

# Study Data Reviewer's Guide

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Study ZRHM-REXA-08-US

Version 2016-03-22

# Study Data Reviewer's Guide

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## 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 Acronyms

Acronym	Translation
SDTM	Study Data Tabulation Model
aCRF	Annotated Case Report Form

### 1.3 Study Data Standards and Dictionary Inventory

Standard or Dictionary	Version
SDTM	SDTM Version 1.3 / SDTM Implementation Guide version 3.1.3 SDTM Draft Implementation Guide for Medical Devices (SDTMIG-MD)
Controlled Terminology	CDISC Controlled Terminology dated 2014-12-19
Data Definitions	Define.xml version 2.0
Medication Dictionary	WHO-DRUG DDEB2 Mar 2013
Medical Events Dictionary	MedDRA Version 16.0
Other standards	C54451/Medical_Device_Problem_Codes_FDA_CDRH

## 2. Protocol Description

### 2.1 Protocol Number and Title

**Protocol Number:** ZRHM-REXA-08-US

**Protocol Title:** Reduced exposure study using THS 2.2 Menthol with 5 days in a confinement setting followed by 86 days in an ambulatory setting

**Protocol Versions:** Final 5.0 (14 April 2014)

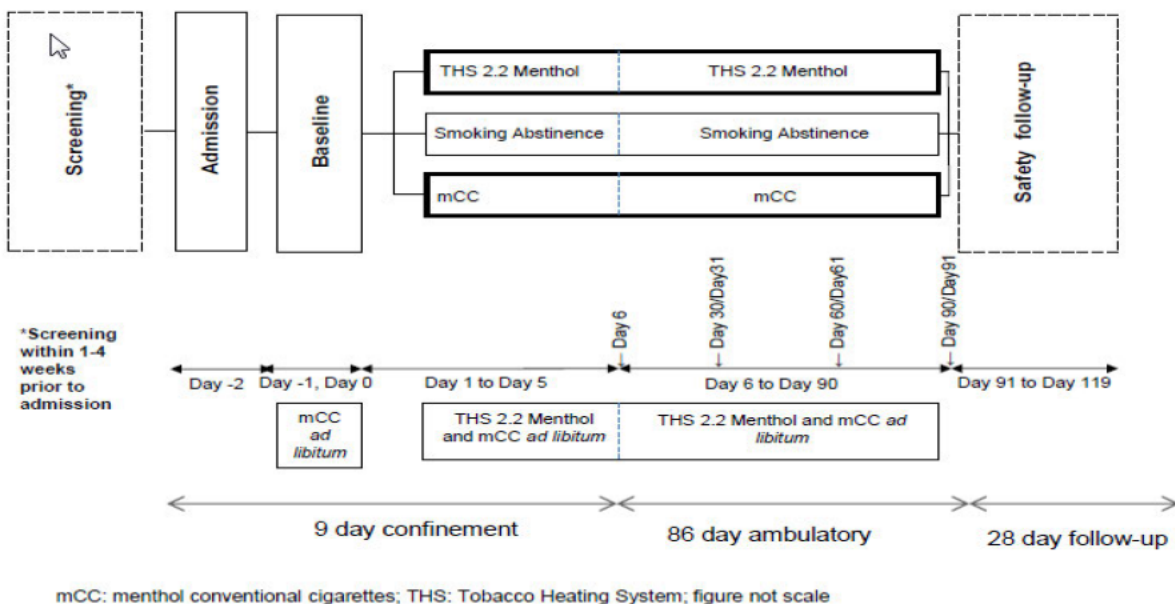
### 2.2 Protocol Design

A randomized, controlled, open-label, 3-arm, parallel group study design with a stratified randomization by sex and average daily cigarette consumption over the last 4 weeks as reported

during the Screening Visit (smokers smoking 10-19 mCC and smokers smoking >19 mCC per day)

This is an *ad libitum* smoking study. In general, smoking/product use during the confinement period will be allowed from 06:30 AM onwards until around 11:00 PM. During the ambulatory period, there will be no smoking/product use restriction except during the three visits on site (Day 30 Visit, Day 60 Visit, and Day 90 Visit), when product use will be allowed from the time of check-in prior to 08:30 AM to around 11:00 PM on Day 30, Day 60, and Day 90. On Day 31, Day 61, product use will be allowed from 06:30 AM onwards. On Day 91, product use will be allowed after the CYP2A6 activity and full lung function have been performed until time of discharge of Day 91.

