

Analysis Data Reviewer's Guide

Philip Morris Products S.A.

Study ZRHR-REXC-03-EU

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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
MNWS	Minnesota Nicotine Dependence/Withdrawal Scale
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

Standard or Dictionary	Versions Used
	ADaM Implementation Guide v1.0 ADaM Data Structure for Adverse Event Analysis v1.0 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 5.2.12), data in the form of excel spreadsheets BANNEDMEDS.XLSX (see Sections 5.2.4 and 8) and DV.XLSX (see Section 5.2.9).

2. Protocol Description

2.1 Protocol Number and Title

Protocol Number: ZRHR-REXC-03-EU

Protocol Title: A randomized, controlled, open-label, 3-arm parallel group, single-center study to demonstrate reductions in exposure to selected smoke constituents in smoking, healthy subjects switching to the Tobacco Heating System 2.2 (THS 2.2) or smoking abstinence, compared to continuing to use conventional cigarettes, for 5 days in confinement

Protocol Versions: Final 25th April 2013

2.2 Protocol Design in Relation to ADaM Concepts

This is an open-label, randomized, 3-arm parallel group. APERIOD has been set to a default of 1 for all study visits.

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 daily CC consumption at baseline. 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

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) baseline is assessed as the period between 6:30 AM on Day -1 until 06:29 AM 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)
TARGR1	Cigarette Tar Yield Classification
TARGR1N	Cigarette Tar Yield Class (N)
COBL	Baseline Cigarette CO Level (mg)
ENRLFL	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
FASFL	Full Analysis Set 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 Imput. 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
TRTP	Planned Treatment
TRTPN	Planned Treatment (N)
TRTA	Actual Treatment
TRTAN	Actual Treatment (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

The Nicotine PK parameters for subject 328 were not reported due to a missing bioanalytical result at 4 hours post dose.

For subjects 8 and 206, the actual time of the 24 hour sample occurred 2 minutes early which prevented calculation of C_{avg} over a nominal time period of 24 hours. Instead, C_{avg} was calculated over the time period to the last actual sampling time (23.967 hours) in these instances. The Nicotine and Cotinine values for this parameter were flagged and footnoted with 'Due to sampling time restrictions C_{avg} calculated as area under the curve from time zero to the last quantifiable concentration divided by the time to the last quantifiable concentration'.

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 11.3. 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?

No.

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
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. The handover documentation from the PK analysis, file 1001000_8278003 PK handover Memo Version 3.pdf, can be referenced under Section 5.2.19.

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	X
ADCM – Concomitant Medication Analysis Dataset	ODS	X			
ADCO – Comments Analysis Dataset	OTHER	X			
ADDE – Device Events 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			

Dataset – Dataset Label	Class	Safety	Baseline or other subject characteristics	PK/PD	Primary Objective
<u>ADEG - ECG Analysis Dataset</u>	BDS	X			
<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>ADMH - Medical History Analysis Dataset</u>	ODS		X		
<u>ADPC - Pharmacokinetic Concentration Analysis Dataset</u>	BDS			X	
<u>ADPE - Physical Examination Analysis Dataset</u>	BDS	X			
<u>ADPP - PK Parameters Analysis Dataset</u>	BDS			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			

Dataset – Dataset Label	Class	Safety	Baseline or other subject characteristics	PK/PD	Primary Objective
ADXT - Smoking Profile Analysis Dataset	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 ENRLFL, Randomized population RANDFL, Safety population SAFFL, Full analysis set population FASFL and Per-protocol population PPROTFL), product variables (actual products TRT01A, TRT01AN and planned products TRT01P, TRT01PN, where 01 refers to the single period as detailed in Section 2.2) and stratification indicator variables (Sex Male, Female – SEXC, SEXN and Daily CC Consumption at baseline 10-19 cig/day, > 19 cig/day – UCPDGR1, UCPDGR1N) are included in all analysis datasets. To identify the required FAS population, FASFL=Y and for the Per Protocol population PPROTFL=Y. 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 6/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.

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 which observations 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 the biomarkers listed below and component data for CYP1A2 and CYP2A6 activity which is derived according to the SAP. Data is selected from LB and SUPPLB and for CYP1A2 and CYP2A6 data, the component and converted values to nmol/L for derivation of the CYP1A2 and 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.

Parameter (PARAM)	PARAMCD
All laboratory Tests (BIOMARKERS OF EXPOSURE)	BELBALL
Caffeine (nmol/L) *	CAF
Caffeine (ng/mL)	CAFFEINE
Carboxyhemoglobin (%)	CARBXHGB
Carbon Monoxide (ppm)	CO
Cotinine (nmol/L) *	COT
Cotinine (ng/mL)	COTININE
Creatinine (mg/dL)	CREAT
CYP1A2 Activity (%) *	CYP1A2
CYP2A6 Activity (%) *	CYP2A6
Trans-3'hydroxycotinine (nmol/L) *	HCOT
Paraxanthine (ng/mL)	PX
Paraxanthine (nmol/L) *	PXC
Trans-3'hydroxycotinine (ng/mL)	TRANS3H
1-aminonaphthalene (pg/mL)	U1NA
1-aminonaphthalene (ng) *	U1NA24U
1-aminonaphthalene (pg/mg creat) *	U1NACRE
Total 1-hydroxypyrene (pg/mL)	U1OHP
Total 1-hydroxypyrene (ng) *	U1OHP24U
Total 1-hydroxypyrene (pg/mg creat) *	U1OHPCRE
2-aminonaphthalene (pg/mL)	U2NA
2-aminonaphthalene (ng) *	U2NA24U
2-aminonaphthalene (pg/mg creat) *	U2NACRE
3-hydroxypropylmercapturic Acid (µg) *	U3HPM24U
3-hydroxypropylmercapturic Acid (ng/mL)	U3HPMA
3-hydroxypropylmercapturic Acid (ng/mg creat) *	U3HPMCRE
4-Aminobiphenyl (pg/mL)	U4ABP
4-Aminobiphenyl (ng) *	U4ABP24U
4-Aminobiphenyl (pg/mg creat) *	U4ABPCRE
Ames Mutagenecity (REV/mL)	UAMES

Parameter (PARAM)	PARAMCD
Ames Mutagenecity (REV/24h) *	UAMES24U
3-hydroxy(a)benzopyrene (fg/mL)	UBAP
3-hydroxy(a)benzopyrene (pg) *	UBAP24U
3-hydroxy(a)benzopyrene (fg/mg creat) *	UBAPCRE
2-cyanoethylmercapturic Acid (ng/mL)	UCEMA
2-cyanoethylmercapturic Acid (µg) *	UCEMA24U
2-cyanoethylmercapturic Acid (ng/mg creat) *	UCEMACRE
Cotinine-Glucuronide (ng/mL)	UCOTG
Cotinine-Glucuronide (umol/L) *	UCOTGC
2-hydroxyethyl Mercapturic Acid (Derived) (pg/mL) *	UDHEMA
Monohydroxybutenyl Mercapturic Acid (Derived) (pg/mL) *	UDMHBMA
S-benzylmercapturic Acid (Derived) (pg/mL) *	UDSBMA
S-phenylmercapturic Acid (Derived) (pg/mL) *	UDSPMA
Free Cotinine (ng/mL)	UFCOT
Free Cotinine (umol/L) *	UFCOTC
Free Nicotine (ng/mL)	UFNIC
Free Nicotine (umol/L) *	UFNICC
Free Trans-3'-hydroxycotinine (umol/L) *	UFTRANSC
Free Trans-3'-hydroxycotinine (ng/mL)	UFTRANSH
2-hydroxyethyl Mercapturic Acid (ng) *	UHEMA24U
2-hydroxyethyl Mercapturic Acid (pg/mg creat) *	UHEMACRE
Hydroxy-1-methylpropylmercapturic Acid (µg) *	UHMPM24U
Hydroxy-1-methylpropylmercapturic Acid (ng/mL)	UHMPMA
Hydroxy-1-methylpropylmercapturic Acid (ng/mg creat) *	UHMPMCRE
All laboratory tests (24H URINE SAMPLE)	ULBALL
Monohydroxybutenyl Mercapturic Acid (ng) *	UMHBM24U
Monohydroxybutenyl Mercapturic Acid (pg/mg creat) *	UMHBMCRE
Nicotine Equivalents (mg) *	UNEQ24U
Nicotine Equivalents (mg/g creat) *	UNEQCRE
Nicotine-Glucuronide (ng/mL)	UNICG
Nicotine-Glucuronide (umol/L) *	UNICGC
NNAL (pg/mL)	UNNAL
NNAL (ng) *	UNNAL24U
NNAL (pg/mg creat) *	UNNALCRE
Total N-nitrosornicotine (pg/mL)	UNNN
Total N-nitrosornicotine (ng) *	UNNN24U
Total N-nitrosornicotine (pg/mg creat) *	UNNNCRE
2-hydroxyethyl Mercapturic Acid (ng/mL)	UOHEMA
Monohydroxybutenyl Mercapturic Acid (ng/mL)	UOMHBMA

