

Analysis Data Reviewer's Guide

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Study ZRHM-PK-05-JP

Version: 2016-04-29 v2.0

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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

In addition to the standard medical or CDISC terminology, the following acronyms are used.

Acronym	Translation
BLQ	Below the limit of quantification
CRF	Case Report Form
FTND	Fagerström Test for Nicotine Dependence
LLOQ	Lower limit of quantification
MCEQ	Modified Cigarette Evaluation Questionnaire
PD	Pharmacodynamic
PK	Pharmacokinetic
QTcF	Fridericia's Correction Formula
SAP	Statistical Analysis Plan

1.3 Study Data Standards and Dictionary Inventory

Standard or Dictionary	Versions Used
SDTM	SDTM Version 1.3 / SDTM Implementation Guide version 3.1.3 SDTM Draft Implementation Guide for Medical Devices (SDTMIG-MD)
Medications Dictionary	WHO DDE Version Q1 2013 – Coded to indication
Medical Events Dictionary	MedDRA version 16.0
Device Events Dictionary	C54451/Medical_Device_Problem_Codes_FDA_CDRH
ADaM	ADaM Model Document 2.1 ADaM Implementation Guide v1.0 ADaM Data Structure for Adverse Event Analysis v1.0

Standard or Dictionary	Versions Used
	ADaM Basic Data Structure for Time-to-Event Analysis v1.0
CDISC Controlled Terminology	2014-06-27
Data Definitions	Define.xml v2.0

1.4 Source Data Used for Analysis Dataset Creation

In addition to the SDTM datasets, the source data contains CRF raw data IE_E, IE_E_ADM, IE_E_SF, IE_I, IE_I_ADM and IE_I_SF (see Section 5.2.10) and DV.XLSX (see Section 5.2.7) and SSO.XPT and SSO12.XPT (see Sections 4.3 and 5.2.14) .

2. Protocol Description

2.1 Protocol Number and Title

Protocol Number: ZRHM-PK-05-JP

Protocol Title: A single-center, open-label, randomized, controlled, crossover study to investigate the nicotine pharmacokinetic profile and safety of Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) following single use in smoking, healthy subjects compared to conventional cigarettes and nicotine gum

Protocol Versions: Final 21st June 2013

2.2 Protocol Design in Relation to ADaM Concepts

This is an open-label, randomized, cross-over study. APERIOD is used to describe the washout days and product use days 0 to 3.

Period 1: Day 0 wash-out, Day 1 single product use.

Period 2: Day 2 wash-out, Day 3 single product use.

A product test was required prior to randomization to determine if subjects were willing and able to use the test product. If a subject tested the product and then subsequently did not take part in the randomization, all data collected up to the point of non-completion, including adverse events and concomitant medication follow-up was included in the analysis datasets. For these subjects, the treatment variables are detailed as 'Enrolled not randomized'.

Data is to be stratified by population, product use, sex and nicotine level. Please refer to Section 5.2.1 for full information.

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?

Yes, refer to Section 5.2 for details of datasets containing screening failure data.

- Are data taken from an ongoing study?

No, study has completed.

Additional Content of Interest

Wash-out and randomization occurred on Day 0 and is reflected in the ADaM datasets using ADAY, EDAY, ASTDAY and AENDAY.

According to the Statistical Analysis Plan (SAP) version 2.0 dated 08 May 2014 baseline is assessed as the last scheduled observation prior to product use on Day -1 excluding unscheduled observations.

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
SUBJIDN	Subject Identifier for the Study (N)
SITEID	Study Site Identifier
AGE	Age
SEX	Sex
SEXC	Sex Decode
SEXN	Sex (N)
RACE	Race
DTHFL	Subject Death Flag
HEIGHT	Screening Height (cm)
WEIGHTBL	Baseline Weight (kg)
BMI	Baseline Body Mass Index (kg/m ²)
UCPDGR1	Usual Daily Cig Consumption Category
UCPDGR1N	Usual Daily Cig Consumption Category (N)
NICOGR1	Cigarette Nicotine Yield Classification
NICOGR1N	Cigarette Nicotine Yield Class (N)
NICOGR2	Cigarette Nicotine Yield Classification 2
NICOGR2N	Cigarette Nicotine Yield Class 2 (N)
TARGR1	Cigarette Tar Yield Classification
TARGR1N	Cigarette Tar Yield Class (N)
ENRFL	Enrolled Population Flag
SCRFFL	Screen Failure Flag
EXFL	Exposed not Enrolled Flag

EXNOTRFL	Exposed not Randomized Flag
ENFL	Enrolled not Randomized Flag
COMPLFL	Completers Population Flag
FUPFL	Follow-up Flag
SAFFL	Safety Population Flag
PPROTFL	Per-Protocol Population Flag
RANDFL	Randomized Population Flag
AVISIT	Analysis Visit
AVISITN	Analysis Visit (N)
ATPT	Analysis Timepoint
ATPTN	Analysis Timepoint (N)
APERIOD	Period
APERIODC	Period (C)
EPOCH	Epoch
TRTSDTM	Datetime of First Exposure to Treatment
TRTSTMF	Time of First Exposure Input. Flag
TRTSDT	Date of First Exposure to Treatment
TRTSDAY	Day of First Exposure to Treatment
TRTEDTM	Datetime of Last Exposure to Treatment
TRTEDT	Date of Last Exposure to Treatment
TRTEDAY	Day of Last Exposure to Treatment
TR01SDT	Date of First Exposure in Period 01
TR01STM	Time of First Exposure in Period 01
TR01SDTM	Datetime of First Exposure in Period 01
TR01STMF	Time 1 st Exposure Period 01 Input. Flag
TR01EDT	Date of Last Exposure in Period 01
TR01ETM	Time of Last Exposure in Period 01
TR01EDTM	Datetime of Last Exposure in Period 01
TR02SDT	Date of First Exposure in Period 02

TR02STM	Time of First Exposure in Period 02
TR02SDTM	Datetime of First Exposure in Period 02
TR02STMF	Time 1 st Exposure Period 02 Imput. Flag
TR02EDT	Date of Last Exposure in Period 02
TR02ETM	Time of Last Exposure in Period 02
TR02EDTM	Datetime of Last Exposure in Period 02
TRTP	Planned Treatment
TRTPN	Planned Treatment (N)
TRTA	Actual Treatment
TRTAN	Actual Treatment (N)
TRTSEQP	Planned Sequence of Treatments
TRTSEQPN	Planned Sequence of Treatments (N)
TRTSEQA	Actual Sequence of Treatments
TRTSEQAN	Actual Sequence of Treatments (N)
ANALGR1	Analysis Group 1
ANALGR1N	Analysis Group 1 (N)

3.3 Treatment Variables

ARM versus TRTxxP

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

Yes.

ACTARM versus TRTxxA

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

Yes.

Use of ADaM Treatment Variables in Analysis

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

No. Actual treatment variables are used in all analysis.