During the confinement period, compliance to product/regimen allocation (exclusive use of THS 2.2 Menthol and mCC in THS 2.2 Menthol and mCC arms, respectively, and full abstinence from smoking in the SA arm) will be ensured by strict distribution of each Menthol Tobacco Stick/mCC when requested by the subject. During the ambulatory period, the subjects randomized to the THS 2.2 Menthol arm will be instructed to exclusively use THS 2.2 Menthol and subjects randomized to the SA arm will be instructed to abstain from smoking.



## 2.3 Trial Design Datasets

Are Trial Design datasets included in the submission? Yes

Dataset	Dataset Label
TA	Trial Arms
TE	Trial Elements
<a href="#">TV</a>	Trial Visits
<a href="#">TI</a>	Trial Inclusion/Exclusion Criteria
TS	Trial Summary

**2.3.1 TV – Trial Visits**

On Day 6, the safety procedures will be conducted before discharge of the subject from the clinic after 9 days in a confined setting and subjects will be instructed to continue their assigned product/regimen in an ambulatory setting for 86 days. For Day 90 Visit, the subject will checked-in in the morning prior to 08:30 AM on Day 90, and will be discharged on Day 91 after having performed all the safety examination procedures. Therefore, a combined DAY 6/DISCHARGE CONFINEMENT, DAY 91/DISCHARGE AMBULATORY visit were created to account for the timings of the procedures performed at Discharge Day.

**2.3.2 TI – Trial Inclusion/Exclusion Criteria**

The trial inclusion/exclusion criteria are not fully described in the TI domain. Please refer to [Appendix I](#) for the full text of the criteria.

### 3. Subject Data Description

#### 3.1 Overview

Are the submitted data taken from an ongoing study? No

Were the SDTM datasets used as sources for the analysis datasets? Yes

Do the submission datasets include screen failures? Yes

If yes, which datasets include screen failure data?

DM

AE

CM

DA

SE

DS

DV

DX

FA

IE

LB

SV

XT

RELREC

Were any domains planned, but not submitted because no data were collected? No

Are the submitted data a subset of collected data? No

#### Additional Content of Interest

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

The primary endpoint data can be found in LB.

Two new finding domains, XP has been created for the spirometry data and XT has been created for the HST Assessments data.

For this study it was decided to use the FA dataset 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

<b>Domain</b>	<b>Datasets</b>	<b>Description</b>	<b>Class</b>	<b>Information captured</b>
DX	DX	Device Exposure	Interventions	Subject exposure with the THS 2.2 Menthol Sticks.
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.
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 and use of Menthol Conventional Cigarette
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 - OXYSTEROLS - PREGNANCY - SEROLOGY - URINALYSIS
XP	XP	Pulmonary Function	Findings	Captures the Spirometry (lung capacity)
XT	XT	HST Assessments	Findings	Captures the HST Assessments



### 3.2 Annotated CRFs

Annotation conventions:

1. Only unique CRF pages were annotated, and the repeated pages were not annotated and linked to the annotated pages.
2. When data is recorded on CRF, but is not submitted, the CRF were annotated NOT SUBMITTED.