Parameter (PARAM)	PARAMCD
S-benzylmercapturic Acid (ng/mL)	UOSBMA
S-phenylmercapturic Acid (ng/mL)	UOSPMA
o-toluidine (pg/mL)	UOTOL
o-toluidine (ng) *	UOTOL24U
o-toluidine (pg/mg creat) *	UOTOLCRE
Prostaglandin F2 Alpha (ng) *	UPGF224U
Prostaglandin F2 Alpha (pg/mL)	UPGF2A
Prostaglandin F2 Alpha (pg/mg creat) *	UPGF2CRE
S-benzylmercapturic Acid (ng) *	USBMA24U
S-benzylmercapturic Acid (pg/mg creat) *	USBMACRE
S-phenylmercapturic Acid (ng) *	USPMA24U
S-phenylmercapturic Acid (pg/mg creat) *	USPMACRE
Trans-3'-hydroxycotinineglucuronide (umol/L) *	UTRANSHC
Trans-3'-hydroxycotinineglucuronide (ng/mL)	UTRANSHY
11-Dehydro-Thromboxane B2 (ng) *	UTXB224U
11-Dehydro-Thromboxane B2 (pg/mg creat) *	UTXB2CRE
11-Dehydro-Thromboxane B2 (pg/mL)	UTXB2D11
Volume (mL)	VOLUME

* Derived

Where a set of data has not been analysed, a summary observation is provided as All laboratory Tests (BIOMARKERS OF EXPOSURE), PARAMCD=BELBALL and All laboratory tests (24H URINE SAMPLE) (PARAMCD=ULBALL).

5.2.4 ADCM – Concomitant Medication Analysis Dataset

ADCM contains all observations and required variables from CM and SUPPCM and also one observation for each subject in ADSL that did not have any medication administered during the study. Reference to an external spreadsheet BANNEDMEDS.XLSX is used to compare the ATC2 coding to the list of medications defined in the protocol section 6.7.3, refer to Appendix 8 for the list of medications referred to for this. CRIT1FL=Y indicates if any medication affects CYP1A2 or CYP2A6 activity. CMFL=Y indicates the medication is concomitant. PMFL=Y indicates the medication is prior.

5.2.5 ADCO – Comments Analysis Dataset

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

5.2.6 ADDE – Device Events Analysis Dataset

ADDE contains all observations and required variables from DE and SUPPDE and also one observation for each subject exposed to the device in ADSL that did not have any device events during the study. The variable ANYDEFL=Y indicates a device event was experienced.

5.2.7 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 follow-up assessments are included in this dataset. This data contains observations for screen failure subjects.

5.2.8 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.

5.2.9 ADDV – Protocol Deviation Analysis Dataset

ADDV contains all observations from DV. PARAMCD and PARAM are derived from the SAP section 11 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..

5.2.10 ADDX - THS Product Exposure Analysis Dataset

ADDX contains all observations from DX. The actual level of nicotine has been added to the analysis data from referral to the protocol section 6.1.1. The Daily THS 2.2 Administration has been derived with PARAMCD = DTHS2_2.

5.2.11 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.

If all expected parameters are missing from a protocol timepoint data are represented using PARAMCD = EGALL with EGREASND providing the reason for the missing data.

5.2.12 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. This data contains observations for screen failure subjects which are listed only.

5.2.13 ADEX – Exposure Analysis Dataset

ADEX contains all observations from EX and SUPPEX. The actual level of nicotine for conventional cigarettes has been included under AVAL from FA data. The Daily Conventional Cigarette Administration has been derived with PARAMCD = DCC.

5.2.14 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.

5.2.15 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.

If all expected parameters are missing from a protocol timepoint data are represented using PARAMCD = CLBALL for Biochemistry, PARAMCD=HLBALL for hematology and ULBALL for Urinalysis with LBREASND providing the reason for the missing data.

5.2.16 ADMH – Medical History Analysis Dataset

ADMH contains all observation from MH. All MH variables have been retained in this dataset with required ADSL variables included. ANYMHFL=Y indicates the observation is a medical history. ANYCDFL=Y indicates the observation is a concomitant disease. MHONGFL=Y indicates the concurrent disease is ongoing during the study.

The data are coded under the System Organ Class variable MHBODSYS and Preferred Term variable MHDECOD.

5.2.17 ADPC – Pharmacokinetic Concentration Analysis Dataset

ADPC contains all observations in PC. ANL01FL=Y indicates values to be used in summary statistics and analysis. Values below the limit of quantification (BLQ) are replaced half the value of quantification and identified in DTYPE as such.

5.2.18 ADPE – Physical Examination Analysis Dataset

ADPE contains all observation from PE. ANL01FL=Y indicates values to be used in summary tables.

If all expected parameters are missing from a protocol timepoint data are represented using PARAMCD = PEALL with PEREASND providing the reason for the missing data.

5.2.19 ADPP – PK Parameters Analysis Dataset

ADPP contains observations from PP. ANL01FL=Y indicates values are to be included in summary statistics and statistical analysis. ANL01FL was populated and data presented following rules as per SAP.

The Nicotine PK parameters for subject 328 were not reported due to a missing bioanalytical result at 4 hours post dose.

For subjects 8 and 206, the actual time of the 24 hour sample occurred 2 minutes early which prevented calculation of C_{avg} over a nominal time period of 24 hours. Instead, C_{avg} was calculated over the time period to the last actual sampling time (23.967 hours) in these instances. The Nicotine and Cotinine values for this parameter were flagged and footnoted with 'Due to sampling time restrictions C_{avg} calculated as area under the curve from time zero to the last quantifiable concentration divided by the time to the last quantifiable concentration'.

This can be referenced in the source documentation [1001000 8278003 PK handover Memo Version 3.pdf](#)

5.2.20 ADQSND – Nicotine Dependence Analysis Dataset

ADQSND contains data from QS for the Fagerström Test for Nicotine Dependence (FTND) and the Minnesota Nicotine Dependence/Withdrawal Scale (MNWS). The MNWS Total Score 1 and Total Score2 has been derived as detailed in the SAP section 7.3.4 with PARAMCD= MNWRWDS1 and MNWRWDS2 respectively, numeric total score is in AVAL. The FTND 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 AVALCAT. ANL01FL=Y indicated values used in summary statistics.

If all expected parameters are missing from a protocol timepoint data are represented using PARAMCD = QSALL with QSREASND providing the reason for the missing data.

5.2.21 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
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If all expected parameters are missing from a protocol timepoint data are represented using PARAMCD = QSALL with QSREASND providing the reason for the missing data.

5.2.22 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= QSUFAC1, Relief has PARAMCD= QSUFAC2 and total score has PARAMCD= QSUTOTAL). ANL01FL=Y indicated values used in summary statistics and analysis.

If all expected parameters are missing from a protocol timepoint data are represented using PARAMCD = QSALL with QSREASND providing the reason for the missing data.

5.2.23 ADQSSYM – Symptoms Questionnaire Analysis Dataset

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

If all expected parameters are missing from a protocol timepoint data are represented using PARAMCD = QSALL with QSREASND providing the reason for the missing data.

