Analysis Data Reviewer's Guide

22nd Century Group, Inc

Study CA24914

Version 1.0

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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
WHO	World Health Organization
PK	Pharmacokinetic
MedDRA	Medical Dictionary for Regulatory Activities

1.3 Study Data Standards and Dictionary Inventory

Standard or Dictionary	Versions Used
SDTM	SDTM IG v3.2
ADaM	ADaM Implementation guide v1.0 ADaM Structure for Occurrence Data v1.0 ADaM Model, Version 2.1
Data Definitions	Define.xml v2.0
Medical Events Dictionary	MedDRA 21.0
Medications Dictionary	WHO DD 01SEP2018

1.4 Source Data Used for Analysis Dataset Creation

The ADaM datasets were derived from SDTM version 3.2. The datasets were derived from the final locked database.

2 Protocol Description

2.1 Protocol Number and Title

Protocol Number: CA24914

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

Protocol Versions: Protocol Amendment 3: 14 Jan 2019

2.2 Protocol Design in Relation to ADaM Concepts.

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

All potential subjects provided informed consent and successfully complete the Screening procedures prior to participation in the study. Subjects were also engage in a brief product trial with the VLN cigarettes. Subjects who reacted negatively (i.e., unwilling to use and/or cannot tolerate the product [experience AEs that were prevent them from continuing to use the product as judged by the Investigator]) to the VLN cigarettes during the product trial period were not continue in the study.

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

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

On Day -1 of Week 1, subjects were randomly selected to either remain smoking their non-menthol (20 subjects) or menthol (20 subjects) UB cigarettes, or to switch to smoking non-menthol (50 subjects) or menthol (50 subjects) VLN cigarettes as per their UB cigarette flavor.

Subjects returned at the end of Weeks 2 and 6, at the time indicated by the CRU, for collection of blood and 24-hour urine samples for BoE assessments. Subjective effects questionnaires were also completed at scheduled times. Subjects continued recording their CPD in their e-diaries. The same subset of 18 non-menthol and 18 menthol smoker subjects selected to complete a puffing topography assessment with their UB cigarette on Week-1, will complete an assessment of puffing topography with the VLN cigarettes at these visits, and a further subset of 12 non-menthol and 12 menthol smoker subjects completed an assessment of nicotine PK at the end of these visits. Subjects undergoing topography and PK assessments have been assigned to switch to smoking VLN cigarettes.

Additionally, all subjects visit the clinic at the end of Week 4 to receive further supplies of cigarettes (if assigned to the VLN groups) and to complete subjective effects questionnaires.

Subjects randomized to the VLN groups will be provided with a supply of VLN cigarettes at each visit, which will be 150 % of their usual daily consumption as reported during Week 1. If subjects run out of cigarettes between clinic visits, they may visit the clinic to receive additional test cigarettes. All subjects were asked to smoke their cigarettes *ad libitum*, recording their actual daily consumption in their e-diaries. Non-compliant nicotine product consumption should also be recorded. Used cigarette butts were also collected during ambulatory periods to verify product use and/or assess compliance. During Week 1 (all subjects) and all subsequent weeks (subjects randomized to continue smoking UB cigarettes) subjects were asked not to change their UB cigarette brand or flavor.

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

The following investigational products were used during this study:

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

UB mentholated cigarette	UB mentholated	Subjects' UB mentholated filtered cigarettes

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?

All subjects in the SDTM database were used in ADaM datasets. 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
USUBJID	Unique subject identifier
STUDYID	Study identifier used for this protocol
SUBJID	Subject identifier for the Study
SITEID	Study Site identifier
AGE	Age
AGEU	Age Units
SEX	Sex
RACE	Race
ETHNIC	Ethnicity
SAFFL	Safety Flag
ITTFL	Intent to Treat Flag
PPROTFL	Per-Protocol Population Flag
COMPLFL	Completers Population Flag
PKANALFL	PK Analysis Flag
PKITTFL	PK Intent to Treat Flag

PKPPFL	PK Per-Protocol Population Flag
COUNTRY	Country

3.3 Treatment Variables

ARMCD versus TRTXXP

- Are the values of ARMCD equivalent in meaning to values of TRTxxP? Yes. ARMCD was used to derive TRTxxP depending on analysis period.

ACTARM versus TRTXXA

- If TRTxxA is used, then are the values of ACTARM equivalent in meaning to values of TRTxxA? No. ARMCD was used to derive actual treatment along with dosing dates. In instances where a subject discontinued the ACTARM was set to UNPLANNED.

