

Study Data Reviewer's Guide

Philip Morris International
Study ZRHR-REXC-03-EU

Version 2016-01-11

Study Data Reviewer's Guide

Contents

1.	Introduction.....	4
1.1	Purpose.....	4
1.2	Study Data Standards and Dictionary Inventory.....	4
2.	Protocol Description	4
2.1	Protocol Number and Title.....	4
2.2	Protocol Design.....	5
2.3	Trial Design Datasets	5
2.3.1.	TI – Trial Inclusion/Exclusion Criteria	6
2.3.2.	TV – Trial Visits	6
3.	Subject Data Description	6
3.1	Overview.....	6
3.2	Annotated CRFs.....	8
3.3	SDTM Subject Domains	11
3.3.1.	AE – Adverse Events	12
3.3.2.	CM - Concomitant Medications.....	12
3.3.3.	DA - Drug Accountability.....	13
3.3.4.	DE - Device Events.....	13
3.3.5.	DM – Demographics	14
3.3.6.	DS – Disposition	14
3.3.7.	DV - Protocol Deviations.....	14
3.3.8.	EG - ECG Test Results	15
3.3.9.	FA - Findings About Events or Interventions	15
3.3.10.	LB - Laboratory Test Results.....	15
3.3.11.	MH – Medical History	16
3.3.12.	PC – Pharmacokinetic Concentrations.....	17
3.3.13.	PE - Physical Examination.....	17
3.3.14.	PP – Pharmacokinetic Parameters.....	17
3.3.15.	VS - Vital Signs	17
3.3.16.	XP - Pulmonary Function	17
3.3.17.	XT – HST.....	17
4.	Data Conformance Summary.....	22
4.1	Conformance Inputs.....	22

4.2 Issues Summary	22
Appendix I: Inclusion/Exclusion Criteria	31

1. Introduction

1.1 Purpose

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

1.2 Study Data Standards and Dictionary Inventory

Standard or Dictionary	Versions Used
SDTM	SDTM Version 1.3 / SDTM Implementation Guide version 3.1.3 SDTM Draft Implementation Guide for Medical Devices (SDTMIG-MD)
Controlled Terminology	2014-06-27
Data Definitions	Define.xml version 2.0
Sponsor specification	The specification contains only the codes that were used in the study while the define.xml provides the full list of allowed terms in the study.
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

2. Protocol Description

2.1 Protocol Number and Title

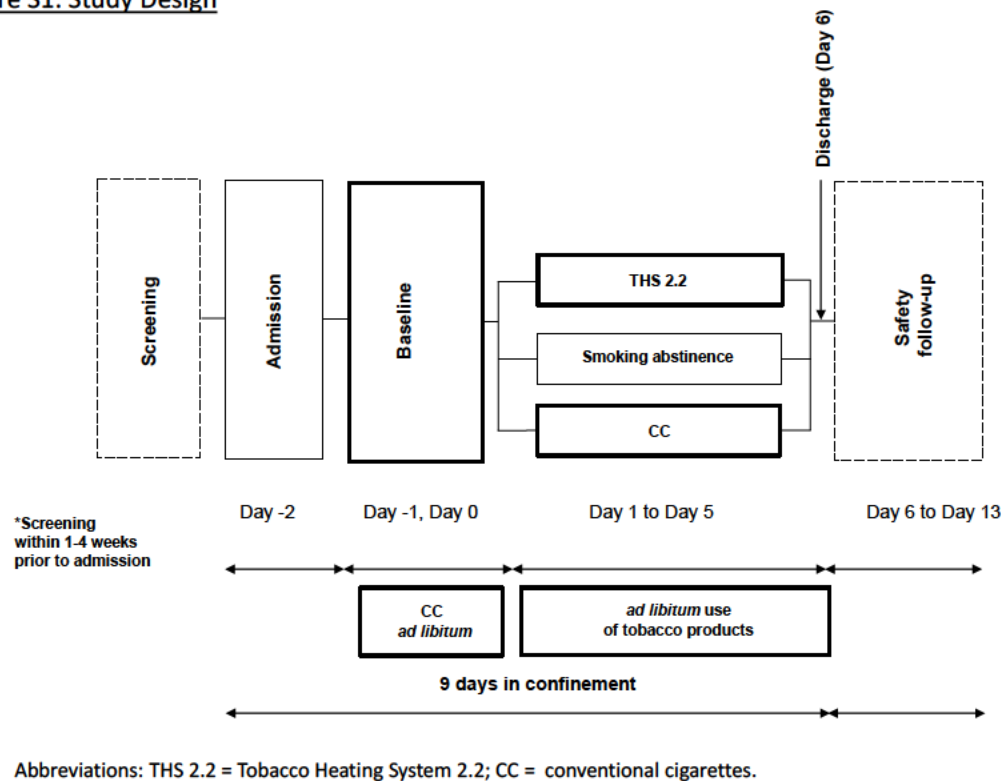
Study Number: ZRHR-REXC-03-EU

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: Version 1.0 25 April 2013

2.2 Protocol Design

Figure S1: Study Design



2.3 Trial Design Datasets

Are Trial Design datasets included in the submission? Yes

Dataset	Dataset Label
TA	Trial Arms
TE	Trial Elements
TV	Trial Visits
TI	Trial Inclusion/Exclusion Criteria
TS	Trial Summary

2.3.1. TI – Trial Inclusion/Exclusion Criteria

The criteria are not fully described in TI. Please refer to [Appendix I](#) for the protocol defined inclusion/exclusion criteria

2.3.2. TV – Trial Visits

Subjects who withdrew from the study were required to perform early termination procedures which are the same as the discharge assessments performed at Day 6. The protocol did not require these procedures to be performed at a separate withdrawal visit but, rather, to perform them at the scheduled visit at which the subject was withdrawn. Therefore, a combined Day 6/ Discharge visit was created to account for the timings of the procedures performed for withdrawn subjects.