5.2.24 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.

5.2.25 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.

If all expected parameters are missing from a protocol timepoint data are represented using PARAMCD = SUVSALL with VSREASND providing the reason for the missing data.

5.2.26 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.

If all expected parameters are missing from a protocol timepoint data are represented using PARAMCD = XPALL with XPREASND providing the reason for the missing data.

5.2.27 ADXT - Smoking Profile Analysis Dataset

ADXT contains all observations from XT as well as the derived per cigarette parameters as detailed in the SAP Section 7.4. ANL01FL=Y indicates the observation was made within the acceptable time window as detailed in the SAP section 11.3. ANL02FL=Y indicates values to be used in summary statistics. All observations made outside the time window were assessed in a blinded manner prior to lock. A list of the derived parameters is listed below:

Parameter (PARAM)	PARAMCD
Analysis Full Filter Absolute UV TAR Absorbance (total over visit)	TFABUVTA
Analysis Full Filter Nicotine Amount per filter (mg/filter) (total over visit)	TFNICOF
Analysis Full Filter Nicotine Amount per mL (mg/mL) (total over visit)	TFNICO
Analysis Full Filter Normalized UV Absorbance (per filter) (total over visit)	TFNMUVAB
Analysis Mouthpiece Absolute UV TAR Absorbance (total over visit)	TMABUVTA
Analysis Mouthpiece Nicotine Amount per filter (mg/filter) (total over visit)	TMNICOF
Analysis Mouthpiece Nicotine Amount per mL (mg/mL) (total over visit)	TMNICO
Analysis Mouthpiece Normalized UV Absorbance (per filter) (total over visit)	TMNMUVAB
Analysis PLA + Hat Absolute UV TAR Absorbance (total over visit)	TPABUVTA
Analysis PLA + Hat Nicotine Amount per filter (mg/filter) (total over visit)	TPNICOF
Analysis PLA + Hat Nicotine Amount per mL (mg/mL) (total over visit)	TPNICO
Analysis PLA + Hat Normalized UV Absorbance (per filter) (total over visit)	TPNMUVAB
Average Peak flow (mL/s)	AVGQCI
Average Peak flow (mL/s) (average over visit)	AAVGQCI
Average Peak pressure drop (mmWg)	AVGPCI
Average Peak pressure drop (mmWg) (average over visit)	AAVGPCI
Average Work (mJ)	AVGWI
Average Work (mJ) (average over visit)	AAVGWI
Average flow (mL/s)	AVGQMI
Average flow (mL/s) (average over visit)	AAVGQMI
Average inter puff interval (s)	AVGII
Average inter puff interval (s) (average over visit)	AAVGII
Average pressure drop (mmWg)	AVGPMI
Average pressure drop (mmWg) (average over visit)	AAVGPMI
Average puff duration (s)	AVGDI
Average puff duration (s) (average over visit)	AAVGDI
Average puff volume (mL)	AVGVI
Average puff volume (mL) (average over visit)	AAVGVI
Puff Frequency (puffs/min)	PFEQ
Puff Frequency (puffs/min) (average over visit)	APFEQ
Puffing Time Index (%)	PTI

Parameter (PARAM)	PARAMCD
Puffing Time Index (%) (average over visit)	APTI
Smoking Intensity (mL/s)	SMINT
Smoking Intensity (mL/s) (average over visit)	ASMINT
Total inter puff interval (s)	TII
Total inter puff interval (s) (average over visit)	ATII
Total number of puffs	NPC
Total number of puffs (average over visit)	ANPC
Total puff duration (s)	TDI
Total puff duration (s) (average over visit)	ATDI
Total puff volume (mL)	TVOL
Total puff volume (mL) (average over visit)	ATVOL
Total smoking duration (s)	TDFI
Total smoking duration (s) (average over visit)	ATDFI
Total work (mJ)	TWI
Total work (mJ) (average over visit)	ATWI

If all expected parameters are missing from a protocol timepoint data are represented using PARAMCD = HSTALL with XTREASND providing the reason for the missing data.

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 OpenCDSIC community validator 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.
ADBX	Inconsistent value for AVALC	ERROR	2	OpenCDISC issue, check performed on INPUT(AVALC,BEST32.) not equal to AVAL., no differences found.
ADBX	calculation error: $PCHG \neq (AVAL - BASE)/BASE * 100$	ERROR	8	Due to SAP rule that BASE is imputed as 1 for PCHG calculation if BASE = 0 - NAR.
ADCM	Neither AVAL nor AVALC are present in dataset	ERROR	1	It was determined that the BDS format was not appropriate to this data type and as such AVAL and AVALC are not appropriate. Structure was based upon ADAE and SDTM.CM structure

Dataset(s)	Diagnostic Message and/or Check ID	Severity	Count and/or Issue Rate	Explanation
ADCM	Required variable is not present	ERROR	2	It was determined that the BDS format was not appropriate to this data type and as such PARAM and PARAMCD are not appropriate. Structure was based upon ADAE and SDTM.CM structure
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.
ADDE	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 these are event data type.
ADDE	Required variable is not present	ERROR	2	PARAM and PARAMCD were not applicable to this data. Data structure reflects ADAE domain as closely as possible as these are event data type.
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.
ADMH	Neither AVAL nor AVALC are present in dataset	ERROR	1	ADMH is not a BDS domain. It is based upon ADAE domain and as detailed under ADAE OpenCDISC does not take this into account yet.
ADMH	Required variable is not present	ERROR	2	PARAM and PARAMCD not required as domain based upon ADAE.
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).
ADQSD	calculation error: $PCHG \neq (AVAL - BASE)/BASE * 100$	ERROR	1502	Due to SAP rule that BASE is imputed as 1 for PCHG calculation if BASE = 0 - NAR.
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.

Dataset(s)	Diagnostic Message and/or Check ID	Severity	Count and/or Issue Rate	Explanation
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.
ADXT	Inconsistent value for AVALC	ERROR	182	OpenCDISC issue, check performed on INPUT(AVALC,BEST32.) not equal to AVAL., no differences found.
Define	Invalid 'DataType' value	ERROR	38	Partial datetime values in ADSL.ICF01DTC as times are missing. No change 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 are internal macros in each program such as `_mprintto` that automatically saves the output and log to specific areas. These will not run on an external system so please exclude the macro call from program execution.

Figure / Table Number	Title	Program	Analysis Dataset	Analysis Variable(s)
15.1.1.1	Figure 15.1.1.1 Evening COHb (%) Geometric Mean and 95% CI - FAS	f_cohb	ADBX	FASFL, PARAM, AVAL, ANL02FL
15.1.1.2	MHBMA Urinary Concentration Adjusted for Creatinine (pg/mg creat) Geometric Mean and 95% CI - FAS	f_mhbma	ADBX	FASFL, PARAM, AVAL, ANL02FL

Figure / Table Number	Title	Program	Analysis Dataset	Analysis Variable(s)
15.1.1.3	3-HPMA Urinary Concentration Adjusted for Creatinine (ng/mg creat) Geometric Mean and 95% CI - FAS	f_hpma	ADBX	FASFL, PARAM, AVAL, ANL02FL
15.1.1.4	S-PMA Urinary Concentration Adjusted for Creatinine (pg/mg creat) Geometric Mean and 95% CI - FAS	f_spma	ADBX	FASFL, PARAM, AVAL, ANL02FL
15.1.1.5	Evening COHb % Change from Baseline Mean and 95% CI - FAS	f_cohbchg	ADBX	FASFL, PARAM, PCHG, AVISIT, ATPT, ANL02FL
15.1.1.6	MHBMA Urinary Concentration Adjusted for Creatinine (pg/mg creat) % Change from Baseline Mean and 95% CI - FAS	f_mhbmachg	ADBX	FASFL, PARAM, PCHG, ANL02FL
15.1.1.7	3-HPMA Urinary Concentration Adjusted for Creatinine (ng/mg creat) % Change from Baseline Mean and 95% CI - FAS	f_hpmachg	ADBX	FASFL, PARAM, PCHG, ANL02FL
15.1.1.8	S-PMA Urinary Concentration Adjusted for Creatinine (pg/mg creat) % Change from Baseline Mean and 95% CI - FAS	f_spmachg	ADBX	FASFL, PARAM, PCHG, ANL02FL
15.1.2.1	Urinary MHBMA Quantity Excreted over 24 hours (ng) Geometric Mean and 95% CI - FAS	f_mhbm24	ADBX	FASFL, PARAM, AVAL, ANL02FL