Use of ADaM Treatment Variables in Analysis

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

No, only actual treatment variables used in analyses.

3.4 Subject Issues that Require Special Analysis Rules

There were no issues that required special analysis rules.

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

- Was windowing used in one or more analysis datasets?

No visit windowing was done in the analysis datasets.

- Were unscheduled visits used in any analyses?

Unscheduled visits were not used in analysis.

- Were there records which are included in one or more analysis datasets that were never used for any analysis (such as after follow-up period, screening, etc.)?

Subject recheck events were only used if prior to first dose. Any rechecks after dosing were not included in the analysis

3.6 Imputation/Derivation Methods

- If date imputation was performed, were there rules that were used in multiple analysis datasets? Date imputation was not applied.

- Was DTYPE used in one or more analysis datasets? No.

- Was BASETYPE used in one or more analysis datasets? No.

4. Analysis Data Creation and Processing Issues

4.1 Split Datasets

No datasets were required to be split.

4.2 Data Dependencies

There are no analysis dataset dependencies other than ADSL.

4.3 Intermediate Datasets

Not Applicable.

4.4 Variable Conventions

Not Applicable.

5. Analysis Dataset Descriptions

5.1 Overview

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

Yes. All analyses were done using the ADaM datasets as input.

5.2 Analysis Datasets

Dataset – Dataset Label	Class	Baseline or other subject characteristics	Safety	PK/PD	Primary Objective	Structure
ADSL-Subject Level Analysis Metadata	ADSL	X				One record per subject
ADAE-Adverse Events -Analysis	OCCDS		X			One record per event per subject
ADLB-Laboratory Tests - Analysis	BDS		X			One record per laboratory parameter per visit per subject
ADPC-Pharmacokinetic Concentrations-Analysis	BDS			X	X	One record per sample per analyte per visit per timepoint per subject
ADPP-Pharmacokinetic Parameters-Analysis	BDS			X	X	One record per parameter per analyte per visit per subject
ADSU-Product Use History-Analysis	OCCDS			X		One record per event per subject
ADVS-Vital Signs - Analysis	BDS		X			One record per vital signs parameter per visit per subject
ADQS-Questionnaire - Analysis	BDS			X		One record per questionnaire parameter per visit per subject

Dataset – Dataset Label	Class	Baseline or other subject characteristics	Safety	PK/PD	Primary Objective	Structure
ADXT-Smoking Topography - Analysis	BDS			X		One record per vital signs parameter per visit per subject
ADEX-Exposure - Analysis	BDS			X	X	One record per e-diary entry per subject
ADDA- Product Returned-Analysis	BDS			X		One record per product returned per visit per subject

5.2.1 ADSL – Subject Level Analysis Dataset

The ADSL (Subject Level Analysis) dataset is the key subject-level dataset, with one record per enrolled subject. It contains all the subject-level variables for demographics, subject characteristics, population flags and stratification variables. Core subject level analysis variables from this dataset are duplicated on the other analysis datasets. The following variables are included in order in other datasets. Study Identifier (STUDYID), Unique Subject Identifier (USUBJID), Study Site Identifier (SITEID), COUNTRY, subject characteristics (AGE, AGEU, SEX, RACE, and ETHNIC), Description of Planned Arm (ARM), and population flags for Safety (SAFFL), Intent to Treat (ITTFL), Per-Protocol (PPROTFL), Completion (COMPFL), PK Analysis (PKANALFL), and PD Analysis (PDANLFL).

5.2.2 ADAE – Adverse Event Analysis dataset.

Subjects who reported any Adverse Events during a period are represented in this dataset .Its data reference is the SDTM AE (Adverse Events) domain.

5.2.3 ADLB – Laboratory Tests Analysis

Contains one record per lab test code per visit per subject. Its data reference is the SDTM LB (Laboratory Tests) domain.

5.2.4 ADPC – Pharmacokinetic Concentration Analysis

Contains one record per sample per analyte per visit per timepoint per subject. Its data reference is SDTM PC (Pharmacokinetic Concentrations) domain.

5.2.5 ADPP – Pharmacokinetic Parameter Analysis

Contains one record per parameter per analyte per visit per subject. Its primary data reference is SDTM PP (Pharmacokinetic Parameters) domain.

5.2.6 ADSU – Product Use History Analysis dataset.

Product use history is represented in this dataset .Its data reference is the SDTM SU (Substance) domain.