3. Subject Data Description**3.1 Overview**

Are the submitted data taken from an ongoing study?	No
If yes, describe the data cut or database status: (Text here)	
Were the SDTM datasets used as sources for the analysis datasets?	Yes
If no, what were the sources of analysis datasets? (Text here)	
Do the submission datasets include screen failures?	Yes
If yes, which datasets include screen failure data?	
CM	
DM	
DS	
DV	
FA	
IE	
SE	
SV	
Were any domains planned, but not submitted because no data were collected?	No
If yes, list domains not submitted: (Text here)	

Are the submitted data a subset of collected data?

No

If yes, describe the reason that all collected data were not provided:

(Text here)

Additional Content of Interest

Safety data for the study can be found in the datasets DE, AE, CM, EG, LB, MH and PE.

The primary endpoints data can be found in LB and XP. The study reference start date (RFSTDTC) was calculated based on the first exposure to the THS device on Day 1 (with subjects on the SA arm mapped to the day 1 visit date). The study reference end date (RFENDTC) was calculated based on last product use or equal to the day 5 visit date for subjects on the SA arm.

2 new domains have been created for the purpose of the study:

- The XP dataset contains spirometry data.
- The XT dataset contains the Human Smoking Topography (HST), filter and tobacco plug analysis data.

For this study it was decided to use the FA datasets for the smoking history information, the cigarette brand and the standardized brand name.

The first record of product use on Day 1 was used as the reference start date (RFSTDTC) for each subject. The study days were calculated with the logic: the reference start date is subtracted from the assessment date, with the addition of 1 day if the assessment date is on or after the reference start date. The variable RFXSTDTC was used to capture the start date of the first use of the THS 2.2 for all subjects, which as per the protocol should be the date when the THS 2.2 product test was performed

The below table provides further clarification on how study data has been presented using the SDTM Implementation Guide which is commonly associated with the presentation of trial study data for pharmaceutical investigational products .

Domain	Datasets	Description	Class	Information captured
DX	DX	Device Exposure	Interventions	Subject exposure with the THS 2.2 device.
DI	DI	Device Identifiers	Special Purpose Domains	Details of the THS 2.2 device holders and chargers used in the study.
DE	DE	Device Events	Events	Details events associated with the THS 2.2 device holders and chargers used in the study.

Domain	Datasets	Description	Class	Information captured
DR	DR	Device Subject Relationship	Special Purpose Domains	The THS 2.2 device and holders used by each subject.
DT	DT	Device Tracking and Disposition	Events	Details the distribution , collection and any replacement dates for the THS 2.2 device holders and chargers
EX	EX	Exposure	Interventions	Conventional cigarettes smoked by the subjects.
FA	FA	Findings About Events or Interventions	Findings	Smoking history information, cigarette brand and the standardize brand name.
LB	LB	Laboratory Test Results	Findings	This domain was used to capture the following lab data: - ALCOHOL TEST - BIOBANKING - BIOMARKERS - CLINICAL CHEMISTRY - COTININE SCREENING - DRUG SCREEN - ENZYME ACTIVITY - HAEMATOLOGY - PREGNANCY - SEROLOGY - URINALYSIS
XT	XT	HST Assessments	Findings	Captures the Human Smoking Topography, Filter and Tobacco Plug analysis data
XP	XP	Pulmonary Function	Findings	Captures the Spirometry (lung capacity)

3.2 Annotated CRFs

The following CRF fields that have not been tabulated have been annotated as “Not Submitted”:

- Responses to the screen failure question ‘Is there a pregnancy event?’, as this is captured in the exclusion criteria (IE) dataset.
- The Y/N responses to the questions prompting the entry of data and used by data management solely for data validation purposes:

- Has the subject given written informed consent for Bio-banking for Biomarkers of Exposure and Risk Markers? The date the consent is given is captured in the DS domain.
- Has the subject given written informed consent for Bio-banking for Transcriptomics (Pharmacogenomics)? The date the consent is given is captured in the DS domain.
- Has the subject experienced any past and/ or concomitant diseases? The relevant information is captured in the MH domain.
- Was there any Adverse Event for this subject? The relevant Adverse Event information is captured in the AE domain.
- Has the subject taken previous or concomitant medication? The relevant Concomitant Medication information is captured in the CM domain.
- Were there any events with the device? The relevant device events information is captured in the DE domain.
- Inclusion Criteria Result and Number. The same information is captured elsewhere in the aCRF.
- Exclusion Criteria Result and Number. The same information is captured elsewhere in the aCRF.
- CC with SODIM? Information regarding whether the SODIM is used is captured within the XT domain
- The medical history category was derived in the SDTMs, based on the start of medical event
- Responses to the questions relating to THS 2.2 Product demonstration and Advice on the risks on smoking and debriefing was not submitted as this data is for data management and site monitoring. If these questions were answered 'no' then the data would be presented as a protocol deviation in the DV dataset
- The subject date of birth from the questionnaires was not captured since this information is already presented in the DM domain. The global assessment status was not captured as the individual question responses were provided for this study
- The variable 'H_NOW' was not submitted as this is a derived variable used to validate information in the database
-
- Subject (Site level). Subject number is captured on the Subject form.
- In site Accountability form: Category, Date of batch dispensed, Number of unused packs returned, Number of unused sticks returned, Number of packs received. These variables were not submitted as the information captured with the subject's exposure to the THS tobacco sticks was used to calculate the compliance information presented in the DA domain
- In LABSTAT result form: Day Number. Study Day number is calculated in the SDTMs themselves
- In LAB-BU form: Data Type unique identifier and Random number, Sex, Date of Birth, Visit ID, Site Number, Derived Form name Information presented elsewhere in the aCRF
- In Biomarker form: Celerion Study Number, Lower Limit of quantification, Detection Method, Information present in other variables used for programming purposes.