Figure / Table Number	Title	Program	Analysis Dataset	Analysis Variable(s)
15.1.2.2	Urinary 3-HPMA Quantity Excreted over 24 hours (µg) Geometric Mean and 95% CI - FAS	f_hpma24	ADBX	FASFL, PARAM, AVAL, ANL02FL
15.1.2.3	Urinary S-PMA Quantity Excreted over 24 hours (ng) Geometric Mean and 95% CI - FAS	f_spma24	ADBX	FASFL, PARAM, AVAL, ANL02FL
15.1.2.4	Exhaled CO Arithmetic Mean and 95% CI - FAS	f_co	ADBX	FASFL, PARAM, AVAL, ANL02FL
15.1.2.5	1-OHP Urinary Concentration Adjusted for Creatinine (pg/mg creat) Geometric Mean and 95% CI - FAS	f_1ohp	ADBX	FASFL, PARAM, AVAL, ANL02FL
15.1.2.6	Urinary 1-OHP Quantity Excreted over 24 hours (ng) Geometric Mean and 95% CI - FAS	f_1ohp24	ADBX	FASFL, PARAM, AVAL, ANL02FL
15.1.2.7	Total NNN Urinary Concentration Adjusted for Creatinine (pg/mg creat) Geometric Mean and 95% CI - FAS	f_nnn	ADBX	FASFL, PARAM, AVAL, ANL02FL
15.1.2.8	Urinary Total NNN Quantity Excreted over 24 hours (ng) Geometric Mean and 95% CI - FAS	f_nnn24	ADBX	FASFL, PARAM, AVAL, ANL02FL
15.1.2.9	4-ABP Urinary Concentration Adjusted for Creatinine (pg/mg creat) Geometric Mean and 95% CI - FAS	f_4abp	ADBX	FASFL, PARAM, AVAL, ANL02FL

Figure / Table Number	Title	Program	Analysis Dataset	Analysis Variable(s)
15.1.2.10	Urinary 4-ABP Quantity Excreted over 24 hours (ng) Geometric Mean and 95% CI - FAS	f_4abp24	ADBx	FASFL, PARAM, AVAL, ANL02FL
15.1.2.11	1-NA Urinary Concentration Adjusted for Creatinine (pg/mg creat) Geometric Mean and 95% CI - FAS	f_1na	ADBx	FASFL, PARAM, AVAL, ANL02FL
15.1.2.12	Urinary 1-NA Quantity Excreted over 24 hours (ng) Geometric Mean and 95% CI - FAS	f_1na24	ADBx	FASFL, PARAM, AVAL, ANL02FL
15.1.2.13	2-NA Urinary Concentration Adjusted for Creatinine (pg/mg creat) Geometric Mean and 95% CI - FAS	f_2na	ADBx	FASFL, PARAM, AVAL, ANL02FL
15.1.2.14	Urinary 2-NA Quantity Excreted over 24 hours (ng) Geometric Mean and 95% CI - FAS	f_2na24	ADBx	FASFL, PARAM, AVAL, ANL02FL
15.1.2.15	o-toluidine Urinary Concentration Adjusted for Creatinine (pg/mg creat) Geometric Mean and 95% CI - FAS	f_otol	ADBx	FASFL, PARAM, AVAL, ANL02FL
15.1.2.16	Urinary o-toluidine Quantity Excreted over 24 hours (ng) Geometric Mean and 95% CI - FAS	f_otol24	ADBx	FASFL, PARAM, AVAL, ANL02FL
15.1.2.17	CEMA Urinary Concentration Adjusted for Creatinine (ng/mg creat) Geometric Mean and 95% CI - FAS	f_cema	ADBx	FASFL, PARAM, AVAL, ANL02FL

Figure / Table Number	Title	Program	Analysis Dataset	Analysis Variable(s)
15.1.2.18	Urinary CEMA Quantity Excreted over 24 hours (µg) Geometric Mean and 95% CI - FAS	f_cema24	ADBX	FASFL, PARAM, AVAL, ANL02FL
15.1.2.19	HEMA Urinary Concentration Adjusted for Creatinine (pg/mg creat) Geometric Mean and 95% CI - FAS	f_hema	ADBX	FASFL, PARAM, AVAL, ANL02FL
15.1.2.20	Urinary HEMA Quantity Excreted over 24 hours (ng) Geometric Mean and 95% CI - FAS	f_hema24	ADBX	FASFL, PARAM, AVAL, ANL02FL
15.1.2.21	B[a]P Urinary Concentration Adjusted for Creatinine (fg/mg creat) Geometric Mean and 95% CI - FAS	f_bap	ADBX	FASFL, PARAM, AVAL, ANL02FL
15.1.2.22	Urinary B[a]P Quantity Excreted over 24 hours (pg) Geometric Mean and 95% CI - FAS	f_bap24	ADBX	FASFL, PARAM, AVAL, ANL02FL
15.1.2.23	HMPMA Urinary Concentration Adjusted for Creatinine (ng/mg creat) Geometric Mean and 95% CI - FAS	f_hmpma	ADBX	FASFL, PARAM, AVAL, ANL02FL
15.1.2.24	Urinary HMPMA Quantity Excreted over 24 hours (µg) Geometric Mean and 95% CI - FAS	f_hmpma24	ADBX	FASFL, PARAM, AVAL, ANL02FL
15.1.2.25	S-BMA Urinary Concentration Adjusted for Creatinine (pg/mg creat) Geometric Mean and 95% CI - FAS	f_sbma	ADBX	FASFL, PARAM, AVAL, ANL02FL

Figure / Table Number	Title	Program	Analysis Dataset	Analysis Variable(s)
15.1.2.26	Urinary S-BMA Quantity Excreted over 24 hours (ng) Geometric Mean and 95% CI - FAS	f_sbma24	ADBX	FASFL, PARAM, AVAL, ANL02FL
15.1.2.27	Total NNAL Urinary Concentration Adjusted for Creatinine (pg/mg creat) Geometric Mean and 95% CI - FAS	f_nnal	ADBX	FASFL, PARAM, AVAL, ANL02FL
15.1.2.28	Urinary Total NNAL Quantity Excreted over 24 hours (ng) Geometric Mean and 95% CI - FAS	f_nnal24	ADBX	FASFL, PARAM, AVAL, ANL02FL
15.1.2.29	NEQ Urinary Concentration Adjusted for Creatinine (mg/g creat) Geometric Mean and 95% CI - FAS	f_neq	ADBX	FASFL, PARAM, AVAL, ANL02FL
15.1.2.30	Urinary NEQ Quantity Excreted over 24 hours (mg) Geometric Mean and 95% CI - FAS	f_neq24	ADBX	FASFL, PARAM, AVAL, ANL02FL
15.1.2.31	Plasma Nicotine Concentrations (ng/mL) Geometric Mean and 95% CI - FAS	f_pkconc	ADPC	FASFL, PARAM, AVAL, ANL01FL
15.1.2.32	Plasma Cotinine Concentrations (ng/mL) Geometric Mean and 95% CI - FAS	f_pkconc2	ADPC	FASFL, PARAM, AVAL, ANL01FL
15.1.2.33	QSU-brief Factors and Total Scores Arithmetic Mean and 95% CI – FAS	f_qsu	ADQSSU	FASFL, PARAM, AVAL, ANL01FL