5.2.7 ADVS – Vital Signs - Analysis

Contains one record per vital sign measurement per timepoint per subject. Its data reference is the SDTM VS (Vital Signs) domain.

5.2.8 ADQS – Questionnaire - Analysis

Contains one record per questionnaire parameter per time point per subject. Its data reference is the SDTM QS (Questionnaire) domain. Records where QSSTAT equal "NOT DONE" were removed. Subjects who had duplicate paper questionnaires had these excluded. AVAL was assigned for the Fagerstrom Questionnaire based on QS.QSSTRESC.

5.2.9 ADXT – Smoking Topography - Analysis

Contains one record per smoking topography parameter per time point per subject. Its data reference is the SDTM XT (Topography) domain. Only records where XT.XTTESTCD equaled "DI","II","QCI","QMI", or "VI" were retained. The first Inter-puff interval was removed from analysis and parameter calculation. The ITTRFL and PPROTRFL record level flags were used to remove subject based on protocol deviations.

5.2.10 ADEX – Exposure - Analysis

One record per e-diary entry per subject. Its data reference is the SDTM EX (E-diary) domain. Subjects who randomized and switched to VLN products but incorrectly answered UB E-diary after randomization were excluded. The ambulatory daily product use was recorded by the subjects via a mobile application loaded onto their personal mobile device or a device provided by the site. The Clinical Ink application was not able to modify the questions from UB questions to VLN referenced questions based on the subject's randomization. As a result all subjects were enrolled onto the UB app on Day -7. Those subjects randomized to VLN were then instructed to remove the UB app and download and use the VLN app upon notice of their randomization. This switch from the UB app to the VLN app occurred at different times depending upon the subject's participation in the sub-study. Therefore, for Site 001, subjects who were randomized to VLN switched from the UB app to the VLN app on Day 1 and therefore had Day 1 E-diary excluded if present. The first data entry for these subjects was Day 2, and run to Day 43. The assignment of week was then dependent on product assignment and site.

5.2.11 ADDA – Product Returned-Analysis

One record per product returned per visit per subject. Its data reference is the SDTM SUPPDA (Drug Accountability) domain.

6. Data Conformance Summary

6.1 Conformance Inputs

- Were the analysis datasets evaluated for conformance with CDISC ADaM Validation Checks?

  Datasets were validated using Pinnacle community 2.2.0

- Were the AdaM datasets evaluated in relation to define.xml? Yes, see below.
- Was define.xml evaluated? Yes, see below.

6.2 Issues Summary

Pinnacle version 2.2.0 was used to assist with the preparation and validation of the transfer package. There are no OpenCDISC errors associated with the ADaM datasets or supporting define.xml.

Dataset(s)	Diagnostic Message and/or Check ID	Severity	Count/ Issue Rate	Explanation
ADSL	Variable label mismatch between dataset and ADaM standard	Error	14	As this is a cigarette study, 'Product ' is used in variable labels
ADLB	Variable label mismatch between dataset and ADaM standard	Error	4	As this is a cigarette study, 'Product ' is used in variable labels
ADSU	Variable label mismatch between dataset and ADaM standard	Error	4	As this is a cigarette study, 'Product ' is used in variable labels
ADVS	Variable label mismatch between dataset and ADaM standard	Error	4	As this is a cigarette study, 'Product ' is used in variable labels
ADDA	Variable label mismatch between dataset and ADaM standard	Error	4	As this is a cigarette study, 'Product ' is used in variable labels
ADEX	Variable label mismatch between dataset and ADaM standard	Error	4	As this is a cigarette study, 'Product ' is used in variable labels
ADPC	Variable label mismatch between dataset and ADaM standard	Error	4	As this is a cigarette study, 'Product ' is used in variable labels
ADPP	Variable label mismatch between dataset and ADaM standard	Error	4	As this is a cigarette study, 'Product ' is used in variable labels
ADQS	Variable label mismatch between dataset and ADaM	Error	6	As this is a cigarette study, 'Product ' is used in variable

Dataset(s)	Diagnostic Message and/or Check ID	Severity	Count/ Issue Rate	Explanation
	standard			labels
ADXT	Variable label mismatch between dataset and ADaM standard	Error	4	As this is a cigarette study, 'Product ' is used in variable labels
Define	Define.xml/CDISC variable Label mismatch	Warnning	2	As this is a cigarette study, 'Product ' is used in variable labels