These fields were used to facilitate certain operational processes including data cleaning and dynamically creating additional forms in the electronic data capture system.

The laboratory safety and biomarker data were provided by vendors and uploaded into the database. . The dates and times of the samples were entered by the site, whilst some values (such as for pregnancy results, alcohol breath test and CYP2A6 activity) were entered by the site.

The submitted annotated CRF (blankcrf.pdf) includes the final version of the eCRF (main study CRF version 5.0 and site level CRF version 4.0)

The CRF also details data which were loaded into the database from other sources. This includes laboratory safety results and biomarker data results for blood and urine, questionnaires completed in the ePROdevice and filter analysis data. The CRF represents only the last version of the database.

3.3 SDTM Subject Domains

Dataset – Dataset Label	Efficacy	Safety	Other	SUPP-	Related Using RELREC	Observation Class
AE - Adverse Events		X		X	CM	Events
CM - Concomitant Medications		X		X	AE, MH	Interventions
CO - Comments			X			Special Purpose Domains
DA - Drug Accountability			X	X		Findings
DE - Device Events		X		X		Events
DI - Device Identifiers			X			Special Purpose Domains
DM - Demographics			X	X		Special Purpose Domains
DR - Device Subject Relationship			X			Special Purpose
DS - Disposition			X	X		Events
DT - Device Tracking and Disposition			X			Events
DV - Protocol Deviations			X	X		Events
DX - Device Exposure			X			Interventions
EG - ECG Test Results		X		X		Findings
EX - Exposure			X			Interventions
FA - Findings About Events or Interventions			X	X		Findings
IE - Inclusion/Exclusion Criteria Not Met			X			Findings
LB - Laboratory Test Results		X		X		Findings
MH - Medical History		X			CM	Events
PC - Pharmacokinetic Concentrations			X		PP	Findings
PE - Physical Examination		X		X		Findings

Dataset – Dataset Label	Efficacy	Safety	Other	SUPP-	Related Using RELREC	Observation Class
PP - Pharmacokinetic Parameters			X		PC	Findings
QS - Questionnaire		X				Findings
SE - Subject Elements			X			Special Purpose Domains
SU - Substance Use			X			Interventions
SV - Subject Visits			X			Special Purpose Domains
VS - Vital Signs		X		X		Findings
XP - Pulmonary Function		X		X		Findings
XT - HST				X		Findings

3.3.1. AE – Adverse Events

A relationship has been defined in RELREC between any adverse event requiring medication and the concomitant medication information captured in CM. The observations are related by AESPID and CMSEQ.

The following variables have been mapped into SUPPAE

QNAM	Description
AERELSP	Relationship to Study Procedure
AEEXPEC	AE Expectedness to THS 2.2
AEACNP1	Action Taken With THS 2.2
AETRTEM	Treatment Emergent Flag

3.3.2. CM - Concomitant Medications

A relationship has been defined in RELREC between any adverse event or active medical history requiring medication and the concomitant medication information captured in CM. The observations are related by AESPID, MHSPID and CMSEQ. The Anatomical Therapeutic Chemical (ATC) coding hierarchy is located in SUPPCM

The following variables have been mapped into SUPPCM

QNAM	Description
ATCCD1	1st level, anatomical main group code
ATCCD2	2 nd level, therapeutic subgroup code
ATCCD3	3 rd level, pharmacological subgroup code
ATCCD4	4 th level, chemical subgroup code
ATCTXT1	1 st level, anatomical main group code
ATCTXT2	2 nd level, therapeutic subgroup
ATCTXT3	3 rd level, pharmacological subgroup
ATCTXT4	4 th level, chemical subgroup
CMPTCD	Preferred Term Code
CMSYCD	Trade Name Code
CMSYN	Trade Name
MHNUM	Concomitant Disease Number
AENUM	AE Number
OTHER	Other

3.3.3. DA - Drug Accountability

The following variables have been mapped into SUPPDA

QNAM	Description
BEXPDTC	Batch Expiration Date

3.3.4. DE - Device Events

The following variables have been mapped into SUPPDE.