Figure / Table Number	Title	Program	Analysis Dataset	Analysis Variable(s)
15.1.2.34	QSU-brief Factors and Total Scores Change from Baseline Least Squares Mean Differences and 95% CI - FAS	tlf_anlqsu	ADQSSU	FASFL, SEX, UCPDGR1, PARAM, CHG, AVISIT
15.1.2.35	MNWS Total Scores Arithmetic Mean and 95% CI – FAS	f_mnws	ADQSND	FASFL, PARAM, AVAL, ANL01FL
15.1.2.36	MNWS Total Scores Change from Baseline Least Squares Mean Differences and 95% CI - FAS	f_anlmnws	ADQSND	FASFL, SEX, UCPDGR1, PARAM, CHG, AVISIT
15.1.2.37	MCEQ Subscales Arithmetic Mean and 95% CI – FAS	f_mceq	ADQSPA	FASFL, PARAM, AVAL, ANL01FL
15.1.2.38	MCEQ Subscales Change from Baseline Least Squares Mean Differences and 95% CI - FAS	tlf_anlmceq	ADQSPA	FASFL, SEX, UCPDGR1, PARAM, CHG
15.1.2.39	HST per Cigarette Parameters Arithmetic Mean and 95% CI – FAS	f_hst	ADXT	FASFL, PARCAT1, PARAM, AVAL, ANL02FL
15.1.2.40	Scatterplot of 8-epi-PGF2 α Urinary Concentration Adjusted for Creatinine vs. NEQ Urinary Concentration Adjusted for Creatinine - FAS	tlf_anlnegrisk	ADBX	FASFL, PARAM, AVAL, AVISIT
15.1.2.41	Scatterplot of Urinary 8-epi-PGF2 α Quantity Excreted over 24 hours vs. Urinary NEQ Quantity Excreted over 24 hours - FAS	tlf_anlnegrisk	ADBX	FASFL, PARAM, AVAL, AVISIT

Figure / Table Number	Title	Program	Analysis Dataset	Analysis Variable(s)
15.1.2.42	Scatterplot of 11-DTX-B2 Urinary Concentration Adjusted for Creatinine vs. NEQ Urinary Concentration Adjusted for Creatinine - FAS	tlf_anlneqrisk	ADBX	FASFL, PARAM, AVAL, AVISIT
15.1.2.43	Scatterplot of Urinary 11-DTX-B2 Quantity Excreted over 24 hours vs. Urinary NEQ Quantity Excreted over 24 hours - FAS	tlf_anlneqrisk	ADBX	FASFL, PARAM, AVAL, AVISIT
15.2.1.1	Summary of Subject Disposition - All Screened Subjects	t_sdisp	ADSL ADFA	SCRFFL, ENRFL, RANDFL, COMPLFL, DTESTDTM PARCAT1, PARAM, AVAL
15.2.1.2	Summary of Reasons for Discontinuations - Randomized Population	t_rsndis	ADDS	RANDFL, COMPLFL, FUPFL, DSCAT, DSDECOD
15.2.1.3	Summary of Protocol Deviations - Safety Population	t_pdev	ADDV	SAFFL, ENRFL, AVALC, DVCAT, PARAM, DVSIG

Figure / Table Number	Title	Program	Analysis Dataset	Analysis Variable(s)
15.2.1.4.1	Summary of Demographics and Other Baseline Characteristics - Safety Population	t_demog	ADSL ADBx ADQsND	SAFFL, TRT01A, SEX, UCPDGR1, AGE, BMI, BMIGR1, HEIGHT, WEIGHTBL, ETHNIC, NICOGR1, NICOBL, TARGR1, TARBL, SAFFL, PARAMCD, AVAL, AVISIT SAFFL, PARAMCD, AVAL, AVALCAT1

[illegible]

[illegible]

Figure / Table Number	Title	Program	Analysis Dataset	Analysis Variable(s)
15.2.1.4.2.2	Summary of Demographics and Other Baseline Characteristics by Cigarette Consumption - FAS Population	t_demog2c	ADSL ADBX ADQSD	FASFL, SEX, UCPDGR1, AGE, BMI, BMIGR1, HEIGHT, WEIGHTBL, ETHNIC, NICOGR1, NICOBL, TARGR1, TARBL, FASFL, PARAMCD, AVAL, AVISIT FASFL, PARAMCD, AVAL, AVALCAT1
15.2.1.5	Summary of Current Cigarette Brands at Admission - Safety Population	t_cigbrand	ADFA	SAFFL, ENRFL, PARCAT2, PARAM, AVAL, AVISIT
15.2.1.6	Summary of Medical History - Safety Population	t_medhis	ADMH	SAFFL, ANYMHFL, MHCAT, MHBODSYS, MHDECOD
15.2.1.7	Summary of Concomitant Diseases - Safety Population	t_condis	ADMH	SAFFL, ANYMHFL, MHCAT, MHBODSYS, MHDECOD

Figure / Table Number	Title	Program	Analysis Dataset	Analysis Variable(s)
15.2.2.1	Descriptive Statistics of Use of THS 2.2 Product and CC - Safety Population	t_ustatss	ADDX ADEX	SAFFL, ENRFL, PARAM, AVISIT,
15.2.3.1	Analysis of Evening Blood COHb (%) versus CC on Day 5 - FAS	tl_anlcohbfas	ADBX	FASFL, SEX, UCPDGR1, PARAM, AVISIT, ATPT, AVAL, ANL02FL
15.2.3.2	Analysis of MHBMA Urinary Concentration Adjusted for Creatinine (pg/mg creat) versus CC on Day 5 - FAS	tl_anlmhbmfa s	ADBX	FASFL, SEX, UCPDGR1, PARAM, AVISIT, AVAL, ANL02FL
15.2.3.3	3-HPMA Urinary Concentration Adjusted for Creatinine (ng/mg creat) versus CC on Day 5 - FAS	tl_anl3hpmafas	ADBX	FASFL, SEX, UCPDGR1, PARAM, AVISIT, AVAL, ANL02FL
15.2.3.4	S-PMA Urinary Concentration Adjusted for Creatinine (pg/mg creat) versus CC on Day 5 - FAS	tl_anlspmaf	ADBX	FASFL, SEX, UCPDGR1, PARAM, AVISIT, AVAL, ANL02FL
15.2.3.5	Descriptive Statistics of % Change from Baseline in Primary Biomarkers on Day 5 - FAS	t_pbio	ADBX	FASFL, PARAM, AVISIT, ATPT, PCHG, ANL02FL
15.2.3.5.1	Descriptive Statistics of % Change from Baseline in Primary Biomarkers on Day 5 by Sex - FAS	t_pbios	ADBX	FASFL, PARAM, SEX, AVISIT, ATPT, PCHG, ANL02FL

Figure / Table Number	Title	Program	Analysis Dataset	Analysis Variable(s)
15.2.3.5.2	Descriptive Statistics of % Change from Baseline in Primary Biomarkers on Day 5 by Cigarette Consumption - FAS	t_pbioc	ADBX	FASFL, PARAM, UCPDRG1, AVISIT, ATPT, PCHG, ANL02FL
15.2.3.6	Descriptive Statistics of COHb (%) - FAS	t_cohb	ADBX	FASFL, PARAM, AVISIT, ATPT, AVAL, PCHG, ANL02FL
15.2.3.6.1	Descriptive Statistics of COHb (%) by Sex - FAS	t_cohbs	ADBX	FASFL, PARAM, SEX, AVISIT, ATPT, AVAL, PCHG, ANL02FL
15.2.3.6.2	Descriptive Statistics of COHb (%) by Cigarette Consumption - FAS	t_cohbc	ADBX	FASFL, PARAM, UCPDRG1, AVISIT, ATPT, AVAL, PCHG, ANL02FL
15.2.3.7	Descriptive Statistics of MHBMA Urinary Concentration Adjusted for Creatinine (pg/mg creat) - FAS	t_mhbma	ADBX	FASFL, PARAM, AVISIT, ATPT, AVAL, PCHG, ANL02FL
15.2.3.7.1	Descriptive Statistics of MHBMA Urinary Concentration Adjusted for Creatinine (pg/mg creat) by Sex - FAS	t_mhbmas	ADBX	FASFL, PARAM, SEX, AVISIT, ATPT, AVAL, PCHG, ANL02FL
15.2.3.7.2	Descriptive Statistics of MHBMA Urinary Concentration Adjusted for Creatinine (pg/mg creat) by Cigarette Consumption - FAS	t_mhbmac	ADBX	FASFL, PARAM, UCPDRG1, AVISIT, ATPT, AVAL, PCHG, ANL02FL