3.4 Subject Issues that Require Special Analysis Rules

Subjects 0107 has been excluded from the PK population as they withdrew from the study during period 1 assessments and did not have a full PK profile for that period. Data were listed but excluded from descriptive statistics and statistical analysis.

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

- Was windowing used in one or more analysis datasets?

Yes. Windows were applied in the datasets as detailed in the SAP section 10.3.2.1. All observations outside the window were reviewed in a blinded manner prior to lock and were determined to be minor deviations. All data were included in descriptive statistics and analysis.

- Were unscheduled visits used in any analyses?

No.

Additional Content of Interest

Inclusion in tables and figures was determined using the ANLxxFL variables. The purpose of these variables are defined within the ADaM specifications for data selection.

3.6 Imputation/Derivation Methods

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

Seconds for product use on Days 1 and 3 was imputed to be 30 for the purpose of PK parameter calculation if the time recorded in the Case Report Form (CRF) was hh:mm as detailed in the SAP section 11.1.5. The flagging of this data were included in all analysis datasets and for biomarker and questionnaire data the imputed times were used in the definition of windows.

- In questionnaire data, total scores and domain or subscale scores may use a degree of imputation using an average across individual item scores as detailed in the SAP section 7.3.
- For the analysis of QSU-brief score for NRT gum as compared to THS 2.2, the QSU-brief values for NRT use at time $T_0+15\text{min}$ will be imputed by the QSU-brief values observed at $T_0+20\text{min}$, given the longer t_{max} expected for NRT use.

Additional Content of Interest.

The following values were used for DTYPE:

Controlled terminology	Definition
AVERAGE	Value derived as an average of 2 or more parameter values
BLQHALF	BLQ values set to half the LLOQ during the profile refer to SAP section 11.1.5
BLQNULL	BLQ values set to missing at the end of the profile refer to SAP section 11.1.5
BLQZERO	BLQ values set to zero at the start of the profile refer to SAP section 11.1.5

FUNCTION	Value derived as a function of 2 or more parameter values or a unit conversion
RATIO	Value derived as a ratio of 2 parameter values
SUM	Value derived as a sum of 2 or more parameter values

4. Analysis Data Creation and Processing Issues

4.1 Split Datasets

There were no datasets requiring a split due to size.

4.2 Data Dependencies

There are no other data dependencies beyond a dependency on ADSL.

4.3 Intermediate Datasets

An intermediate spreadsheet of deviation data from SDTM.DV was produced in order for the client to approve classification under PARAM and PARAMCD. This spreadsheet was then read back into the code for the production of ADDV to populate PARAM and PARAMCD. The data is uniquely identified by USUBJID and DVSEQ between SDTM.DV, DV.XLSX and ADDV.

A separate pkmerge file is used to derive PK parameters. This file is created using ADSL, ADEX, ADDX and SDTM.PC. The code used to create this file is also used in the creation of ADPC in order to preserve data handling rules. The parameter data from the analysis is found in ADPP. Parameters for the start and end of terminal elimination phase (NSTART, NSTART12, NEND, NEND12) were not retained in the SDTM.PP and so were sourced from SSO.XPT and SSO12.XPT. The handover documentation from the PK analysis, file 1001000_8278005 PK handover Memo Version 4.pdf, can be referenced from section 5.2.16.

4.4 Variable Conventions

There are no variable conventions to report.

5. Analysis Dataset Descriptions

5.1 Overview

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

Yes.

Additional Content of Interest

As mentioned in section 3.1, as this study uses reference to Day 0, the ADY, EDY, ASTDY and AENDY variables have been replaced by ADAY, EDAY, ASTDAY and AENDAY. These are derived as observation date – first treatment date (ADSL.TRTSDT) + 1.

5.2 Analysis Datasets

Dataset – Dataset Label	Class	Safety	Baseline or other subject characteristics	PK/PD	Primary Objective
ADSL – Subject Level Analysis Dataset	ADSL		X		
ADAE – Adverse Event Analysis Dataset	ODS	X			
ADBX – Biomarker Exposure Analysis Dataset	BDS			X	
ADCO – Comments Analysis Dataset	OTHER	X			
ADDS – Disposition Analysis Dataset	OTHER		X		
ADDT – Device Tracking and Disposition Analysis Dataset	OTHER	X			
ADDV - Protocol Deviation Analysis Dataset	OTHER	X			
ADDX - THS Product Exposure Analysis Dataset	BDS	X			
ADEG - ECG Analysis Dataset	BDS	X			

Dataset – Dataset Label	Class	Safety	Baseline or other subject characteristics	PK/PD	Primary Objective
<u>ADEL - Eligibility Analysis Dataset</u>	BDS		X		
<u>ADEX - Exposure Analysis Dataset</u>	BDS	X			
<u>ADFA - Findings About Events or Interventions Analysis Dataset</u>	BDS		X		
<u>ADLB - Laboratory Analysis Dataset</u>	BDS	X			
<u>ADPC - Pharmacokinetic Concentration Analysis Dataset</u>	BDS			X	X
<u>ADPE - Physical Examination Analysis Dataset</u>	BDS	X			
<u>ADPP - PK Parameters Analysis Dataset</u>	BDS			X	X
<u>ADQSND - Nicotine Dependence Analysis Dataset</u>	BDS		X		
<u>ADQSPA - Product Assessment Analysis Dataset</u>	BDS			X	
<u>ADQSSU - Smoking Urges Analysis Dataset</u>	BDS			X	
<u>ADQSSYM - Symptoms Questionnaire Analysis Dataset</u>	BDS			X	
<u>ADSV - Visit Incidence Analysis Dataset</u>	BDS	X			
<u>ADVS - Vital Signs Analysis Dataset</u>	BDS	X			
<u>ADXP - Pulmonary Function Analysis Dataset</u>	BDS	X			

5.2.1 ADSL – Subject Level Analysis Dataset

ADSL contains variables to support all analysis and baseline characteristics and disposition analysis. The population indicator variables (Enrolled population ENRFL, Randomized population RANDFL, Safety population SAFFL, Full analysis set population FASFL and Per-protocol population PPROTFL), product variables (actual products TRT01A, TRT01AN, TRT02A, TRT02AN and planned products TRT01P, TRT01PN, TRT02P, TRT02PN where 01 and 02 refer to the appropriate period as detailed in Section 2.2) and stratification indicator variables (Sex Male, Female – SEXC, SEXN and Conventional cigarette Nicotine level at Admission ≤ 0.6 mg, $> 0.6 - 1.0$ mg – NICOGR1, NICOGR1N) are included in all analysis datasets. To identify the required PK population, PPROTFL=Y and select the relevant ANALGR1 variable for identification of the randomization group (Group-1 or Group-2). All subjects in DM were included in ADSL including screen failure data.