- The following CRF fields that have been annotated as “Not Submitted” are:

- Subject (Site level)
- In site Accountability form: Category
- Responses to the screen failure question ‘Is there a pregnancy event?’, as this is Not Submitted in the SDTM dataset.
- The Y/N responses to the questions prompting the entry of data used by data management solely for data validation purposes:
  - 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
  - THS 2.2 Menthol product demonstration form
    - Has the subject seen a THS 2.2 menthol product demonstration?
  - Advice on the risk of smoking and debriefing
    - Has the subject received advices on the risks of smoking?
    - Has a debriefing been performed about THS 2.2?
  - Adverse Events Y/N
    - Was there any Adverse Event for this subject?
  - Previous and Concomitant Medication Y/N
    - Has the subject taken previous or concomitant medication?
  - Date of Discharge
    - Is the subject continuing in the ambulatory period?
  - Additional Informed Consent
    - Has the subject given written informed consent for Bio-banking for Biomarkers of Exposure and Risk Markers?
    - Has the subject given written informed consent for Bio-banking for Transcriptomics (Pharmacogenomics), Nasal Epithelial collection and Buccal Collection?
  - Device report - THS 2.2 menthol Cigarette Holder
    - Were there any events with the device

- Medical History/Concomitant Disease
  - Has the subject experienced any past and/ or concomitant diseases?
- Consent Withdrawal
  - Did the subject withdraw it's consent to the biobanking for BoExp and risk markers?
  - Did the subject withdraw it's consent to the transcriptomics analysis?
- Inclusion Criteria
  - Inclusion Criterion Number
- Exclusion Criteria
  - Result
- Date of Visit< Ambulatory>: This panel is only for VISIT/SVSTDTC. Other information like visit not done/reason not done can be NOT SUBMITTED.
- The variable 'H\_NOW' was not submitted as this is a derived variable used to validate information in the database
- Advice on the risk of smoking and debriefing: Date
- The medical history category was derived in the SDTMs, based on the start of medical event
- 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
- THS 2.2 menthol product demonstration: If the subject did not see the demonstration please explain
- Product administration-mCC: CC with SODIM?
- Now (Derived) is also Not Submitted.
- Product use diary
  - Type
  - Date of Birth
  - Date of completion
  - Time of completion
  - Assessment Status
- Minnesota Nicotine Dependence/Withdrawal Scale (MNWS):
  - Type
- Assessment Status
- In Biomarker form: Celerion Study Number, Lower Limit of quantification, Detection Method, 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, Urine Cotinine Test) were entered by the site.

- The data of Lab-BU-LabCorp form is from external files and some of variables in this panel are used only by data management. These variables are not kept in the SDTM, like below:

- Date of Birth: have been kept in the SDTM.DM
- Code: LBTESTCD is recoded and can't be the number in the source, and it is only used by data management
- Please document clinically relevant abnormalities in the AE form: The data is in the source.AE
- Derived Form name(Lab Type-Date): Not Collected

- The data of Lab\_BU\_CCLS form is from external files and some of variables in this panel are used only by data management. These variables are not kept in the SDTM, like below:

- Transmission Type: Not necessary to submit, and get this source from sponsor directly.
- Subject ID or Number: Have been kept in the DM domain
- Subject Sex: Have been kept in the DM domain
- Subject Date of Birth: Have been kept in the DM domain
- Visit Name: Not necessary to submit, VISIT/VISITNUM are both from source of sample taken
- Visit Type: Not necessary to submit, VISIT is from source of sample taken
- Battery ID: Not submitted, used only by DM domain
- Battery Name: Not submitted, used only by data management
- Lab Test ID: LBTESTCD is recoded and can't be the number in the source, and it is only used by data management

- The submitted annotated CRF (blankcrf.pdf) includes the final version of the eCRF (main study CRF version 5.0 )

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 (ePRO)device. The CRF represents only the last version of the database.

Organization of Bookmarks: there are no timepoint bookmarks and topic bookmarks are organized in the order that they appear in the aCRF.

Organization of content: Primary CRF first, Central Laboratory Data second.

blankcrf.pdf includes only the last version.

3. Domain annotations always appeared on the left of the CRF page and on the top of all its variable annotations. To distinguish the domain level annotation and variable level annotation, green and cyan background colors of green and cyan were used for domains and variables respectively.