Figure / Table Number	Title	Program	Analysis Dataset	Analysis Variable(s)
15.2.3.8	Descriptive Statistics of 3-HPMA Urinary Concentration Adjusted for Creatinine (ng/mg creat) - FAS	t_hpma	ADBX	FASFL, PARAM, AVISIT, ATPT, AVAL, PCHG, ANL02FL
15.2.3.8.1	Descriptive Statistics of 3-HPMA Urinary Concentration Adjusted for Creatinine (ng/mg creat) by Sex - FAS	t_hpmas	ADBX	FASFL, PARAM, SEX, AVISIT, ATPT, AVAL, PCHG, ANL02FL
15.2.3.8.2	Descriptive Statistics of 3-HPMA Urinary Concentration Adjusted for Creatinine (ng/mg creat) by Cigarette Consumption - FAS	t_hpmac	ADBX	FASFL, PARAM, UCPDRG1, AVISIT, ATPT, AVAL, PCHG, ANL02FL
15.2.3.9	Descriptive Statistics of S-PMA Urinary Concentration Adjusted for Creatinine (pg/mg creat) - FAS	t_spma	ADBX	FASFL, PARAM, AVISIT, ATPT, AVAL, PCHG, ANL02FL
15.2.3.9.1	Descriptive Statistics of S-PMA Urinary Concentration Adjusted for Creatinine (pg/mg creat) by Sex - FAS	t_spmas	ADBX	FASFL, PARAM, SEX, AVISIT, ATPT, AVAL, PCHG, ANL02FL
15.2.3.9.2	Descriptive Statistics of S-PMA Urinary Concentration Adjusted for Creatinine (pg/mg creat) by Cigarette Consumption - FAS	t_spmac	ADBX	FASFL, PARAM, UCPDRG1, AVISIT, ATPT, AVAL, PCHG, ANL02FL
15.2.4.1	Primary Biomarkers of Exposure versus SA on Day 5 - FAS	tl_anlprimbiosa fas	ADBX	FASFL, SEX, UCPDGR1, PARAM, AVAL, AVISIT, ATPT, ANL02FL

Figure / Table Number	Title	Program	Analysis Dataset	Analysis Variable(s)
15.2.4.2	Urinary Quantity Excreted of MHBMA, 3-HPMA and S-PMA over 24 hours on Day 5 - FAS	tl_anluexcbiosafas	ADBX	FASFL, SEX, UCPDGR1, PARAM, AVAL, AVISIT, ATPT, ANL02FL
15.2.4.3	Descriptive Statistics of Urinary Quantity Excreted of MHBMA over 24 hours (ng) - FAS	t_uquant	ADBX	FASFL, PARAM, AVAL, PCHG, AVISIT, ATPT, ANL02FL
15.2.4.4	Descriptive Statistics of Urinary Quantity Excreted of 3-HPMA over 24 hours (µg) - FAS	t_uquant2	ADBX	FASFL, PARAM, AVAL, PCHG, AVISIT, ATPT, ANL02FL
15.2.4.5	Descriptive Statistics of Urinary Quantity Excreted of S-PMA over 24 hours (ng) - FAS	t_uquant3	ADBX	FASFL, PARAM, AVAL, PCHG, AVISIT, ATPT, ANL02FL
15.2.4.6	Analysis of Exhaled CO (ppm) on Day 5 - FAS	tl_anlsecondbi_o	ADBX	FASFL, SEX, UCPDGR1, PARAM, AVAL, AVISIT, ATPT, ANL02FL
15.2.4.7	Descriptive Statistics of Exhaled CO (ppm) - FAS	t_co	ADBX	FASFL, PARAM, AVAL, AVISIT, ATPT, ANL02FL
15.2.4.8	Descriptive Statistics of Time Matched Changes (%) in Exhaled CO - FAS	t_cotmc	ADBX	FASFL, PARAM, PCHG, AVISIT, ATPT, ANL02FL

Figure / Table Number	Title	Program	Analysis Dataset	Analysis Variable(s)
15.2.4.9	Analysis of Urinary 1-OHP on Day 5 - FAS	tl_anlsecondbi_o	ADBX	FASFL, SEX, UCPDGR1, PARAM, AVAL, AVISIT, ATPT, ANL02FL
15.2.4.10	Descriptive Statistics of Urinary 1-OHP - FAS	t_1ohp	ADBX	FASFL, PARAM, AVAL, PCHG, AVISIT, ANL02FL
15.2.4.11	Analysis of Urinary Total NNN on Day 5 - FAS	tl_anlsecondbi_o	ADBX	FASFL, SEX, UCPDGR1, PARAM, AVAL, AVISIT, ATPT, ANL02FL
15.2.4.12	Descriptive Statistics of Urinary Total NNN - FAS	t_tnnn	ADBX	FASFL, PARAM, AVAL, PCHG, AVISIT, ANL02FL
15.2.4.13	Analysis of Urinary 4-ABP on Day 5 - FAS	tl_anlsecondbi_o	ADBX	FASFL, SEX, UCPDGR1, PARAM, AVAL, AVISIT, ATPT, ANL02FL
15.2.4.14	Descriptive Statistics of Urinary 4-ABP - FAS	t_4abp	ADBX	FASFL, PARAM, AVAL, PCHG, AVISIT, ANL02FL
15.2.4.15	Analysis of Urinary 1-NA on Day 5 - FAS	tl_anlsecondbi_o	ADBX	FASFL, SEX, UCPDGR1, PARAM, AVAL, AVISIT, ATPT, ANL02FL

Figure / Table Number	Title	Program	Analysis Dataset	Analysis Variable(s)
15.2.4.16	Descriptive Statistics of Urinary 1-NA - FAS	t_1na	ADBX	FASFL, PARAM, AVAL, PCHG, AVISIT, ANL02FL
15.2.4.17	Analysis of Urinary 2-NA on Day 5 - FAS	tl_anlsecondbi o	ADBX	FASFL, SEX, UCPDGR1, PARAM, AVAL, AVISIT, ATPT, ANL02FL
15.2.4.18	Descriptive Statistics of Urinary 2-NA - FAS	t_2na	ADBX	FASFL, PARAM, AVAL, PCHG, AVISIT, ANL02FL
15.2.4.19	Analysis of Urinary o-toluidine on Day 5 - FAS	tl_anlsecondbi o	ADBX	FASFL, SEX, UCPDGR1, PARAM, AVAL, AVISIT, ATPT, ANL02FL
15.2.4.20	Descriptive Statistics of Urinary o-toluidine - FAS	t_otol	ADBX	FASFL, PARAM, AVAL, PCHG, AVISIT, ANL02FL
15.2.4.21	Analysis of Urinary CEMA on Day 5 - FAS	tl_anlsecondbi o	ADBX	FASFL, SEX, UCPDGR1, PARAM, AVAL, AVISIT, ATPT, ANL02FL
15.2.4.22	Descriptive Statistics of Urinary CEMA - FAS	t_cema	ADBX	FASFL, PARAM, AVAL, PCHG, AVISIT, ANL02FL