7. Submission of Programs

The submitted programs include the programs that produce each analysis datasets. The name of the creation program is identical to the name of the analysis dataset. For example, ADSL.SAS produces the dataset ADSL. All inputs, such as SDTM domains or other analysis datasets, are specified in the program header and outlined in the table below:

Program Name	Output	Inputs
adsl-sas.txt	ADSL	DM, PP, SUPPDM, DS, EX, VS
adae-sas.txt	ADAE	AE,SUPPAE,ADSL
advs-sas.txt	ADVS	VS,SUPPVS,ADSL
adlb-sas.txt	ADLB	LB,SUPPLB,ADSL
adpc-sas.txt	ADPC	PC,SUPPPC,ADSL
adpp-sas.txt	ADPP	PP,SUPPPP,ADSL
adsu-sas-txt	ADSU	SU, SUPPSU, ADSL
adxt-sas-txt	ADXT	XT, SUPPXT, ADSL
adex-sas-txt	ADEX	EX, SUPPEX, ADSL
adqs-sas-txt	ADQS	QS, SUPPQS, ADSL
adda-sas-txt	ADDA	DA, SUPPDA, ADSL

The submitted package also includes programs that produce safety tables and PK tables. The audit list included associates the table number with the program that produced it. All inputs, such as ADaM domains or other analysis datasets, are specified in the program header along with the corresponding output tables.

The following macros used to perform and support analysis can also be found included in the package

Macro Name	Description
adamfreq-sas.txt	Calculates frequency counts.
adammean-sas.txt	Calculates mean summaries.
adamttest-sas.txt	Performs PK statistical analysis.
adamntrt-sas.txt	Creates number of treatments or sequences.
adamtreat-sas.txt	Sets treatment variable.
adamtreattot-sas.txt	Sets treatment variable. Creates overall treatment.
adamaecnt-sas.txt	Puts total counts together.
adamaesubjcnt.txt	Counts number of subjects with Adverse Events.
adamaesubjcnt2-sas.txt	Counts number of subjects with Adverse Events.
adamaerel-sas.txt	Calculates summaries by relationship.
adamaesev-sas.txt	Calculates summaries by severity.
adamtreatidfig-sas.txt	Provides treatment descriptions for PK tables.
adamtreatids-sas.txt	Provides treatment descriptions for PK figures.
adammeanpk-sas.txt	Calculates mean PK summary statistics.
adamtoptreat-sas.txt	Sets treatment variable for Topography section.
adammeantop-sas.txt	Calculates mean summaries for Topography section.
adamtoptreatid-sas.txt	Provides treatment descriptions for Topography tables.
adamtoptreatidg-sas.txt	Provides treatment descriptions for Topography figures.
adamtopttest-sas.txt	Performs Topography T-test statistical analysis for PP population.
adamtopttest2-sas.txt	Performs Topography T-test statistical analysis for ITT population.
adamparamdefine-sas.txt	Defines Topography parameter characteristics.
adammeanqs-sas.txt	Calculates mean summaries for CPD and Questionnaire section.

adammeanur-sas.txt	Calculates mean summaries for Urine section.
adammeanbd-sas.txt	Calculates mean summaries for Blood section.
adamtoptreatid-sas.txt	Provides treatment descriptions for Topography tables.
adamtoptreatidg-sas.txt	Provides treatment descriptions for Topography figures.
adamcigttest-sas.txt	Performs CPD T-test statistical analysis.
adamcigmixed-sas.txt	Performs CPD statistical analysis.
adamqsttest-sas.txt	Performs Questionnaire T-test statistical analysis.
adamqsmixed-sas.txt	Performs Questionnaire statistical analysis.
adamurinettest-sas.txt	Performs Urine T-test statistical analysis.
adammixedur-sas.txt	Performs Urine statistical analysis.
adamBDttest-sas.txt	Performs Blood T-test statistical analysis.
adammixedbd-sas.txt	Performs Blood statistical analysis.
adamqstreat-sas.txt	Sets treatment variable for CPD and Questionnaire section.
adamqstreatid-sas.txt	Provides treatment descriptions for CPD and Questionnaire tables.
adamtreatidur-sas.txt	Provides treatment descriptions for Urine tables and figures.
adamtreatidbd-sas.txt	Provides treatment descriptions for Blood tables and figures.
adamqstreatidg-sas.txt	Provides treatment descriptions for CPD and Questionnaire figures.
adamqstreatidgc-sas.txt	Provides treatment descriptions for CPD combined flavor figures.