4. When findings domains were annotated, the format of "--ORRES where --TESTCD = XXXX" was used to indicate which --TESTCD the result is for.

5. SUPPQUAL variable is annotated as "SUPPXX.QVAL where QNAM = XXXX".

6. For customized domains, 'X-' is used to represent findings domains.

The dataset including investigator signature and sign date were not submitted.

### 3.3 SDTM Subject Domains

Dataset – Dataset Label	Efficacy	Safety	Other	SUPP-	Related Using RELREC	Observation Class
<a href="#">AE – Adverse Events</a>		X		X	CM	Events
<a href="#">CM – Concomitant Medications</a>		X		X	AE, MH	Interventions
CO - Comments			X			Special Purpose
<a href="#">DA – Drug Accountability</a>			X	X		Findings
<a href="#">DE – Device Events</a>		X		X	DT	Events
DI - Device Identifiers			X			Special Purpose Domains
<a href="#">DM – Demographics</a>			X	X		Special Purpose Domains
DR - Device Subject Relationship			X			Special Purpose Domains
<a href="#">DS – Disposition</a>			X	X		Events
DT - Device Tracking and Disposition			X		DE	Events
<a href="#">DV – Protocol Deviations</a>			X	X		Events
<a href="#">DX – Device Exposure</a>			X	X		Interventions
<a href="#">EG – ECG Test Results</a>		X		X		Findings
<a href="#">EX – Exposure</a>			X	X	FA	Interventions

<b>Dataset – Dataset Label</b>	<b>Efficacy</b>	<b>Safety</b>	<b>Other</b>	<b>SUPP-</b>	<b>Related Using RELREC</b>	<b>Observation Class</b>
<a href="#">FA – Findings About Events or Interventions</a>			X	X	EX	Findings About
IE - Inclusion/Exclusion Criterion Not Met			X			Findings
<a href="#">LB – Laboratory Test Results</a>		X		X		Findings
MH - Medical History			X		CM	Events
PC - pharmacokinetic Concentrations			X			Findings
<a href="#">PE – Physical Examination</a>		X		X		Findings
<a href="#">PP – Pharmacokinetic Parameters</a>			X			Findings
QS - Questionnaire		X				Findings
SE - Subject Elements			X			Special Purpose Domains
<a href="#">SU – Substance Use</a>			X			Interventions
SV - Subject Visits			X			Special Purpose
<a href="#">VS – Vital Signs</a>		X		X		Findings
<a href="#">XP – Pulmonary Function</a>			X	X		Findings
<a href="#">XT – HST Assessments</a>			X	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 Study Product 1
AETRTEM	Treatment Emergent Flag
AEACNP1	Action Taken with Study Product 1

**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
MHNUM	Concomitant Disease Number
AENUM	AE Number
OTHER	Other
CMPTCD	Preferred Term Code
ATCTXT1	ATCTXT1
ATCTXT2	ATCTXT2
ATCTXT3	ATCTXT3
ATCTXT4	ATCTXT4
ATCCD1	ATCCD1
ATCCD2	ATCCD2
ATCCD3	ATCCD3
ATCCD4	ATCCD4
CMSYCD	Trade Name Code
CMSYN	Trade Name

**3.3.3. DA – Drug Accountability**

The following variables have been mapped into SUPPDA

QNAM	Description
BEXPDTC	Batch Expiration Date
UNUSPKRT	Number of unused packs returned
UNUSSTRT	Number of unused sticks returned
PCKRCVD	number of packs received

**3.3.4. DE – Device Events**

The following variables have been mapped into SUPPDE. Since no device events were linked to adverse events then the RELREC dataset was not required for this domain.

