of First Exposure to Treatment
TRTEDT	Date of Last Exposure to Treatment
TRTEDTM	Datetime of Last Exposure to Treatment
TRT01P	Planned Treatment for Period 01
TRT01PN	Planned Treatment for Period 01 (N)
TRT01A	Actual Treatment for Period 01
TRT01AN	Actual Treatment for Period 01 (N)
TRTP	Planned Treatment
TRTPN	Planned Treatment (N)
TRTA	Actual Treatment
TRTAN	Actual Treatment (N)

Variable Name	Variable Description
EPOCH	Epoch

3.3 Treatment Variables

ARM versus TRTxxP

- *Are the values of ARM equivalent in meaning to values of TRTxxP?*

  No. This is a multiple treatments study and values of ARM reflect the treatment sequence, while values of TRTxxP where xx=01, 02, 03, 04, 05 or 06 correspond to treatment which subjects were planned to receive during each treatment period.

ACTARM versus TRTxxA

- *If TRTxxA is used, then are the values of ACTARM equivalent in meaning to values of TRTxxA?*

  No. This is a multiple treatments study and values of ACTARM reflect the treatment sequence, while values of TRTxxA where xx=01, 02, 03, 04, 05 or 06 correspond to treatment which subjects actually received during each treatment period.

Use of ADaM Treatment Variables in Analysis

- *Are both planned and actual treatment variables used in analyses?*

  Planned treatment sequence variable ARM was used for the summary tables when populating results by sequence whereas actual treatment variables (TRTxxA) were used to assign an assessment to a treatment (e.g. AEs).

3.4 Subject Issues that Require Special Analysis Rules

There were no subjects who required any special analysis rules in this study.

3.5 Use of Visit Windowing, Unscheduled Visits, and Record Selection

- *Was windowing used in one or more analysis datasets?* **No.**
- *Were unscheduled visits used in any analyses?*

  Unscheduled visits could potentially be used as baseline visits (ABLFL = 'Y') if the latest assessment prior to the start of the study product happened to be unscheduled.

3.6 Imputation/Derivation Methods

- *If date imputation was performed, were there rules that were used in multiple analysis datasets?*

  For any duration calculation, the following rules were applied:

- If the seconds, minutes or hours were missing, they were replaced by "00";
- If the day was missing, it was replaced by "01";
- If the month was missing, it was replaced by "January";
- If the date and time were not available, then no imputation was performed and the duration was left missing.

4. Analysis Data Creation and Processing Issues

4.1 Split Datasets

Split datasets were not used.

4.2 Data Dependencies

There are no analysis dataset dependencies other than ADSL.

4.3 Intermediate Datasets

No intermediate analysis datasets were created in this trial.

4.4 Variable Conventions

For vital signs (ADVS), laboratory findings (ADLB), ECG parameters (ADEG) pharmacokinetic concentrations (ADPC) and pharmacokinetic parameters (ADPP), the values of SDTM xxTESTCD (where xx is equal to VS, LB or EG accordingly) are used for the value of PARAMCD while the text of PARAM indicates the test and units of the test.

In ADEG, ADEX, ADLB, ADPC, ADPE, ADPP, ADQS, ADVS, analysis flag ANL01FL marks the records suitable for the analysis. There is always a single record per USUBJID/PARAMCD/AVISITN/ASTDTM with ANL01FL = 'Y'.

5. Analysis Dataset Descriptions

5.1 Overview

- *Do the analysis datasets support all protocol- and statistical analysis plan-specified objectives?*

  Yes, all protocol- and statistical analysis plan-specified objectives are supported by the analysis datasets.

5.2 Analysis Datasets

Dataset - Dataset Label	Class	Safety	Baseline or other subject characteristics	PK/PD	Other	Primary Objective	Structure
ADSL - Subject-Level Analysis Dataset	ADSL		X				One record per subject
ADAE - Adverse Event Analysis Dataset	OCCDS	X					One record per subject per adverse event
ADEG - ECG Analysis Dataset	BDS	X					One or more records per subject per analysis parameter per analysis timepoint
ADEX - Analysis Exposure Dataset	ADAM OTHER				X	X	One or more records per subject per treatment per analysis timepoint
ADLB - Laboratory Analysis	BDS	X					One or more records per subject per analysis parameter per analysis timepoint
ADPC - Pharmacokinetic Concentrations	BDS			X		X	One or more records per subject per analysis parameter per analysis timepoint

Dataset - Dataset Label	Class	Safety	Baseline or other subject characteristics	PK/PD	Other	Primary Objective	Structure
ADPE - Physical Examinations	BDS	X					One or more records per subject per analysis parameter per analysis timepoint
ADPP - Pharmacokinetic Parameters	BDS			X		X	One or more records per subject per analysis parameter per analysis timepoint
ADQS - Questionnaires Analysis Dataset	BDS			X		X	One or more records per subject per analysis parameter per analysis timepoint
ADSU - Substance Use Analysis Dataset	BDS				X		One or more records per subject per analysis parameter per analysis timepoint
ADVS - Vital Signs Analysis Dataset	BDS	X					One or more records per subject per analysis parameter per analysis timepoint

5.2.1 ADSL - Subject-Level Analysis Dataset

ADSL has the same number of subjects and records as in the SDTM.DM domain. ADSL includes the following categories of subject-level variables:

- Demographic and baseline characteristics;
- Population flags;
- Disposition;
- Eligibility;
- Treatment assignment;
- Key dates: treatment, informed consent, study completion or discontinuation.