Figure / Table Number	Title	Program	Analysis Dataset	Analysis Variable(s)
15.2.4.23	Analysis of Urinary HEMA on Day 5 - FAS	tl_anlsecondbi o	ADBX	FASFL, SEX, UCPDGR1, PARAM, AVAL, AVISIT, ATPT, ANL02FL
15.2.4.24	Descriptive Statistics of Urinary HEMA - FAS	t_hema	ADBX	FASFL, PARAM, AVAL, PCHG, AVISIT, ANL02FL
15.2.4.25	Analysis of Urinary 3-hydroxy(a)benzopyrene on Day 5 - FAS	tl_anl3OH BA P	ADBX	FASFL, SEX, UCPDGR1, PARAM, AVAL, AVISIT, ATPT, ANL02FL
15.2.4.26	Descriptive Statistics of Urinary B[a]P - FAS	t_bap	ADBX	FASFL, PARAM, AVAL, PCHG, AVISIT, ANL02FL
15.2.4.27	Analysis of Urinary HMPMA on Day 5 - FAS	tl_anlsecondbi o	ADBX	FASFL, SEX, UCPDGR1, PARAM, AVAL, AVISIT, ATPT, ANL02FL
15.2.4.28	Descriptive Statistics of Urinary HMPMA - FAS	t_hmpma	ADBX	FASFL, PARAM, AVAL, PCHG, AVISIT, ANL02FL
15.2.4.29	Analysis of Urinary S-BMA on Day 5 - FAS	tl_anlsecondbi o	ADBX	FASFL, SEX, UCPDGR1, PARAM, AVAL, AVISIT, ATPT, ANL02FL

Figure / Table Number	Title	Program	Analysis Dataset	Analysis Variable(s)
15.2.4.30	Descriptive Statistics of Urinary S-BMA - FAS	t_bma	ADBX	FASFL, PARAM, AVAL, PCHG, AVISIT, ANL02FL
15.2.4.31	Analysis of Urinary Total NNAL on Day 5 - FAS	tl_anlsecondbi o	ADBX	FASFL, SEX, UCPDGR1, PARAM, AVAL, AVISIT, ATPT, ANL02FL
15.2.4.32	Descriptive Statistics of Urinary Total NNAL - FAS	t_nnal	ADBX	FASFL, PARAM, AVAL, PCHG, AVISIT, ANL02FL
15.2.4.33	Analysis of Urinary NEQ on Day 5 - FAS	tl_anlsecondbi o	ADBX	FASFL, SEX, UCPDGR1, PARAM, AVAL, AVISIT, ATPT, ANL02FL
15.2.4.34	Descriptive Statistics of Urinary Total NEQ - FAS	t_neq	ADBX	FASFL, PARAM, AVAL, PCHG, AVISIT, ANL02FL
15.2.4.35	Descriptive Statistics of Plasma Nicotine Concentrations (ng/mL) - FAS	t_pkconc	ADPC	FASFL, PARAM, AVAL, PCHG, AVISIT, ATPT, ANL01FL
15.2.4.36	Table 15.2.4.36 Descriptive Statistics of Plasma Cotinine Concentrations (ng/mL) - FAS	t_pkconc2	ADPC	FASFL, PARAM, AVAL, PCHG, AVISIT, ATPT, ANL01FL

Figure / Table Number	Title	Program	Analysis Dataset	Analysis Variable(s)
15.2.4.37	Descriptive Statistics of Plasma Nicotine Concentration Parameters on Day 5 - FAS	t_pkparam	ADPP	FASFL, PARCAT1, PARAM, AVAL, ANL01FL
15.2.4.38	Descriptive Statistics of Plasma Cotinine Concentration Parameters on Day 5 - FAS	t_pkparam2	ADPP	FASFL, PARCAT1, PARAM, AVAL, ANL01FL
15.2.4.39	Analysis of Plasma Nicotine Concentration Parameters on Day 5 - FAS	tl_anlpkparm	ADPP	PPROTFL, SEX, UCPDGR1, PARCAT1, PARAM, AVAL, ANL01FL
15.2.4.40	Analysis of Plasma Cotinine Concentration Parameters on Day 5 - FAS	tl_anlpkparm	ADPP	PPROTFL, SEX, UCPDGR1, PARCAT1, PARAM, AVAL, ANL01FL
15.2.4.41	Analysis of Change from Day 0 Plasma Nicotine and Cotinine Concentrations at 08:00 PM on Day 5 - FAS	tl_anlpkconc	ADPC	FASFL, SEX, UCPDGR1, PARAM, AVAL, AVISIT, ANL01FL
15.2.4.42	Descriptive Statistics of Ames Mutagenicity Test (YG1024+S9) (REV/24h) - FAS	t_ames	ADBX	FASFL, PARAM, AVAL, PCHG, AVISIT, ANL02FL
15.2.4.43	Descriptive Statistics of QSU-brief Questionnaire Factors and Total Score - FAS	t_qsu	ADQSSU	FASFL, PARAM, AVAL, PCHG, AVISIT, ANL01FL

Figure / Table Number	Title	Program	Analysis Dataset	Analysis Variable(s)
15.2.4.44	Analysis of Change from Baseline QSU-brief Questionnaire Factors and Total Score - FAS	tlf anlqsu	ADQSSU	FASFL, PARAM, SEX, UCPDGR1, CHG, AVISIT, ANL01FL
15.2.4.45	Descriptive Statistics of MNWS Questionnaire Total Scores - FAS	t mnws	ADQSND	FASFL, PARAM, AVAL, PCHG, AVISIT, ANL01FL
15.2.4.46	Analysis of Change from Baseline MNWS Questionnaire Total Scores - FAS	tlf anlmnws	ADQSND	FASFL, PARAM, CHG, AVISIT, ANL01FL
15.2.4.47	Descriptive Statistics of MCEQ Questionnaire Subscales – FAS	t mceq	ADQSPA	FASFL, PARAM, AVAL, PCHG, AVISIT, ANL01FL
15.2.4.48	Analysis of Change from Baseline in MCEQ Questionnaire Subscales - FAS	tlf anlmcceq	ADQSPA	FASFL, SEX, UCPDGR1, PARAM, CHG, AVISIT
15.2.4.49	Descriptive Statistics of CYP1A2 Activity (%)- FAS	t cyp1	ADBX	FASFL, PARAM, AVISIT, AVAL, PCHG, ANL02FL
15.2.4.50	Analysis of CYP1A2 Activity (%) on Day 5 - FAS	tl anlcpyp	ADBX	FASFL, SEX, UCPDGR1, PARAM, AVAL, CHG, ANL02FL
15.2.4.51	Descriptive Statistics of CYP2A6 Activity (%)- FAS	t cyp2	ADBX	FASFL, PARAM, AVISIT, AVAL, PCHG, ANL02FL

Figure / Table Number	Title	Program	Analysis Dataset	Analysis Variable(s)
15.2.4.52	Analysis of CYP2A6 Activity (%) on Day 5 - FAS	tl_anlcyp	ADBX	FASFL, SEX, UCPDGR1, PARAM, AVAL, CHG, ANL02FL
15.2.4.53	Analysis of Urinary 8-epi-PGF2 Alpha on Day 5 - FAS	tl_anlsecondbi o	ADBX	FASFL, SEX, UCPDGR1, PARAM, AVAL, AVISIT, ATPT, ANL02FL
15.2.4.54	Descriptive Statistics of Urinary 8-epi-PGF2 α - FAS	t_8epi	ADBX	FASFL, PARAM, AVISIT, AVAL, PCHG, ANL02FL
15.2.4.55	Analysis of Urinary 11-DTX-B2 on Day 5 - FAS	tl_anlsecondbi o	ADBX	FASFL, SEX, UCPDGR1, PARAM, AVAL, AVISIT, ATPT, ANL02FL
15.2.4.56	Descriptive Statistics of Urinary 11-DTX-B2 - FAS	t_11dtx	ADBX	FASFL, PARAM, AVISIT, AVAL, PCHG, ANL02FL
15.2.4.57	Statistical Analysis of Relationship Between NEQ and Risk Markers on Day 5 - FAS	tlf_anlneqrisk	ADBX	FASFL, PARAM, AVAL, AVISIT
15.2.4.58	Descriptive Statistics of HST Parameters per Cigarette - FAS	t_hst	ADXT	FASFL, PARCAT1, PARAM, AVAL, PCHG, AVISIT, ANL02FL
15.2.4.59	Analysis of HST Parameters (Averaged over all Cigarettes per Day) - FAS	tl_anlhst	ADXT	FASFL, PARAM, AVAL, AVISIT, ANL02FL