QNAM	Description
AEREL	Adverse Event Relationship
NDSN	New Device Serial Number

3.3.5. DM – Demographics

The following variables have been mapped into SUPPDM

QNAM	Description
DMRANDNO	Randomization Number

3.3.6. DS – Disposition

The Disposition domain shows, where relevant, the date of screen failures, dates of discontinuation from enrolment, the dates of randomization, the reasons for screening failure and the various informed consents for sampling (i.e. to biobanking for biomarkers of exposure and risk markers, biobanking for transcriptomics) and the main informed consent. Both the reason for screen failure and for study withdrawal (post-randomization) was captured, although the mapping of reason in the parent DS domain and SUPPDS domain differed. The following variables have been mapped into SUPPDS

QNAM	Description
OTHER	Other Reason for Screen Failure

3.3.7. DV - Protocol Deviations

The protocol deviations are captured in the study database. The sponsor assigned the deviation category (i.e. major/minor) and the evaluation category, if applicable, against the deviations recorded by the CRA.

The following variables have been mapped into SUPPDV

QNAM	Description
COHORT	Cohort
ASSESS	Assessment
DVOTH	Other, Specify
DVREPDTC	Date Deviation Reported
RESOL	Deviation Resolution
SOURCE	Deviation Source
DVSIG	Deviation Type
DVTIMEPT	Deviation Timepoint

3.3.8. EG - ECG Test Results

The following variables have been mapped into SUPPEG

QNAM	Description
EGCLSIG	Clinically Significant

3.3.9. FA - Findings About Events or Interventions

The FA domain was used to map the smoking history as the data relates to previous exposure of the subjects (EX) but does not fit any of the pre-existing domain classes. The domain captured the subjects smoking history alongside their current cigarette brand (with a standardised brand name presented in the SUPPFA domain).

The following variables have been mapped into SUPPFA

QNAM	Description
BRAND	Standardised Brand Name

The information presented in the dataset using the following categorisation pairings.

FACAT	FASCAT
THS 2.2	PRODUCT USE
TOBACCO	CIGARETTE BRAND
TOBACCO	SMOKING HISTORY

3.3.10. LB - Laboratory Test Results

Toxicity grading of the laboratory safety data, as outlined in Appendix 5 of the study protocol, is presented in the variables LBTOX and LBTOXGR. The toxicity grades presented in these variables were derived in the SDTM programming based on Appendix 5 of the study protocol.

The following variables have been mapped into SUPPLB

QNAM	Description
LBCLSIG	Clinically Significant
LB_FLG	Flag
SAMPDTC	Date of Sample Collection
PRIMTUB	Primary tubes
BACTUB	Back Up Tubes

The following pairings of LBCAT and LBSCAT were used in the dataset.

LBCAT	LBSCAT
ALCOHOL TEST	
BIOBANKING	BIOMARKERS OF EXPOSURE
BIOBANKING	TRANSCRIPTOMICS
BIOMARKERS	
BIOMARKERS	24H URINE SAMPLE
CLINICAL CHEMISTRY	
COTININE SCREENING	
DRUG SCREEN	
ENZYME ACTIVITY	CYTOCHROME 1A2
ENZYME ACTIVITY	CYTOCHROME 2A6
HAEMATOLOGY	
PREGNANCY	
SEROLOGY	
URINALYSIS	

The variable LBGRPID was used to group the parameter as Risk Markers or Biomarkers of Exposure.

3.3.11. MH – Medical History

The RELREC dataset shows the relationships between concomitant medications (CM) taken for active medical histories.

3.3.12. PC – Pharmacokinetic Concentrations

The RELREC dataset shows the relationship between pharmacokinetic concentration records (PC) and the corresponding pharmacokinetic parameter results (PP).

3.3.13. PE - Physical Examination

The following variables have been mapped into SUPPPE

QNAM	Description
PECLSIG	Clinically Significant

3.3.14. PP – Pharmacokinetic Parameters

The RELREC dataset shows the relationship between pharmacokinetic parameter results (PP) and the corresponding pharmacokinetic concentration records (PC).

3.3.15. VS - Vital Signs

The following variables have been mapped into SUPPVS

QNAM	Description
SMOK15P	Smoked within 15 min prior to assessment

3.3.16. XP - Pulmonary Function

This is a custom findings domain that captures the spirometry data recorded in the study.

The following variables have been mapped into SUPPXP

QNAM	Description
XPCLSIG	Clinically Significant

3.3.17. XT – HST

This is a custom findings domain that captures the Human Smoking Topography (HST), filter analysis and visual inspection of tobacco plug data.

The following variables have been mapped into SUPPXT

QNAM	Description
ANALYDTC	Date of analysis
ATMPCORR	Atm. Pressure Correction

QNAM	Description
ATMPSPAN	Atm P Span
CIGID	Cigarette ident.
CODE	Code
COHORT	Cohort number
CONSMON	Cons. Since Morning
FILEDTC	Date of File Assessed
FILESTAT	File Status
FILTNUM	Number of filters
FLWSPAN	Flow Span
FLWTHLD	Flow Threshold
FNEGFZ	Force Negative Flow to Zero
INDEX	Indice
INTPFMIN	Inter Puff Min Time
INTRFER	Interference Time
KCOEFF	Coeff.
KIT_NUM	Kit Number
MODEFLOW	Mode of Flow Correction
MODEVOL	Mode of Volume Correction
MOFILNUM	Modified File Number
PDSPAN	P Span
PDTHSLD	PD Threshold
PFFMINTM	Puff Min Time
PORTNUM	Port numero
REJREAS	Rejection Error Reason
RTDBTHD	RTD Base Threshold
RUNNUM	Run numero
SMOKNB	Smoker Smoking Number
SMPLAQ	Sample Acquisition

QNAM	Description
SODENUM	SODIM Device Number
SOSHNUM	SODIM Sample Holder Number
TESTDTC	Date of File Creation
USLCIG	Usual Cigarette
VERSION	Version
VIAL_NUM	Vial Number
VOLTHLD	Volume Threshold

The following data types are categorized within the XT dataset using the following combinations of category (XTCAT) and subcategory (XTSCAT).