All subjects in DM were included in ADSL.

The following population indicator variables were created in ADSL:

Population Flag	Population
ENRLFL	Enrolled Population Flag
SAFFL	Safety Population Flag
RANDAFL	Randomized Population Flag in part A
RANDBFL	Randomized Population Flag in part B
COMPLFL	Completers Population Flag
PKFL	Pharmacokinetic Population Flag
PDFL	PD Population Flag

5.2.2 ADAE - Adverse Event Analysis Dataset

Dataset contains all information about adverse events and supports safety analysis.

In addition to SDTM and common variables, it includes treatment emergent flag, elapsed time of AE since last dose taken and AE duration according to each treatment period.

5.2.3 ADEG - ECG Analysis Dataset

Dataset contains ECG parameters and supports safety analysis.

5.2.4 ADEX - Analysis Exposure Dataset

Dataset includes the same information as the SDTM.EX dataset, in addition to common ADaM variables such as population flags and planned and actual treatment. Analysis variables were added as well such the duration of product used.

5.2.5 ADLB - Laboratory Analysis

Dataset contains all information for analysis of laboratory tests and supports safety analysis.

5.2.6 ADPC - Pharmacokinetic Concentrations

Dataset includes the same information as the SDTM.PC dataset, in addition to common ADaM variables such as population flags and planned and actual treatment.

5.2.7 ADPE - Physical Examinations

Dataset contains all information for analysis of physical examinations and supports safety analysis.

5.2.8 ADPP - Pharmacokinetic Parameters

This dataset supports analyses of PK parameters.

It includes records from SDTM.PP dataset where PP.PPSTAT was not "NOT DONE", just adds ADaM common variables such as population flags or planned and actual treatment taken among other standard variables.

5.2.9 ADQS - Questionnaires Analysis Dataset

This dataset supports analyses of PD parameters.

It includes the same information as the SDTM.QS dataset, just adds ADaM common variables such as population flags or planned and actual treatment taken among other standard variables.

5.2.10 ADSU - Substance Use Analysis Dataset

Dataset contains all information for analysis of tobacco product use habits.

5.2.11 ADVS - Vital Signs Analysis Dataset

Dataset contains all information for analysis of vital signs and supports safety analysis.

6. Data Conformance Summary

6.1 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 ADaM datasets evaluated in relation to define.xml?	**Yes**
Was define.xml evaluated?	**Yes**

6.2 Issues Summary

Dataset	Diagnostic Message	Severity	Count (Issue Rate)	Explanation
ADQS	Inconsistent value for TRTPN	Error	196 (0.62%)	Due to study design (two cross-overs 3x3 with the same treatments), each treatment is taken twice: once during Day 1 to 3 with a corresponding TRTPN (1, 2 or 3) and once during Day 4 to 6 with a different corresponding TRTPN (4, 5 or 6)

Dataset	Diagnostic Message	Severity	Count (Issue Rate)	Explanation
ADQS	Inconsistent value for TRTAN	Error	196 (0.62%)	Due to study design (two cross-overs 3x3 with the same treatments), each treatment is taken twice: once during Day 1 to 3 with a corresponding TRTAN (1, 2 or 3) and once during Day 4 to 6 with a different corresponding TRTAN (4, 5 or 6)
ADQS	Inconsistent value for PARCAT2 within a unique PARAMCD	Error	29411 (89.62%)	Due to study design, PK parameters were calculated twice at each visit: once for the first use and once for the second use and the use is populated in PARCAT2.
ADQS	Multiple baseline records exist for a unique USUBJID, PARAMCD, BASETYPE	Error	3679 (81.56%)	The baseline is defined as the pre-dose value for each product use session. Therefore there is a unique baseline record each USUBJID, PARCAT2, VISIT, PARAMCD
ADEG	Secondary variable is present but its primary variable is not present	Error	1 (25.00%)	EGPREC is not a secondary variable.
ADPC	Secondary variable is present but its primary variable is not present	Error	1 (20.00%)	NBPREC is not a secondary variable.

Dataset	Diagnostic Message	Severity	Count (Issue Rate)	Explanation
ADPP	Secondary variable is present but its primary variable is not present	Error	2 (33.33%)	NBPREC, PPSPEC are not secondary variables.
ADSL	Secondary variable is present but its primary variable is not present	Error	1 (25.00%)	ETHNIC is not a secondary variable.