LVISIT is recorded as Screening if the subject is a screen failure or Day 4/Discharge if the subject was enrolled onto the study. The dates associated with last visit, LVISDT and LVISDTC are the final dates contact was made with the subject and includes the any unscheduled visit dates, discharge and the safety followup call. LVISDAY is the number of days between first product use on Day 1 and the final date of contact with the subject (LVISDT-TR01SDT+1).

DSREAS is the primary term for discontinuation as recorded in the CRF with reason 'OTHER' information presented in DSREASP.

5.2.2 ADAE – Adverse Event Analysis Dataset

ADAE contains all observations from AE and SUPPAE and also one observation for each subject in ADSL that did not experience an adverse event during the study. TRTEMFL = Y is used to indicate exposure emergent AEs which were used in summary tables. This data contains observations for screen failure subjects which are listed only.

The data are coded under the System Organ Class variable AEBODSYS and Preferred Term variable AEDECOD.

The following flagging variables were provided:

ANL01FL – Indicates the AE was product emergent (TRTEMFL=Y).

ANL02FL – Indicates the subject withdrew due to that AE (no observations populated for this study).

ANL03FL – Indicates if the AE is related to the study product and action was taken (AEREL1=RELATED and AEACNP1 not equal to NONE. No observations populated for this study).

ANL04FL - Indicates if concomitant medication was taken for the AE (AECONTRT=Y).

ANL05FL – Indicates if other action was taken (AEACNOTH populated).

5.2.3 ADBX – Biomarker Exposure Analysis Dataset

ADBX contains all original data values for Carbon Monoxide, Carboxyhaemoglobin and component data for CYP2A6 activity which is derived according to the SAP. Data is selected from LB and SUPPLB and for CYP2A6 data, the component and converted values to nmol/L for derivation of the CYP2A6 activity is retained. ANL01FL=Y indicates the sample was collected during the required time window.

ANL02FL=Y indicates which values were used in summary statistics and statistical analysis.

For product use of NRT gum, timepoint ATPT=T0+20 was incorrectly referred to as T0+15 for Carboxyhaemoglobin data.

5.2.4 ADCO – Comments Analysis Dataset

ADCO contains all observations from CO as well as values from the xxREASND variable when populated from LB, PE, QS and VS. RDOMAIN indicates the source dataset and ASEQ indicates the sequence number from the source dataset for traceability.

5.2.5 ADDS - Disposition Analysis Dataset

ADDS contains all observations from DS and SUPPDS. Follow-up has not been included as a visit as it was undertaken as a telephone call so information on subjects taking part in the followup assessments are included in this dataset. This data contains observations for screen failure subjects.

5.2.6 ADDT - Device Tracking and Disposition Analysis Dataset

ADDT takes data from DT and DR and puts into one analysis dataset for the identification of devices and collection and distribution information from the CRF.

5.2.7 ADDV – Protocol Deviation Analysis Dataset

ADDV contains all observations from DV. PARAMCD and PARAM are derived from the SAP section 10.3 and with agreement from the client to label protocol deviations for summary tables using excel spreadsheet DV.XLSX for review and agreement. This is read in to the code producing ADDV for consistency and audit trail. This data contains observations for screen failure subjects which are listed only.

DVSIG indicates if the protocol deviation category is (Minor/Major). For any major protocol deviations, the EVALCAT indicates if it impacts (EVALCAT=NON EVALUABLE) or not impacts (EVALCAT=EVALUABLE) the evaluability of the subject for the Per Protocol population.

5.2.8 ADDX - THS Product Exposure Analysis Dataset

ADDX contains all observations from DX. ASTDTM contains imputed times when the time recorded for exposure to THS 2.2 menthol device is hh:mm as detailed in Section 3.6, where this has occurred, this is identified by ASTTMF=S. The actual level of nicotine has been added to the analysis data from referral to the protocol section 6.1.1.

5.2.9 ADEG – ECG Analysis Dataset

ADEG contains all observations from EG and SUPPEG. Fridericia's Correction Formula (QTcF) is derived and included in all output for ECG data. ANL01FL=Y is used to indicate which values are used in summary statistics. Reference ranges were not used to assess this data.

5.2.10 ADEL – Eligibility Analysis Dataset

The CRF datasets IE_E, IE_E_ADM, IE_E_SF, IE_I, IE_I_ADM and IE_I_SF are used to create this dataset as only abnormal responses are stored in SDTM.IE. The description of the eligibility criteria is

defined in the ADaM specifications Value Level Metadata sheet contained within the define.xml under complex algorithms. This data contains observations for screen failure subjects which are listed only.

5.2.11 ADEX – Exposure Analysis Dataset

ADEX contains all observations from EX and SUPPEX. ASTDTM contains imputed times when the time recorded for exposure to conventional cigarettes or NRT gum is hh:mm as detailed in Section 3.6, where this has occurred, this is identified by ASTTMF=S. The actual level of nicotine for conventional cigarettes and NRT gum has been included under AVAL from FA data.

5.2.12 ADFA – Findings About Events or Interventions Analysis Dataset

ADFA contains all observations from FA and SUPPFA. This data contains observations for screen failure subjects which are listed only.

5.2.13 ADLB – Laboratory Analysis Dataset

ADLB contains all observation from LB and SUPPLB identified under LBCAT of HAEMATOLOGY, CLINICAL CHEMISTRY, SEROLOGY, URINALYSIS, COTININE SCREENING, ALCOHOL TEST, DRUG SCREEN and PREGNANCY and LBTESTCD is not UVOL. ANL01FL=Y indicates the values to be used in summary statistics. The dataset contains source values as well as values in preferred units as derived parameters. The original out of range indicator LBNRIND, clinical significance LBCLSIG and toxicity grading LBTOXGR values for converted values has been carried forward in ANRIND, ACLSIG and ATOXGR. This data contains observations for screen failure subjects which are listed only.

5.2.14 ADPC – Pharmacokinetic Concentration Analysis Dataset

ADPC contains all observations in PC and also the elimination phase start and end points (NSTART start of elimination phase over the period 0 to 24 hours, NSTART12 start of elimination phase over the period 0 to 12 hours, NEND end of elimination phase over the period 0 to 24 hours, NEND12 end of elimination phase over the period 0 to 12 hours) derived during the PK analysis from data SSO.XPT and SSO12.XPT. ANL01FL=Y indicates values to be used in summary statistics and analysis. Values below the limit of quantification (BLQ) are replaced according to section 11.1.5 of the SAP. BLQ is derived into one of 3 classes, missing, zero or half the limit of quantification and identified in DTYPE as such.

Parameters based on the period 0 to 12 hours have been included in the data as additional information, analysis was performed on 0 to 24 hours as per SAP.

5.2.15 ADPE – Physical Examination Analysis Dataset

ADPE contains all observations from PE. ANL01FL=Y indicates values to be used in summary tables. ABLFL and ANL01FL incorrectly show the screening assessments as baseline and values to be used in summaries but the Day 0 values have been used in summary tables as the baseline value.