XTCAT	XTSCAT
FILTER ANALYSIS	ANALYSIS FULL FILTER
FILTER ANALYSIS	ANALYSIS MOUTHPIECE
FILTER ANALYSIS	ANALYSIS PLA + HAT
FILTER ANALYSIS	EXTRACTION
TOPOGRAPHY	
VISUAL INSPECTION OF TOBACCO PLUG	

Notable extensions to CDISC terminology.

The following table shows notable extensions to CDISC terminology for this study.

Domain	Variable (Codelist)	Value
XP	DOMAIN (C66734)	XP

XT	DOMAIN (C66734)	XT
EG	EGTEST (C71152)	All ECG examinations
EG	EGTESTCD (C71153)	EGALL
DM	ETHNIC(C66790)	CAUCASIAN
DM	ETHNIC(C66790)	NOT CAUCASIAN
DS	DSDECOD(C66727)	ADVERSE EVENTS
DS	DSDECOD(C66727)	DISCONTINUED FROM ENROLLMENT
DS	DSDECOD(C66727)	INFORMED CONSENT OBTAINED
DS	DSDECOD(C66727)	RANDOMIZED
DS	DSDECOD(C66727)	
PC	METHOD (C85492)	LC-MS/MS
XP	METHOD (C85492)	SPIROMETRY
XT	METHOD (C85492)	TOPOGRAPHY
LB	LBTEST (C67154)	1-aminonaphthalene
LB	LBTEST (C67154)	2-aminonaphthalene
LB	LBTEST (C67154)	2-cyanoethylmercapturic Acid
LB	LBTEST (C67154)	2-hydroxyethyl Mercapturic Acid
LB	LBTEST (C67154)	3-hydroxypropylmercapturic Acid
LB	LBTEST (C67154)	3-hydroxypropylmercapturic Acid
LB	LBTEST (C67154)	4-Aminobiphenyl
LB	LBTEST (C67154)	Ames Mutagenecity
LB	LBTEST (C67154)	Free Cotinine
LB	LBTEST (C67154)	Free Nicotine
LB	LBTEST (C67154)	Free Trans-3'- Hydroxycotinine
LB	LBTEST (C67154)	Hydroxy-1-methylpropylmercapturic Acid
LB	LBTEST (C67154)	Nicotine-Glucuronide
LB	LBTEST (C67154)	NNAL

LB	LBTEST (C67154)	o-toluidine
LB	LBTEST (C67154)	Paraxanthine
LB	LBTEST (C67154)	S-benzylmercapturic Acid
LB	LBTEST (C67154)	S-phenylmercapturic Acid
LB	LBTEST (C67154)	Total 1-hydroxypyrene
LB	LBTEST (C67154)	Total N-nitrosomonicotine
LB	LBTEST (C67154)	Trans-3 Hydroxycotinine
LB	LBTEST (C67154)	Trans-3'- Hydroxycotinineglucuronide
LB	LBSTRESU (C71620)	ERYT/uL
LB	LBSTRESU (C71620)	GI/L
LB	LBSTRESU (C71620)	REV/ml
LB	LBSTRESU (C71620)	T/L
LB	LBSTRESU (C71620)	ng/mL
LB	LBSTRESU (C71620)	pg/mL
XT	XTSTRESU (C71620)	mJ
XT	XTSTRESU (C71620)	mg/filter
XT	XTSTRESU (C71620)	mg/mL
XT	XTSTRESU (C71620)	mmWG
XT	XTSTRESU (C71620)	mmWG/mL/s
XT	XTSTRESU (C71620)	per filter
XT	XTSTRESU (C71620)	S

4. Data Conformance Summary

4.1 Conformance Inputs

Was OpenCDISC used to evaluate conformance? Yes

If yes, specify the versions of OpenCDISC and the OpenCDISC validation rules:

OpenCDISC v1.5, SDTM 3.1.3, Controlled Terminology version 2014-06-27 and MedDRA 16.0

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

If yes, describe any significant sponsor-defined validation rules:

(Text here)

Were the SDTM datasets evaluated in relation to define.xml? No

Was define.xml evaluated? Yes

Provide any additional compliance evaluation information:

OpenCDISC v1.5

4.2 Issues Summary

OpenCDISC was used as part of the SDTM programming QC. The process followed was :

- errors were always corrected when possible.
- warnings that potentially had an impact on the analysis or interpretation were also corrected
- other warnings and notices considered minor without any impact on either analyses or interpretation were not corrected