QNAM	Description
AEREL	Adverse Event Relationship
AENUM	AE Number
NDSN	New Device Serial Number

**3.3.5. DM – Demographics**

The following variables have been mapped into SUPPDM

QNAM	Description
DMRANDNO	Randomization Number
RACEOTH	Race, other

**3.3.6. DS – Disposition**

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

DSCAT	DSSCAT
PROTOCOL MILESTONE	
OTHER EVENT	
DISPOSITION EVENT	CONSENT MAIN
DISPOSITION EVENT	SAMPLES CAN BE ANALYSED
DISPOSITION EVENT	WITHDRAW PHI
DISPOSITION EVENT	

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
DVTIMEPT	Deviation Timepoint
DVREPDTC	Date Deviation Reported
RESOL	Deviation Resolution
SOURCE	Deviation Source
DVSIG	Deviation Type
EVALCAT	Evaluation Category

**3.3.8. DX – Device Exposure**

This dataset captures the THS 2.2 exposure data.

The following variables have been mapped into SUPPDX

QNAM	Description
DXOTH	Other Product Used

**3.3.9. EG – ECG Test Results**

The following variables have been mapped into SUPPEG

QNAM	Description
EGCLSIG	Clinically Significant

**3.3.10. EX – Exposure**

This dataset captures the cigarette exposure data.

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

EXCAT	EXSCAT
MENTHOL CONVENTIONAL CIGARETTES	PRODUCT USE CONFINEMENT
MENTHOL CONVENTIONAL CIGARETTES	PRODUCT USE DIARY - ELECTRONIC

The following variables have been mapped into SUPPEX

QNAM	Description
OTHER	Other Product Used



**3.3.11. 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 information presented in the dataset using the following categorisation pairings.

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

The following variables have been mapped into SUPPFA

QNAM	Description
BRAND	Standardised Brand Name

**3.3.12. LB – Laboratory Test Results**

Toxicity grading of the laboratory safety data, as outlined in Appendix 6 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 6 of the study protocol.

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

LBCAT	LBSCAT
BIOBANKING	BIOMARKERS OF EXPOSURE
BIOBANKING	BUCCAL COLLECTION
BIOBANKING	NASAL EPITHELIAL COLLECTION
BIOBANKING	TRANSCRIPTOMICS
BIOMARKERS	
BIOMARKERS	24H URINE SAMPLE
BIOMARKERS	4H URINE SAMPLE
HAEMATOLOGY	
ALCOHOL TEST	
ENZYME ACTIVITY	CYTOCHROME 1A2
ENZYME ACTIVITY	CYTOCHROME 2A6
OXYSTEROLS	
CLINICAL CHEMISTRY	
SEROLOGY	

COTININE SCREENING	
DRUG SCREEN	
URINALYSIS	
URINALYSIS	24H URINE SAMPLE
URINALYSIS	4H URINE SAMPLE
PREGNANCY	

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

The following variables have been mapped into SUPPLB

QNAM	Description
PRIMTUB	Primary tubes
BACTUB	Back Up Tubes
LB_FLG	Flag
LBCLSIG	Clinically Significant
LBCONC	Conventional Text Result
LBCONN	Conventional Numeric Result
LBCONRLO	Conventional Reference Range Low
LBCONRHI	Conventional Reference Range High
LBCONU	Conventional Reference Range Units
LBSIC	SI Text Result
LBSIN	SI Numeric Result
LBSIRLO	SI Reference Range Low
LBSIRHI	SI Reference Range High
LBSIU	SI Units

### 3.3.13. PE – Physical Examination

The following variable has been mapped into SUPPPE

QNAM	Description
PECLSIG	Clinically Significant

### 3.3.14. PP – Pharmacokinetic Parameters

The following pairings of PPCAT and PPSCAT were used in the dataset.

PPCAT	PPSCAT
MENTHOL CONVENTIONAL CIGARETTE	COTININE
MENTHOL CONVENTIONAL CIGARETTE	NICOTINE
TOBACCO HEATING SYSTEM 2.2 MENTHOL	COTININE
TOBACCO HEATING SYSTEM 2.2 MENTHOL	NICOTINE

### 3.3.15. SU – Substance Use

The SU domain contains the average daily cigarette consumption over the last 4 weeks reported for each subject at Screening and used for the stratification. It also captures the caffeine intake for the Cytochrome 1A2 assessment and it was also used to capture the tobacco product use and NRT product use (with the exception of CC and THS) during the ambulatory period through the subject's daily report into the ePRO. The following SUCAT and SUSCAT were used in the dataset.