5.2.16 ADPP – PK Parameters Analysis Dataset

ADPP contains observations from PP and SUPPPP. ANL02FL=Y indicates which values are listed, otherwise values are set to NC as the derivation is considered unreliable as detailed below. ANL01FL=Y indicates values are to be included in summary statistics and statistical analysis. ANL01FL and ANL02FL were populated and data presented following rules as per SAP and the flagging variables provided in SUPPPP. The following subject had an incomplete profile:

USUBJID	SUBJID	APERIOD	TRTA	PK data available
ZRHM-PK-05-JP-AGE-0107	0107	1	THS	Up to 6h

For this subject, C_{max}, T_{max} and AUC_(0-t) are presented in listings only (PARAMCD of CMAX, TMAX and AUCINT respectively). All other PK parameters are presented as NC and footnoted with the reason for exclusion as 'Partial concentration versus time profile due to subject withdrawal; derived parameters not calculated'. The subject is excluded from the PK population as they did not complete a single exposure day.

Additionally subject 129, THS 2.2 Menthol, PARAMCD = AUCINT12 could not be calculated as this area could not be extrapolated from C_{last} due to λ_z not being calculable (R_{sq}_adjusted <0.7), therefore, for this subject AVAL was set to missing and presented as not calculable (NC) and flagged in the listing with the footnote as 'Not calculated; R_{sq}_adjusted <0.7'

This can be referenced in the source documentation [1001000 8278005 PK handover Memo Version 4.pdf](#)

Parameters based on the period 0 to 12 hours have been included in the data as additional information, analysis was performed on 0 to 24 hours as per SAP.

5.2.17 ADQSND – Nicotine Dependence Analysis Dataset

ADQSND contains data from QS for the Fagerström Test for Nicotine Dependence (FTND). The total score has been derived as detailed in the SAP section 7.3.1 with PARAMCD=FTNDSC, numeric total score is in AVAL and the category is recorded under AVALCAT1. ANL01FL=Y indicated values used in summary statistics.

5.2.18 ADQSPA – Product Assessment Analysis Dataset

ADQSPA contains data from QS for the Modified Cigarette Evaluation Questionnaire (MCEQ). Subscales have been derived according to the SAP section 7.3.3. ANL01FL=Y indicated values used in summary statistics and analysis.

The subscale parameter information are in the following table:

Subscale	Paramcd
Aversion Subscale	MCEQA
Craving Reduction Subscale	MCEQCR
Enjoyment of Respiratory Tract Sensation Subscale	MCEQERTS

Psychological Reward Subscale	MCEQPR
Smoking Satisfaction Subscale	MCEQSS

5.2.19 ADQSSU – Smoking Urges Analysis Dataset

ADQSSU contains data from QS for the Questionnaire On Smoking Urges. Factors have been derived according to the SAP section 7.3.2 (Reward has PARAMCD= QSUFACT1, Relief has PARAMCD= QSUFACT2 and total score has PARAMCD= QSUTOTAL). ANL01FL=Y indicated values used in summary statistics and analysis.

5.2.20 ADQSSYM – Symptoms Questionnaire Analysis Dataset

ADQSSYM contains data from QS for the Cough Assessment Questionnaire. ANL01FL=Y indicated values used in summary statistics.

5.2.21 ADSV – Visit Incidence Analysis Dataset

ADSV contains all visit information from SV. It does not contain information on the telephone followup visit. This information is contained within ADDS. This data contains observations for screen failure subjects.

5.2.22 ADVS – Vital Signs Analysis Dataset

ADVS contains all observations from VS and SUPPVS. As weight was assessed at Day -1 baseline, BMI has been derived based on height at screening and weight at baseline and presented. ANL01FL=Y indicated values used in summary statistics. Reference ranges were not used to assess this data.

Where a set of supine vital signs data were not assessed, the data are represented by PARAMCD=SUVSALL and the reason for missing data provided in VSSTAT.

5.2.23 ADXP – Pulmonary Function Analysis Dataset

ADXP contains all observation from XP. The ratio between FEV₁ and FVC was included in the CRF for assessment of eligibility, to continue the comparison of subsequent timepoints to baseline, this parameter has also been derived for all timepoints. ANL01FL=Y indicates values used in summary statistics, excluding predicted values for FEV₁ and FVC.

6. Data Conformance Summary

6.1 Conformance Inputs

- Were the analysis datasets evaluated for conformance with CDISC ADaM Validation Checks?
Yes
If yes:

- Version of CDISC ADaM Validation Checks: Engine Version 1.5
- Specify software used:
 - OpenCDISC
- Were the ADaM datasets evaluated in relation to define.xml? Yes – see below
- Was define.xml evaluated? Yes using community validator version 2.0.1 – see below

6.2 Issues Summary

Dataset(s)	Diagnostic Message and/or Check ID	Severity	Count and/or Issue Rate	Explanation
ADAE	Neither AVAL nor AVALC are present in dataset	ERROR	1	– ADAE is not a BDS domain and as such AVAL and AVALC are not required as per CDISC ADaM Data Structure for Adverse Event Analysis Version 1.0. Not amended as this is an OpenCDISC issue where it has not yet had appropriate class information for the ADAE domain.
ADAE	Required variable is not present	ERROR	2	As above, PARAM and PARAMCD are not required under CDISC ADaM Data Structure for Adverse Event Data Analysis version 1.0.
ADCO	Required variable is not present	ERROR	2	PARAM and PARAMCD were not applicable to this data type due to the collection method of the comments. Data structure reflects BDS domain as closely as possible.
ADDS	Neither AVAL nor AVALC are present in dataset	ERROR	1	AVAL and AVALC were not applicable to this data type. Data structure reflects ADAE domain as closely as possible as this reflected the data type.
ADDS	Required variable is not present	ERROR	2	PARAM and PARAMCD were not applicable to this data type. Data structure reflects ADAE domain as closely as possible as this reflected the data type.

Dataset(s)	Diagnostic Message and/or Check ID	Severity	Count and/or Issue Rate	Explanation
ADDT	Neither AVAL nor AVALC are present in dataset	ERROR	1	AVAL and AVALC were not applicable to this data type. Data structure reflects ADAE domain as closely as possible as this reflected the data type.
ADDT	Required variable is not present	ERROR	2	PARAM and PARAMCD were not applicable to this data type. Data structure reflects ADAE domain as closely as possible as this reflected the data type.
ADEL	Required variable is not present	ERROR	1	TRTP - Deemed not applicable for this data type as all IE criteria are prior to first period. Implementation guide indicates that TRTP was a required variable and this was not included in error, however it would be blank for all observations. Product sequence information is provided as it would be of more use.
ADFA	Required variable is not present	ERROR	1	TRTP - Deemed not applicable for this data type as all IE criteria are prior to first period. Implementation guide indicates that TRTP was a required variable and this was not included in error, however it would be blank for all observations. Product sequence information is provided as it would be of more use.