Dataset	Diagnostic Message	Severity	Count	Explanation
AE	SDTM Expected variable not found	Warning	1	AEACN was not used in this study due to the variable's association with a treatment. The data was captured in a SUPPAE variable, AEACNP1, with a codelist specific to the investigational product.
AE	Duplicate records	Warning	1	These are two different adverse events (the verbatim terms, AETERM, are different)
AE	Permissible AESCONG variable with missing value for all records	Notice	1	Required for the production of the ADaMs.
AE	Permissible AESDISAB variable with missing value for all records	Notice	1	Required for the production of the ADaMs.
AE	Permissible AESDTH variable with missing value for all records	Notice	1	Required for the production of the ADaMs.
AE	Permissible AESHOSP variable with missing value for all records	Notice	1	Required for the production of the ADaMs.
AE	Permissible AESLIFE variable with missing value for all records	Notice	1	Required for the production of the ADaMs.
CM	Missing Start Time-Point value	Warning	4	'UNKNOWN' CMENRTPT value.. It was recorded as UNKNOWN in the CRF, therefore CMSTDTC is empty.
CM	Missing values for CMSTDTC, CMSTRF and CMSTRTPT, when CMENDTC, CMENRF or CMENRTPT is provided	Warning	4	UNKNOWN' CMENRTPT value.. It was recorded as UNKNOWN in the CRF, therefore all related values are empty.
CM	Value for CMDOSU not found in (UNIT) CT codelist	Notice	1	The codelist is extensible. The unit is 'OTHER'

Dataset	Diagnostic Message	Severity	Count	Explanation
CM	Invalid CMENRTPT value	Notice	4	Mapped to UNKNOWN. There is a discrepancy between the SDTM IG version 3.1.3 and the controlled terminology. The IG has the value as 'U', whilst the controlled terminology has the value as 'UNKNOWN'. It was decided to use the value 'UNKNOWN'.
DA	Value for DASTRESU not found in (UNIT) CT codelist	Warning	1134	The codelist is extensible. The unit is 'STICK'
DA	Value for DAORRESU not found in (UNIT) CT codelist	Notice	1134	The codelist is extensible. The unit is 'STICK'
DA	Permissible DAREASND variable with missing value for all records	Notice	1	Required for the production of the ADaMs.
DA	Permissible DASTAT variable with missing value for all records	Notice	1	Required for the production of the ADaMs.
DE	Variable appears in dataset, but is not in SDTM standard	Error	2	The variables SPDEVID DEACNDEV which are part of the standard.
DE	Duplicate records	Warning	1	These are not duplicates as they have different device IDs (SPDEVID).
DI	Unrecognized domain	Warning	1	This version of OpenCDISC has an issue with device domains
DM	No records for 'SCRFAIL' subject are found in IE domain	Warning	18	Subjects discontinued for reasons other than I/E failure

Dataset	Diagnostic Message	Severity	Count	Explanation
DM	Value for ETHNIC not found in (ETHNIC) CT codelist	Notice	328	Mapped to sponsor's standard.. The value is 'CAUCASIAN'
DR	Unrecognized domain	Warning	1	This version of OpenCDISC has an issue with device domains
DS	Missing DSDY variable, when DSDTC variable is present	Warning	1	Not in the sponsor's standard
DS	Duplicate records	Warning	162	The terms are different (DSTERM)
DS	Value for DSDECOD not found in (NCOMPLT) CT codelist	Notice	17	Codelist is extensible. The values are 'DISCHARGE', 'RANDOMISED' and 'DISCONTINUED FROM ENROLLMENT'
DT	Variable appears in dataset, but is not in SDTM standard	Error	3	SPDEVID, DTPARTY and DTPRTYID are part of the standard
DT	SDTM Expected variable not found	Warning	1	This domain is not a subject –level domain. Consequently, USUBJID is missing.
DV	DVSTDTC date is after RFPENDTC	Error	2	Subject performed labs after the EOS for a follow up on an AE..
DV	DVENDTC date is after RFPENDTC	Error	7	The end date of the deviation can be after the end of study for a subject
DV	USUBJID/VISIT/VISITNUM values do not match SV domain data	Warning	1	A protocol deviation was mistakenly recorded in the database to subject 275, regarding a baseline spirometry protocol deviation. This subject was a screening failure. This deviation relates to subject 277, and a deviation to this effect was recorded against this subject.
DV	Duplicate records	Warning	42	The DVTERMs are different, along with the

Dataset	Diagnostic Message	Severity	Count	Explanation
				population of the SUPPDV variables (in particular, the qnam ASSESS)
DV	Model permissible variable added into standard domain	Notice	4	FDA preferred variables added (VISIT, VISITNUM, DVSTDY and DVENDY).
DX	Value for DXDOSU not found in (UNIT) CT codelist	Notice	7354	The codelist is extensible. The unit is 'STICK'
EG	Value for EGSTRESC not found in (EGSTRESC) CT codelist	Notice	332	ECG interpretations. The codelist is extensible
EG	Value for EGTEST not found in (EGTEST) CT codelist	Notice	6	The codelist is extensible. The EGTEST is 'All ECG examinations'
EG	Value for EGTESTCD not found in (EGTESTCD) CT codelist	Notice	6	The codelist is extensible. The EGTESTCD is 'EGALL'
EX	EX record is present, when subject is not assigned to an arm	Warning	308	Subjects that discontinued from enrollment. For all subjects the cigarette consumption has to be recorded before randomization in order to have a baseline.
EX	Model permissible variable added into standard domain	Notice	2	FDA preferred variables added (VISITNUM and VISIT).
FA	Value for FASTRESU not found in (UNIT) CT codelist	Warning	169	The codelist is extensible The unit is 'STICK'
FA	USUBJID/VISIT/VISITNUM values do not match SV domain data	Warning	160	Subjects have information recorded at this visit even though they discontinued The subjects are screening failures and did not perform any other assessments for Day -2.