Figure / Table Number	Title	Program	Analysis Dataset	Analysis Variable(s)
15.2.4.60	Descriptive Statistics of HST Questionnaire Data - FAS	t_hstqu	ADQSPA	FASFL, PARCAT1, AVAL, AVISIT, ANL01FL
15.2.4.61	Descriptive Statistics of Visual Inspection of the THS 2.2 Tobacco Plugs Data - FAS	t_plug	ADXT ADDX	FASFL, PARCAT1, PARAM, AVALC, XTREASND, ANL02FL AVAL
15.2.4.62	Descriptive Statistics of Filter Analysis from the THS 2.2 Products - FAS	t_filter	ADXT ADDX	FASFL, PARCAT1, PARAM, AVAL, ANL02FL AVAL
15.2.5.1	Summary of Compliance as Measured by Exhaled CO (ppm) in the SA Arm- Safety Population	t_comp	ADBx	FASFL, PARAM, AVALCAT1, AVISIT, ATPT
15.2.6.1	Summary of Adverse Events - Safety Population	t_adv1	ADAE	SAFFL, AEBODSYS, AEDECOD, AEREL. AERELSP, AESEV, AEACNP1, AESER, ANYAEFL, ANL01FL

Figure / Table Number	Title	Program	Analysis Dataset	Analysis Variable(s)
15.2.6.2.1	Summary of Adverse Events by System Organ Class and Preferred Term - Safety Population	t_adv2	ADAE	SAFFL, AEBODSYS, AEDECOD, ANYAEFL, ANL01FL
15.2.6.2.2	Summary of Adverse Events by System Organ Class - Safety Population	t_adv3	ADAE	SAFFL, AEBODSYS, ANYAEFL, ANL01FL
15.2.6.2.3	Summary of Adverse Events by Preferred Term - Safety Population	t_adv4	ADAE	SAFFL, AEDECOD, ANYAEFL, ANL01FL
15.2.6.3	Summary of Adverse Events by System Organ Class, Preferred Term and Relationship to Study Product Exposure and Expectedness - Safety Population	t_adv10	ADAE	SAFFL, AEBODSYS, AEDECOD, AEREL, AEEXPEC, ANYAEFL, ANL01FL,
15.2.6.4	Summary of Adverse Events Leading to Product Discontinuation or Reduction by System Organ Class and Preferred Term - Safety Population	t_adv11	ADAE	SAFFL, AEBODSYS, AEDECOD, AEACNP1, ANYAEFL, ANL01FL
15.2.6.5	Summary of Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term - Safety Population	t_adv5	ADAE	SAFFL, AEBODSYS, AEDECOD, ANYAEFL, ANL01FL, ANL02FL

Figure / Table Number	Title	Program	Analysis Dataset	Analysis Variable(s)
15.2.6.6	Summary of Adverse Events Related to Study Procedure by System Organ Class and Preferred Term - Safety Population	t_adv6	ADAE	SAFFL, AEBODSYS, AEDECOD, AERELSP, ANYAEFL, ANL01FL
15.2.6.7	Summary of Adverse Events by System Organ Class, Preferred Term and Severity - Safety Population	t_adv7	ADAE	SAFFL, AEBODSYS, AEDECOD, AESEV, ANYAEFL, ANL01FL
15.2.6.8	Summary of Serious Adverse Events - Safety Population	t_adv8	ADAE	SAFFL, AESER, ANYAEFL, ANL01FL
15.2.6.9	Summary of Serious Adverse Events by System Organ Class and Preferred Term - Safety Population	t_adv9	ADAE	SAFFL, AEBODSYS, AEDECOD, AESER, ANYAEFL, ANL01FL
15.2.6.10	Table 15.2.6.10 Summary of THS 2.2 Device Events and Malfunctions - Safety Population	t_device	ADDE	SAFFL, ENRLFL, AEREL, DETERM, DESEV, ANYDEFL
15.2.6.11.1	Summary of Prior Medication by Anatomical Therapeutic Classes (ATC) 1 and 2 - Safety Population	t_priatc	ADCM	SAFFL, ANYCMFL, PMFL, CMATC1, CMATC2,

Figure / Table Number	Title	Program	Analysis Dataset	Analysis Variable(s)
15.2.6.11.2	Summary of Prior Medication by Preferred Drug Name - Safety Population	t_primed	ADCM	SAFFL, ANYCMFL, PMFL, CMDECOD,
15.2.6.12.1	Summary of Concomitant Medication by Anatomical Therapeutic Classes (ATC) 1 and 2 - Safety Population	t_conatc	ADCM	SAFFL, ANYCMFL, CMFL, CMATC1, CMATC2
15.2.6.12.2	Summary of Concomitant Medication by Preferred Drug Name - Safety Population	t_conmed	ADCM	SAFFL, ANYCMFL, CMFL, CMDECOD,
15.2.6.13	Summary of Clinical Chemistry Parameters - Safety Population	t_labchem	ADLB	SAFFL, PARCAT1, PARAM, AVAL, CHG, ANRLO, ANRHI, ANRIND, ACLSIG, AVISIT, ANL01FL
15.2.6.14	Summary of Hematology Parameters - Safety Population	t_labhem	ADLB	SAFFL, PARCAT1, PARAM, AVAL, CHG, ANRLO, ANRHI, ANRIND, ACLSIG, AVISIT, ANL01FL

Figure / Table Number	Title	Program	Analysis Dataset	Analysis Variable(s)
15.2.6.15	Summary of Urinalysis Parameters - Safety Population	t_laburin	ADLB	SAFFL, PARCAT1, PARAM, AVAL, AVALC, CHG, ANRLO, ANRHI, ANRIND, ACLSIG, AVISIT, ANL01FL
15.2.6.16	Summary of Supine Vital Signs - Safety Population	t_vit	ADVS	SAFFL, PARAM, AVAL, CHG, AVISIT, ANL01FL
15.2.6.17	Summary of ECG Measurements - Safety Population	t_ecg	ADEG	SAFFL, PARAM, AVAL, CHG, EGCLSIG, AVISIT, ANL01FL
15.2.6.18	Summary of Spirometry Measurements - Safety Population	t_spiro	ADXP	SAFFL, PARAM, AVAL, AVAL, AVALC, XPCLSIG, AVISIT, ANL01FL
15.2.6.19	Summary of Weight and BMI Measurements - Safety Population	t_bmi	ADVS	SAFFL, ENRFL, PARAM, AVAL, CHG, AVALCAT1, AVISIT, ANL01FL,
15.2.6.20	Summary of Cough Assessments Over Study- Safety Population	t_cough	ADQSSYM	SAFFL, PARAM, AVALC, ANL01FL

Figure / Table Number	Title	Program	Analysis Dataset	Analysis Variable(s)
15.2.6.20.1	Summary of Cough Assessments by Study Day - Safety Population	t_cough2	ADQSSYM	SAFFL, PARAM, AVAL, AVALC, AVISIT, ANL01FL

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

- 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
Amlodipine
Cimetidine
Ciprofloxacin
Fluoxetine
Fluvoxamine
Fospropofol
Gemfibrozil
Ketoconazole
Diclofenac
Lidocaine
Methoxsalen
Mexiletine
Miconazole
Nifedipine
Norfloxacin
Propofol
Primaquine
Ofloxacin
Thiabendazole
Tranylcycromine
Zilleuton
Inducer
Carbamazepine
Phenobarbital
primidone
Rifampin
Substrate
Acenocoumarol
Alosetron
Aminophylline
Betaxolol
Caffeine
Clomipramine
Clozapine
Cyclobenzaprine
Dacarbazine
Duloxetine
Estradiol

Estrogens, conjugated A/synthetic
Estrogen, conjugated equine
Estrogen, esterified
Estropipate
Flutamide
Fluvoxamine
Guanabenz
Mexiletine
Mirtazapine
Olanzapine
Pimozide
Propranolol
Ramelteon
Rasagiline
Riluzole
Ropinirole
Ropivacaine
Tacrine
Theophylline
Thiothixene
Tizanidine
Trifluoperazine