Dataset(s)	Diagnostic Message and/or Check ID	Severity	Count and/or Issue Rate	Explanation
ADPE	ABLFL is present but BASE is not present	ERROR	1	BASE is not applicable to this data, BASEC is included instead. It would not be appropriate to include BASE as a null variable because this would result in a new error (BASEC and BASE not one-to-one).
ADPP	Inconsistent value for AVALC	ERROR	83	Issue between SAS and opendisc validator - compare has been made between AVAL and AVALC using SAS code and no issues noted
ADQSND	Required variable is not present	ERROR	1	TRTP - Deemed not applicable for this data type as all records prior to first period. Implementation guide indicates that TRTP was a required variable and this was not included in error, however it would be blank for all observations. Product sequence information is provided as it would be of more use.
ADSV	Neither AVAL nor AVALC are present in dataset	ERROR	1	Structure is not a BDS domain for this data type. Data is not used for any analysis but can be used for supporting information.
ADSV	Required variable is not present	ERROR	2	PARAM and PARAMCD are not appropriate for this data type. Data is not used for any analysis in its own right but can be used for information.

Dataset(s)	Diagnostic Message and/or Check ID	Severity	Count and/or Issue Rate	Explanation
Define	Invalid 'DataType' value	ERROR	24	Relates to partial dates within LBDTC. This is source data and it can be expected that times are missing occasionally. No changes to be made to data.

7. Submission of Programs

ADaM dataset production programs have been submitted and referred to in the define.xml.

Programs for the production of primary and secondary analysis, descriptive statistics tables and figures and associated macros have also been submitted and are defined below.

There is an internal macro `_mprintto` that automatically saves the output and log to specific areas. This will not run on an external system so please exclude this macro from program execution.

Figure / Table Number	Title	Program	Analysis Dataset	Analysis Variable(s)
15.1.1.1	Primary Pharmacokinetic Parameters of Nicotine – Group - 1 PK Population	F_pkprim	ADPP	PPROTFL, PARAM, AVAL, ANL01FL
15.1.2.1.1	Nicotine Plasma Concentration (ng/mL) Profiles Geometric Mean and 95% CI - Group-1 PK Population	F_pkconc	ADPC	PPROTFL, PARAM, AVAL, ANL01FL
15.1.2.1.1.1	Nicotine Plasma Concentration (ng/mL) Profiles Geometric Mean and 95% CI - Group-1 PK Population	F_pkconc_1	ADPC	PPROTFL, PARAM, AVAL, ANL01FL
15.1.2.1.2	Nicotine Plasma Concentration (ng/mL) Profiles Geometric Mean and 95% CI - Group-2 PK Population	F_pkconc2	ADPC	PPROTFL, PARAM, AVAL, ANL01FL
15.1.2.1.2.1	Nicotine Plasma Concentration (ng/mL) Profiles Geometric Mean and 95% CI - Group-2 PK Population	F_pkconc2_1	ADPC	PPROTFL, PARAM, AVAL, ANL01FL
15.1.2.2.1	Nicotine Plasma Concentration (ng/mL) Profiles for All Subjects - Group-1 PK Population	F_pkconc3	ADPC	PPROTFL, PARAM, AVAL, ANL01FL

Figure / Table Number	Title	Program	Analysis Dataset	Analysis Variable(s)
15.1.2.2.1.1	Nicotine Plasma Concentration (ng/mL) Profiles for All Subjects - Group-1 PK Population	F_pkconc3_1	ADPC	PPROTFL, PARAM, AVAL, ANL01FL
15.1.2.2.2	Nicotine Plasma Concentration (ng/mL) Profiles for All Subjects - Group-2 PK Population	F_pkconc4	ADPC	PPROTFL, PARAM, AVAL, ANL01FL
15.1.2.2.2.1	Nicotine Plasma Concentration (ng/mL) Profiles for All Subjects - Group-2 PK Population	F_pkconc4_1	ADPC	PPROTFL, PARAM, AVAL, ANL01FL
15.1.2.3	Nicotine Plasma Concentration (ng/mL) Profiles by Subject – PK Population	F_pkconc5	ADPC	PPROTFL, PARAM, AVAL, ANL02FL
15.1.2.4	Secondary Pharmacokinetic Parameters of Nicotine – Group - 1 PK Population	F_pkparam	ADPP	PPROTFL, PARAM, AVAL, ANL02FL
15.1.2.5	Pharmacokinetic Parameters of Nicotine – Group -2 PK Population	F_pkparam2	ADPP	PPROTFL, PARAM, AVAL, ANL01FL
15.1.2.6.1	Blood COHb (%) Profiles Geometric Mean and 95% CI - Group-1 PK Population	F_cohb	ADBx	PPROTFL, PARAM, AVAL, ANL02FL
15.1.2.6.2	Blood COHb (%) Profiles Geometric Mean and 95% CI - Group-2 PK Population	F_cohb2	ADBx	PPROTFL, PARAM, AVAL, ANL02FL
15.1.2.7.1	Blood COHb (%) Profiles Geometric Least Squares Mean Ratio (THS 2.2 Menthol:mCC) (\pm 95% CI) - Group-1 PK Population	tlf_anlcohb.sas	ADBx	PPROTFL, PARAM, AVAL, ANL02FL

Figure / Table Number	Title	Program	Analysis Dataset	Analysis Variable(s)
15.1.2.7.2	Blood COHb (%) Profiles Geometric Least Squares Mean Ratio (THS 2.2 Menthol:NRT gum) (\pm 95% CI)- Group-2 PK Population	tlf_anlcohb.sas	ADBX	PPROTFL, PARAM, AVAL, ANL02FL
15.1.2.8.1	Exhaled CO (ppm) Profiles During Single Use Day Arithmetic Mean and 95% CI – Group-1 PK Population	F_co	ADBX	PPROTFL, PARAM, AVAL, ANL02FL
15.1.2.8.2	Exhaled CO (ppm) Profiles During Single Use Day Arithmetic Mean and 95% CI – Group-2 PK Population	F_co2	ADBX	PPROTFL, PARAM, AVAL, ANL02FL
15.1.2.9.1	Exhaled CO (ppm) Profiles During Single Use Day Arithmetic Least Squares Mean Differences (THS 2.2 Menthol - mCC) (\pm 95% CI) - Group-1 PK Population	tlf_anlco	ADBX	PPROTFL, PARAM, AVAL, ANL02FL
15.1.2.9.2	Exhaled CO (ppm) Profiles During Single Use Day Arithmetic Least Squares Mean Differences (THS 2.2 Menthol - NRT gum) (\pm 95% CI) - Group-2 PK Population	tlf_anlco	ADBX	PPROTFL, PARAM, AVAL, ANL02FL
15.1.2.10.1	QSU-brief Factors and Total Score Profiles Arithmetic Mean and 95% CI - Group-1 PK Population	F_gsu	ADQSSU	PPROTFL, PARAM, AVAL, ANL01FL
15.1.2.10.2	QSU-brief Factors and Total Score Profiles Arithmetic Mean and 95% CI - Group-2 PK Population	F_gsu2	ADQSSU	PPROTFL, PARAM, AVAL, ANL01FL