Dataset	Diagnostic Message	Severity	Count	Explanation
FA	Value for FAORRESU not found in (UNIT) CT codelist	Notice	169	The codelist is extensible. The unit is 'STICK'
IE	Missing IEDY variable, when IEDTC variable is present	Warning	1	IEDY variable would be null if added.
IE	Model permissible variable added into standard domain	Notice	1	FDA preferred variable added (EPOCH).
LB	LBDTC date is after RFPENDTC	Error	34	Unscheduled lab safety performed post study completion for subject 117
LB	Value for LBSTRESU not found in (UNIT) CT codelist	Warning	29042	The codelist is extensible. The units are: 'ERYT/uL', 'GI/L', 'REV/mL', 'T/L', 'ng/mL' and 'pg/mL'
LB	Missing LBENDY variable, when LBENDTC variable is present	Warning	1	As per the sponsor's specification.
LB	Missing LBSTRESC value for Baseline record	Warning	46	The affected values relate to enzyme activity and biomarkers.
LB	Value for LBTEST not found in (LBTEST) CT codelist	Notice	29143	The codelist is extensible. The tests are biomarkers and the 'All laboratory tests' indicator test.
LB	Value for LBTESTCD not found in (LBTESTCD) CT codelist	Notice	29143	The codelist is extensible. The testcds are biomarkers and the 'All laboratory tests' indicator test.
LB	Value for LBORRESU not found in (UNIT) CT	Notice	29042	The codelist is extensible. The units are: 'ERYT/uL', 'GI/L', 'REV/mL', 'T/L', 'ng/mL'

Dataset	Diagnostic Message	Severity	Count	Explanation
	codelist			and 'pg/mL'
MH	Model permissible variable added into standard domain	Notice	10	These are additional coding variables: MHHLTCD, MHPTCD, MHHLT, MHHLGT, MHLTCD, MHSOC, MHLT, MHBDSYSCD, MHSOCCD and MHHLGTCD
PE	Missing PESTRESC value for Baseline record	Warning	165	Instances of the body system 'Other' not being completed at baseline.
PE	Model permissible variable added into standard domain	Notice	1	FDA preferred variable added (PEBLFL).
PP	Permissible PPREASND variable with missing value for all records	Notice	1	Required for the production of the ADaMs.
PP	Permissible PPSTAT variable with missing value for all records	Notice	1	Required for the production of the ADaMs.
QS	Missing QSSTRESC value for Baseline record	Warning	55	Cough assessments that are 'not applicable'.for self-abstinence subjects
SE	Variable is in wrong order within domain	Warning	2	FDA preferred variables added. (SESTDY and SEENDY)
SE	Model permissible variable added into standard domain	Notice	2	FDA preferred variables added. (SESTDY and SEENDY)
SU	Redundancy in paired variables values	Warning	328	Mapped to sponsor's specification. The affected variables are sutrt and sudecod.
SV	SVSTDTC date is after RFPENDTC	Error	1	Unscheduled lab safety post study completion for one subject (117)
SV	SVENDTC date is after RFPENDTC	Error	1	Unscheduled lab safety post study completion

Dataset	Diagnostic Message	Severity	Count	Explanation
				for one subject (117).
SV	Model permissible variable added into standard domain	Notice	1	FDA preferred variable added. (EPOCH)
TS	TSPARM and TSPARMCD values do not have the same Code in CDISC CT	Error	1	Maps to the SDTM IG. TSPARM=' Clinical Study Sponsor' and TSPARMCD=' SPONSOR'
TS	TSPARM and TSPARMCD values do not have the same Code in CDISC CT	Error	1	Maps to the SDTM IG. . TSPARM=' Clinical Study Sponsor' and TSPARMCD=' SPONSOR'
TS	SDTM/dataset variable label mismatch	Warning	1	Maps to the SDTM IG. The variable in question is TSVAL1.
TS	Value for TSVAL not found in (TPHASE) CT codelist	Notice	1	Maps to the SDTM IG. The TSVAL value in question is 'NA'
VS	Duplicate records	Warning	7	Caused by missing vital types in some instances. VSPOS population differentiates between the two VSALLs.
VS	Value for VSTEST not found in (VSTEST) CT codelist	Notice	19	The codelist is extensible. The affected VSTEST is 'All Vital Signs'.
VS	Value for VSTESTCD not found in (VSTESTCD) CT codelist	Notice	19	The codelist is extensible. The affected VSTESTCD='ALL'.
XT	XTSTDTC date is after RFPENDTC	Error	111384	Filter analysis dates (analysis occurred after subject study completion).
XT	Value for XTSTRESU not found in (UNIT) CT codelist	Warning	511830	The codelist is extensible. The units in question are: S, mJ, mg/filter, mg/mL,

Dataset	Diagnostic Message	Severity	Count	Explanation
				mmWG, mmWG/mL/s and per filter.
XT	Missing value for XTORRESU, when XTORRES is provided	Warning	125960	Not all parameters have units.
XT	Missing value for XTSTRESU, when XTSTRESC is provided	Warning	125960	Not all parameters have units.
XT	Duplicate records	Warning	885843	Other variables, such as XTSPID, need to be used to show record uniqueness.
XT	Missing XTSTRESC value for Baseline record	Warning	1711	More than one file is considered for baseline
XT	Value for XTEVAL not found in (EVAL) CT codelist	Notice	775525	Mapped to the database value.
XT	Value for XTORRESU not found in (UNIT) CT codelist	Notice	511830	The codelist is extensible. The units in question are: S, mJ, mg/filter, mg/mL, mmWG, mmWG/mL/s and per filter.