SUCAT	SUSCAT
TOBACCO	CIGARETTE CONSUMPTION
CAFFEINE	
TOB_USE	PRODUCT USE DIARY - ELECTRONIC
NRT_USE	PRODUCT USE DIARY - ELECTRONIC

### 3.3.16. VS – Vital Signs

The following variable has been mapped into SUPPVS

QNAM	Description
SMOK15P	Smoked within 15 min prior to assessment

### 3.3.17. XP – Pulmonary Function

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

The following pairings of XPCAT and XPSCAT were used in the dataset.

XPCAT	XPSCAT
GAS TRANSFER	
LUNG CAPACITY	WITHOUT SHORT ACTING BRONCHODILATOR
LUNG CAPACITY	WITH SHORT ACTING BRONCHODILATOR
LUNG VOLUME MEASUREMENT	

The following variable has been mapped into SUPPXP

QNAM	Description
XPCLSIG	Clinically Significant
SMOK1HP	Smoked within 1 hour prior to assessment

**3.3.18. XT – HST Assessments**

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

The following variable has been mapped into SUPPXT

QNAM	Description
FILESTAT	File Status
ANALYDTC	Date of analysis
MOFILNUM	Modified File Number
SODENUM	SODIM Device Number
SOSHNUM	SODIM Sample Holder Number
KIT_NUM	Kit Number
VIAL_NUM	Vial Number
FILEDTC	Date of File Assessed
TESTDTC	Date of File Creation
VERSION	Version
MODEFLOW	Mode of Flow Correction
MODEVOL	Mode of Volume Correction
CIGID	Cigarette ident.
ATMPCORR	Atm. Pressure Correction
FNEGFZ	Force Negative Flow to Zero
INTPFMIN	Inter Puff Min Time
SMOKNB	Smoker Smoking Number
RTDBTHD	RTD Base Threshold
PFFMINTM	Puff Min Time
CODE	Code
INTRFER	Interference Time
ATMPSPAN	Atm P Span
USLCIG	Usual Cigarette
PDTHSLD	PD Threshold
FLWSPAN	Flow Span
CONSMON	Cons. Since Morning

FLWTHLD	Flow Threshold
PDSPAN	P Span
SMPLAQ	Sample Acquisition
VOLTHLD	Volume Threshold
KCOEFF	Coeff.
INDEX	Indice

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

Domains	Variable (Codelist)	Value
CM	C66729	OTHER
DE	C111109	CHARGER
DE	C111109	HOLDER
DI	C106480	BATCH IDENTIFIER
DI	C106480	DEVICE TYPE
DI	C106480	MANUFACTURER
DI	C106480	MODEL
DI	C106481	TYPE
DM	C74457	OTHER
DS	C66727	DISCHARGE
DS	C66727	DISCONTINUED FROM ENROLLMENT
DS	C66727	INFORMED CONSENT OBTAINED
DS	C66727	RANDOMIZED
DS	C66727	INFORMED CONSENT WITHDRAWAL
DS	C66727	PROTOCOL VIOLATION
DT	C112037	COLLECTION
DT	C112037	DISTRIBUTION
DT	C112037	REPLACED
EG	C71152	All ECG examinations
EG	C71152	Summary (Mean) Heart Rate
EG	C71153	EGALL