Figure / Table Number	Title	Program	Analysis Dataset	Analysis Variable(s)
15.1.2.11.1	QSU-brief Factors and Total Score Profiles Arithmetic Least Squares Mean Differences (THS 2.2 Menthol - mCC) and 95% CI - Group-1 PK Population	tlf_anlqsu	ADQSSU	PPROTFL, PARAM, AVAL, ANL01FL
15.1.2.11.2	QSU-brief Factors and Total Score Profiles Arithmetic Least Squares Mean Differences (THS 2.2 Menthol - NRT gum) and 95% CI - Group-2 PK Population	tlf_anlqsu	ADQSSU	PPROTFL, PARAM, AVAL, ANL01FL
15.2.1.1	Summary of Subject Disposition - All Screened Subjects	T_sdisp	ADSL	SCRFFL, ENRLFL, RANDFL, COMPLFL
15.2.1.2	Summary of Reasons for Discontinuations - Randomized Population	T_rsndis	ADDS	DSTERM, RANDFL
15.2.1.3	Summary of Protocol Deviations - Safety Population	T_pdev	ADDV	DVSIG, AVAL, SAFFL
15.2.1.4.1	Summary of Demographics and Other Baseline Characteristics - Safety Population	T_demog	ADSL ADBX ADQSND	SAFFL, SEXC, NICOGR1, AGE, BMI, BMIGR1, HEIGHT, WEIGHTBL, ETHNIC, UCPDGR1, NICOB1, TARBL, TARGR1, AVAL AVALCAT1, AVAL

Figure / Table Number	Title	Program	Analysis Dataset	Analysis Variable(s)
15.2.1.4.2	Summary of Demographics and Other Baseline Characteristics - Group-1 PK Population	T_demog2	ADSL ADBX ADQSND	PPROTFL, SEXC, NICOGR1, AGE, BMI, BMIGR1, HEIGHT, WEIGHTBL, ETHNIC, UCPDGR1, NICOBL, TARBL, TARGR1, AVAL AVALCAT1, AVAL
15.2.1.4.2.1	Summary of Demographics and Other Baseline Characteristics by Sex - Group-1 PK Population	T_demog2s	ADSL ADBX ADQSND	PPROTFL, SEXC, NICOGR1, AGE, BMI, BMIGR1, HEIGHT, WEIGHTBL, ETHNIC, UCPDGR1, NICOBL, TARBL, TARGR1, AVAL AVALCAT1, AVAL

Figure / Table Number	Title	Program	Analysis Dataset	Analysis Variable(s)
15.2.1.4.2.2	Summary of Demographics and Other Baseline Characteristics by Nicotine Level - Group-1 PK Population	T_demog2c	ADSL ADBX ADQSND	PPROTFL,SEXC, NICOGR1, AGE, BMI, BMIGR1, HEIGHT, WEIGHTBL, ETHNIC, UCPDGR1, NICOB1, TARBL, TARGR1, AVAL AVALCAT1, AVAL
15.2.1.4.3	Summary of Demographics and Other Baseline Characteristics - Group-2 PK Population	T_demog3	ADSL ADBX ADQSND	PPROTFL, SEXC, NICOGR1, AGE, BMI, BMIGR1, HEIGHT, WEIGHTBL, ETHNIC, UCPDGR1, NICOB1, TARBL, TARGR1, AVAL AVALCAT1, AVAL

Figure / Table Number	Title	Program	Analysis Dataset	Analysis Variable(s)
15.2.1.4.3.1	Summary of Demographics and Other Baseline Characteristics by Sex - Group-2 PK Population	T_demog3s	ADSL ADBX ADQSND	PPROTFL, SEXC, NICOGR1, AGE, BMI, BMIGR1, HEIGHT, WEIGHTBL, ETHNIC, UCPDGR1, NICOBL, TARBL, TARGR1, AVAL AVALCAT1, AVAL
15.2.1.4.3.2	Summary of Demographics and Other Baseline Characteristics by Nicotine Level - Group-2 PK Population	T_demog3c	ADSL ADBX ADQSND	PPROTFL, SEXC, NICOGR1, AGE, BMI, BMIGR1, HEIGHT, WEIGHTBL, ETHNIC, UCPDGR1, NICOBL, TARBL, TARGR1, AVAL AVALCAT1, AVAL
15.2.1.5	Summary of Current Cigarette Brands at Admission - Safety Population	T_cigbrand	ADFA	SAFFL, BRAND, AVAL
15.2.1.6	Summary of Medical History - Safety Population	T_medhis	No data recorded	SAFFL, MHBODSYS, MHDECOD
15.2.1.7	Summary of Concomitant Diseases - Safety Population	T_condis	No data recorded	SAFFL, MHBODSYS, MHDECOD

Figure / Table Number	Title	Program	Analysis Dataset	Analysis Variable(s)
15.2.2.1	Descriptive Statistics of Product Use - Safety Population	T_ustatss	ADDX ADEX	SAFFL, SUBJID AVALCAT1
15.2.3.1	Analysis of Primary Pharmacokinetic Parameters of Nicotine - Group 1 PK Population	tl_anlpk31	ADPP	PPROTFL, PARAM, AVAL, ANL01FL
15.2.3.2	Analysis of Primary Pharmacokinetic Parameters of Nicotine by Sex and Nicotine Level - Group 1 PK Population	tl_anlpk32	ADPP	PPROTFL, PARAM, AVAL, SEXC, NICOGR1, ANL01FL
15.2.3.3	Analysis of Pharmacokinetic Parameters of Nicotine C_{max} , $AUC_{(0-last)}$, t_{max} - PK Population	t_anlpk33	ADPP	PPROTFL, AVAL, ANL01FL
15.2.4.1	Analysis of Secondary Pharmacokinetic Parameters of Nicotine - Group 1 PK Population	tl_anlpk41	ADPP	PPROTFL, PARAM, AVAL, ANL01FL
15.2.4.2	Analysis of Pharmacokinetic Parameters of Nicotine - Group-2 PK Population	tl_anlpk42	ADPP	PPROTFL, PARAM, AVAL, ANL01FL
15.2.4.3.1	Analysis of Pharmacokinetic Parameters of Nicotine by Bootstrapping Techniques - PK Population	tl_anlpk431	ADPP	PPROTFL, PARAM, AVAL, CRIT3FL
15.2.4.3.2	Supportive Analysis of Pharmacokinetic Parameters of Nicotine Excluding Subject with T_0 Value >5% of Their C_{max} Value - PK Population	tl_anlpk432	ADPP	PPROTFL, PARAM, AVAL, ANL01FL, CRIT3FL, CRIT4FL