Appendix I: Inclusion/Exclusion Criteria

Protocol/ Amendment Version	Category	IETESTCD	Full Text of Criterion
1.0	Inclusion	INC01	Subject has signed the ICF and is able to understand the information provided in the Subject Information Sheet and ICF.
1.0	Inclusion	INC02	Subject is aged from 21 to 65 years (inclusive).
1.0	Inclusion	INC03	Subject is of Caucasian origin.
1.0	Inclusion	INC04	Smoking, but healthy subject as judged by the Investigator or designee based on all available assessments from the Screening period/Day of Admission (e.g., safety laboratory*, spirometry* Forced expiratory volume in 1 second [(FEV ₁)/Forced vital capacity (FVC) >0.7 at post-bronchodilator spirometry, post-bronchodilator FEV ₁ >80% predicted value, and post-bronchodilator FVC >80% predicted value], vital signs, physical examination, electrocardiogram [ECG], chest X-ray, and medical history).
1.0	Inclusion	INC05	Subject is a current smoker (based on self-reporting), who for the last 4 weeks has smoked at least 10 commercially available non-menthol CCs per day (no brand restrictions) with a maximum yield of 1 mg nicotine ISO per cigarette, as labeled on the cigarette package. Furthermore, the subject has smoked for at least the last 3 consecutive years. The smoking status will be verified with a urinary cotinine test (cotinine ≥200 ng/ml).
1.0	Inclusion	INC06	The subject is a current smoker who does not plan to quit smoking in the next 3 months.
1.0	Inclusion	INC07	The subject is ready to accept 5 days of SA.
1.0	Inclusion	INC08	The subject is ready to accept using the THS 2.2 product.

Protocol/ Amendment Version	Category	IETESTCD	Full Text of Criterion
1.0	Exclusion	EXC01	As per Investigator or designee judgment, the subject cannot participate in the study for any reason (e.g., medical, psychiatric, and/or social reason).
1.0	Exclusion	EXC02	A subject who is legally incompetent, physically or mentally incapable of giving consent (e.g., emergency situation, under guardianship, subject in a social or sanitary establishment, prisoners or subjects who are involuntarily incarcerated).
1.0	Exclusion	EXC03	The subject has a medical condition requiring smoking cessation, or clinically relevant diseases (including but not limited to gastrointestinal, renal, hepatic, neurological, hematological, endocrine, oncological, urological, immunological, pulmonary, and cardiovascular disease or any other medical condition [including but not limited to clinically relevant abnormal laboratory parameters]) in the judgment of the Investigator or designee.
1.0	Exclusion	EXC04	The subject has a body mass index (BMI) <18.5 or ≥ 32 kg/m ² .
1.0	Exclusion	EXC05	As per Investigator or designee judgment, the subject has medical conditions which require or will require in the course of the study, a medical intervention (e.g., start of treatment, surgery, hospitalization) which may interfere with the study participation and/or study results.
1.0	Exclusion	EXC06	The subject has used nicotine-containing products other than commercially available CC (either tobacco-based products or nicotine replacement therapy [NRT]) as well as electronic cigarettes and similar devices, within 4 weeks prior to assessment.
1.0	Exclusion	EXC07	The subject has received medication (prescription or over-the-counter) within 14 days or within 5 half-lives of the drug (whichever is longer) prior to the Admission Day (Day -2), which has an impact on CYP1A2 or CYP2A6 activity.

Protocol/ Amendment Version	Category	IETESTCD	Full Text of Criterion
1.0	Exclusion	EXC08	If a subject has received any medication (prescribed or over-the-counter) within 14 days prior to Screening or prior to the Admission Day (Day -2), it will be decided at the discretion of the Investigator or designee if these can potentially interfere with the study objectives or subject's safety.
1.0	Exclusion	EXC09	Concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) or acetylsalicylic acid.
1.0	Exclusion	EXC10	The subject has a positive alcohol test and/or the subject has a history of alcohol abuse that could interfere with the subject's participation in the study.
1.0	Exclusion	EXC11	The subject has a positive urine drug test.
1.0	Exclusion	EXC12	Positive serology test for human immunodeficiency virus (HIV)1/2, hepatitis B surface antigen (HbsAg), or hepatitis C virus (HCV).
1.0	Exclusion	EXC13	Donation or receipt of whole blood or blood products within 3 months prior to Admission.
1.0	Exclusion	EXC14	The subject is a current or former employee of the tobacco industry or of their first-degree relatives (parent, sibling, or child).
1.0	Exclusion	EXC15	The subject is an employee of the investigational site or any other parties involved in the study or of their first-degree relatives (parent, sibling, or child).
1.0	Exclusion	EXC16	The subject has participated in a clinical study within 3 months prior to the Screening Visit.
1.0	Exclusion	EXC17	The subject has previously participated in the same study at a different time (i.e., each subject can be included in the study population only once).

Protocol/ Amendment Version	Category	IETESTCD	Full Text of Criterion
1.0	Exclusion	EXC18	For women only: Subject is pregnant (does not have negative pregnancy tests at Screening and at Admission) or is breast feeding.
1.0	Exclusion	EXC19	For women only: Subject does not agree to use an acceptable method of effective contraception.*