Figure / Table Number	Title	Program	Analysis Dataset	Analysis Variable(s)
15.2.4.4.1	Analysis of Pharmacokinetic Parameters of Nicotine by Zero Second Imputation - PK Population	tl_anlpk441	ADPP	PPROTFL, PARAM, AVAL, ANL01FL, CRIT3FL
15.2.4.4.2	Analysis of Pharmacokinetic Parameters of Nicotine Where >20% Missing Observations - PK Population	tl_anlpk442	ADPP	PPROTFL, PARAM, AVAL, ANL01FL, CRIT3FL
15.2.4.5	Descriptive Statistics of Pharmacokinetic Parameters of Nicotine - PK Population	T_nic	ADPP	PPROTFL, PARAM, AVAL, ANL01FL
15.2.4.5.1	Descriptive Statistics of Pharmacokinetic Parameters of Nicotine by Sex - PK Population	T_nic2	ADPP	PPROTFL, PARAM, AVAL, SEXC, ANL01FL
15.2.4.5.2	Descriptive Statistics of Pharmacokinetic Parameters of Nicotine by Nicotine Level - PK Population	T_nic3	ADPP	PPROTFL, PARAM, AVAL, NICOGR1, ANL01FL
15.2.4.6	Descriptive Statistics of the Plasma Nicotine Concentrations (ng/mL) - PK Population	T_pkconc	ADPC	PPROTFL, PARAM, AVAL, ATPT, ANL01FL
15.2.4.6.1	Descriptive Statistics of the Plasma Nicotine Concentrations (ng/mL) by Sex - PK Population	T_pkconc2	ADPC	PPROTFL, PARAM, AVAL, ATPT, SEXC, ANL01FL
15.2.4.6.2	Descriptive Statistics of the Plasma Nicotine Concentrations (ng/mL) by Nicotine Level - PK Population	T_pkconc3	ADPC	PPROTFL, PARAM, AVAL, ATPT, NICOGR1, ANL01FL
15.2.4.7	Analysis of Blood COHb (%) - PK Population	tlf_anlcohb	ADBx	PPROTFL, PARAM, AVAL, ATPT, ANL01FL

Figure / Table Number	Title	Program	Analysis Dataset	Analysis Variable(s)
15.2.4.8.1	Descriptive Statistics of Blood COHb (%) Continuous Measurements - PK Population	T_cohb	ADBX	PPROTFL, PARAM, AVAL, ATPT, ANL02FL
15.2.4.8.1.1	Descriptive Statistics of Blood COHb (%) by Sex - PK Population	T_cohb2	ADBX	PPROTFL, PARAM, AVAL, ATPT SEXC, ANL02FL
15.2.4.8.1.2	Descriptive Statistics of Blood COHb (%) by Nicotine Level - PK Population	T_cohb3	ADBX	PPROTFL, PARAM, AVAL, ATPT, NICOGR1, ANL02FL
15.2.4.8.2	Descriptive Statistics of Blood COHb (%) Categorical Measurements - PK Population	t_cohbcat	ADBX	PPROTFL, PARAM, AVALCAT1, ATPT, ANL02FL
15.2.4.9	Analysis of Exhaled CO (ppm) During Single Use Day - PK Population	tif_anlco	ADBX	PPROTFL, PARAM, AVAL, ATPT, ANL02FL
15.2.4.10.1	Descriptive Statistics of Exhaled CO (ppm) During Single Use Continuous Measurements - PK Population	t_cosing	ADBX	PPROTFL, PARAM, AVAL ATPT, ANL02FL
15.2.4.10.1.1	Descriptive Statistics of Exhaled CO (ppm) During Single Use by Sex - PK Population	T_cosing2	ADBX	PPROTFL, PARAM, AVAL, ATPT, SEXC, ANL02FL
15.2.4.10.1.2	Descriptive Statistics of Exhaled CO (ppm) During Single Use by Nicotine Level – PK Population	T_cosing3	ADBX	PPROTFL, PARAM, AVAL, ATPT, NICOGR1, ANL02FL

Figure / Table Number	Title	Program	Analysis Dataset	Analysis Variable(s)
15.2.4.10.2	Descriptive Statistics of Exhaled CO (ppm) During Single Use Categorical Measurements - PK Population	T_cosingcat	ADBX	PPROTFL, PARAM, AVALCAT1, ATPT, ANL02FL
15.2.4.11.1	Descriptive Statistics of Exhaled CO (ppm) During Days -1, 0, 2 and 4 Continuous Measurements - PK Population	T_coday	ADBX	PPROTFL, PARAM, AVAL, AVISIT, ANL02FL
15.2.4.11.1.1	Descriptive Statistics of Exhaled CO (ppm) During Days -1, 0, 2 and 4 by Sex - PK Population	T_coday2	ADBX	PPROTFL, PARAM, AVAL, SEXC, AVISIT, ANL02FL
15.2.4.11.1.2	Descriptive Statistics of Exhaled CO (ppm) During Days -1, 0, 2 and 4 by Nicotine Level - PK Population	T_coday3	ADBX	PPROTFL, PARAM, AVAL, NICOGR1, AVISIT, ANL02FL
15.2.4.11.2	Descriptive Statistics of Exhaled CO (ppm) During Days -1, 0, 2 and 4 Categorical Measurements - PK Population	T_codaycat	ADBX	PPROTFL, PARAM, AVALCAT1, AVISIT, ANL02FL
15.2.4.12	Analysis of QSU-brief Questionnaire Factors and Total Score - PK Population	tlf_anlqsu	ADQSSU	PPROTFL, PARAM, AVAL, ANL01FL
15.2.4.13	Analysis of QSU-brief Questionnaire Factors and Total Score by Bootstrapping Techniques - PK Population	tl_banlqsu	ADQSSU	PPROTFL, PARAM, AVAL, ANL01FL
15.2.4.14	Descriptive Statistics of QSU-brief Questionnaire Factors and Total Score - PK Population	T_qsu	ADQSSU	PPROTFL, PARAM, AVAL, ATPT, ANL01FL

Figure / Table Number	Title	Program	Analysis Dataset	Analysis Variable(s)
15.2.4.14.1	Descriptive Statistics of QSU-brief Questionnaire Factors and Total Score by Sex - PK Population	T_gsu2	ADQSSU	PPROTFL, PARAM, AVAL, ATPT, SEXC, ANL01FL
15.2.4.14.2	Descriptive Statistics of QSU-brief Questionnaire Factors and Total Score by Nicotine Level - PK Population	T_gsu3	ADQSSU	PPROTFL, PARAM, AVAL, ATPT, NICOGR1, ANL01FL
15.2.4.15	Analysis of MCEQ Subscales - PK Population	tl_anlmceq	ADQSPA	PPROTFL, PARAM, AVAL, ANL01FL
15.2.4.16	Analysis of MCEQ Subscales by Bootstrapping Techniques - PK Population	tl_banlmceq	ADQSPA	PPROTFL, PARAM, AVAL, ANL01FL
15.2.4.17	Descriptive Statistics of MCEQ Subscales - PK Population	T_mceq	ADQSPA	PPROTFL, PARAM, AVAL, ANL01FL
15.2.4.17.1	Descriptive Statistics of MCEQ Subscales by Sex - PK Population	T_mceq2	ADQSPA	PPROTFL, PARAM, AVAL, SEXC, ANL01FL
15.2.4.17.2	Descriptive Statistics of MCEQ Subscales by Nicotine Level - PK Population	T_mceq3	ADQSPA	PPROTFL, PARAM, AVAL, NICOGR1, ANL01FL
15.2.4.18	Descriptive Statistics of Sex, Age and Nicotine Level - PK Population	t_sanic	ADSL	PPROTFL, SEXC, AGE, NICOGR1
15.2.5.1	Descriptive Statistics of Compliance Based on CO Breath Test - All Randomized Subjects	T_comp	ADSL	RANDFL. COMPL1FL, COMPL2FL, COMPL3FL

Figure / Table Number	Title	Program	Analysis Dataset	Analysis Variable(s)
15.2.6.1	Summary of Adverse Events - Safety Population	T_adv1	ADAE	SAFFL, AESER, AEREL1, AEREL2, AEEXPEC, AEEXPEC1, AESEV, AERELSP, AECONTRT, ANL01FL, ANL02FL, ANL03FL, ANL05FL
15.2.6.2.1	Summary of Adverse Events by System Organ Class and Preferred Term - Safety Population	T_adv2	ADAE	SAFFL, ANL01FL, AEBODSYS, AEDECOD
15.2.6.2.2	Summary of Adverse Events by System Organ Class - Safety Population	T_adv3	ADAE	SAFFL, ANL01FL, AEBODSYS
15.2.6.2.3	Summary of Adverse Events by Preferred Term - Safety Population	T_adv4	ADAE	SAFFL, ANL01FL, AEDECOD
15.2.6.3	Summary of Adverse Events by System Organ Class and Preferred Term and Relationship to Study Product Exposure for Investigational Product (THS 2.2 or CC) and Reference Point Product (NRT gum) - Safety Population	T_adv6	ADAE	SAFFL, ANL01FL, AEBODSYS, AEDECOD, SAFFL, AEREL1, AEREL2, AEEXPEC, AEEXPEC1

Figure / Table Number	Title	Program	Analysis Dataset	Analysis Variable(s)
15.2.6.4	Summary of Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term - Safety Population	T_adv5	ADAE	SAFFL, ANL01FL, AEBODSYS, AEDECOD, ANL02FL
15.2.6.5	Summary of Adverse Events by System Organ Class, Preferred Term and Severity - Safety Population	T_adv7	ADAE	SAFFL, ANL01FL, AEBODSYS, AEDECOD, AESEV
15.2.6.6	Summary of Adverse Events Related to Study Procedure by System Organ Class and Preferred Term - Safety Population	T_adv8	ADAE	SAFFL, ANL01FL, AEBODSYS, AEDECOD, AERELSP
15.2.6.7	Summary of THS 2.2 Device Events and Malfunctions - Safety Population	T_device	ADDE	SAFFL, DEDECOD, AEREL, DESEV
15.2.6.8.1	Summary of Prior Medication by Anatomical Therapeutic Classes (ATC) 1 and 2 - Safety Population	t_priatc	ADCM	SAFFL, CMATC1, CMATC2, PMFL
15.2.6.8.2	Summary of Prior Medication by Preferred Drug Name - Safety Population	T_primed	ADCM	SAFFL, CMDECOD, PMFL
15.2.6.9.1	Summary of Concomitant Medication by Anatomical Therapeutic Classes (ATC) 1 and 2 - Safety Population	T_conatc	ADCM	SAFFL, CMATC1, CMATC2, CMFL

Figure / Table Number	Title	Program	Analysis Dataset	Analysis Variable(s)
15.2.6.9.2	Summary of Concomitant Medication by Preferred Drug Name - Safety Population	T_comed	ADCM	SAFFL, CMDECOD, CMFL
15.2.6.10	Summary of Clinical Chemistry Parameters - Safety Population	T_labchem	ADLB	SAFFL, ANL01FL, PARAM, AVAL,CHG, ANRLO, ANRHI, ANRIND, ACLSIG, AVISIT
15.2.6.11	Summary of Hematology Parameters - Safety Population	T_labhem	ADLB	SAFFL, ANL01FL, PARAM, AVAL,CHG, ANRLO, ANRHI, ANRIND, ACLSIG, AVISIT
15.2.6.12	Summary of Urinalysis Parameters - Safety Population	T_laburin	ADLB	SAFFL, ANL01FL, PARAM, AVAL,CHG, ANRLO, ANRHI, ANRIND, ACLSIG, AVISIT
15.2.6.13	Summary of Supine Vital Signs - Safety Population	T_vit	ADVS	SAFFL, ANL01FL, PARAM, AVAL, CHG, AVISIT
15.2.6.14	Summary of ECG Measurements - Safety Population	T_ecg	ADEG	SAFFL, ANL01FL, PARAM, AVAL, CHG, AVISIT

Figure / Table Number	Title	Program	Analysis Dataset	Analysis Variable(s)
15.2.6.15	Summary of Spirometry Measurements - Safety Population	T_spiro	ADXP	SAFFL, ANL01FL, PARAM, AVAL, AVISIT
15.2.6.16	Summary of Weight and BMI Measurements - Safety Population	T_bmi	ADVS	SAFFL, ANL01FL, PARAM, AVAL, AVALCAT1, AVISIT
15.2.6.17	Summary of Physical Examination of Body Systems - Safety Population	T_phyex	ADPE	SAFFL, ANL01FL, PARAM, AVALC, PECLSIG, AVISIT
15.2.6.18	Summary of Cough Assessments - Safety Population	T_cough	ADQSSYM	SAFFL, PARAM, AVALC,
15.2.6.18.1	Summary of Cough Assessments by Study Day - Safety Population	T_cough2	ADQSSYM	SAFFL, ANL01FL, PARAM, AVALC, AVISIT

Macro Program Name	Macro used in
M_totper	Analysis datasets for derivation of period assessment
M_perall	Analysis datasets for allocation of TRTP, TRTPN, TRTA and TRTAN
M_cyp	Analysis datasets for derivation of biomarker parameters
m_mergeadpc	Code for the production of PKmerge for PK group also used in ADPC for consistency of data handling.

- Submitted programs will execute on a Linux environment running Windows and SAS version 9.3. Library definitions will need to be modified to reflect the actual environment where run.

8. Appendix

Table 1 Contents of File BANNEDMED.XLSX

Inhibitor

Amiodarone
Desipramine
Isoniazid
Ketoconazole
Letrozole
Methoxsalen
Miconazole
Tranylcypromine

Inducer

Amobarbital
Pentobarbital
Phenobarbital
Rifampin
Secobarbital

Substrate

Dexmedetomidine
Ifosfamide