EG	C71153	HRMEAN
FA	C101832	CONYR3
FA	C101832	NICOTH
FA	C101832	NUMSTIC
FA	C101832	PERFORM
FA	C101832	QUIT
FA	C101832	SMOKHIST
FA	C101832	WILLABL
FA	C101832	TYIELD
FA	C101832	WKMENT4
FA	C101833	Cigarettes per Day Last 4 Weeks
FA	C101833	Nicotine-Containing Products
FA	C101833	Number of Sticks
FA	C101833	Plan to Quit Smoking Next 3 Months
FA	C101833	Smoke for at Least 3 Consecutive Years
FA	C101833	Smoke Menthol Cigarettes Last 4 Weeks
FA	C101833	Was the THS 2.2M Product Trial Performed
FA	C101833	ISO Tar Yield
FA	C101833	Willing to Use the Product
LB	C67154	22(R)-hydroxycholesterol
LB	C67154	24(R)-hydroxycholesterol
LB	C67154	25-hydroxycholesterol
LB	C67154	27-hydroxycholesterol
LB	C67154	4b-hydroxycholesterol
LB	C67154	5a,6a-epoxycholestanol
LB	C67154	5b,6b-epoxycholestanol
LB	C67154	6a-hydroxy-5a-cholestane
LB	C67154	7a-hydroxycholesterol
LB	C67154	7b-hydroxycholesterol

LB	C67154	7-ketocholesterol
LB	C67154	11-Dehydro-Thromboxane B2
LB	C67154	1-aminonaphthalene
LB	C67154	2-aminonaphthalene
LB	C67154	2-cyanoethylmercapturic Acid
LB	C67154	2-hydroxyethyl Mercapturic Acid
LB	C67154	3-hydroxy(a)benzopyrene
LB	C67154	3-hydroxypropylmercapturic Acid
LB	C67154	3-hydroxy-1-methylpropylmercapturic Acid
LB	C67154	4-Aminobiphenyl
LB	C67154	All laboratory tests
LB	C67154	Ames Mutagenecity
LB	C67154	Bio-Banking
LB	C67154	Carbon Monoxide
LB	C67154	Cotinine-Glucuronide
LB	C67154	Free Cotinine
LB	C67154	Free Nicotine
LB	C67154	Free Trans-3'- Hydroxycotinine
LB	C67154	HIV-1/2 Antibody Qual
LB	C67154	Monohydroxybutenyl Mercapturic Acid
LB	C67154	Nicotine-Glucuronide
LB	C67154	O-Toluidine
LB	C67154	Paraxanthine
LB	C67154	Pregnancy Test
LB	C67154	Intercellular Adhesion Molecule 1
LB	C67154	S-phenylmercapturic Acid
LB	C67154	Total 1-hydroxypyrene
LB	C67154	Total 4-(methylnitrosamino)-1-(3-pyridyl
LB	C67154	Total N-Nitrosornicotine

LB	C67154	Trans-3 Hydroxycotinine
LB	C67154	Trans-3- Hydroxycotinineglucuronide
LB	C5047	_22HYDCH
LB	C5047	_24HYDCH
LB	C5047	_25HYDCH
LB	C5047	_27HYDCH
LB	C5047	_4BHYDCH
LB	C5047	_56AEPCH
LB	C5047	_56BEPCH
LB	C5047	_6HYDCH
LB	C5047	_7AHYDCH
LB	C5047	_7BHYDCH
LB	C5047	_7KETCH
LB	C5047	_1_NA
LB	C5047	_1_OHP
LB	C5047	_1_OHP
LB	C5047	_2_NA
LB	C5047	_3_HPMA
LB	C5047	_4_ABP
LB	C5047	_BAP
LB	C5047	AMES
LB	C5047	BIOBANK
LB	C5047	CEMA
LB	C5047	CO
LB	C5047	COTG
LB	C5047	FCOT
LB	C5047	FNIC
LB	C5047	FTRANSHY
LB	C5047	HEMA



LB	C5047	HIV12ABI
LB	C5047	HIV12ABQ
LB	C5047	HMPMA
LB	C5047	LBALL
LB	C5047	MHBMA
LB	C5047	NICG
LB	C5047	NNAL
LB	C5047	NNN
LB	C5047	O_TOL
LB	C5047	PREGTEST
LB	C5047	PX
LB	C5047	S_BMA
LB	C5047	S_PMA
LB	C5047	ICAM1
LB	C5047	TRANS3H
LB	C5047	TRANSHYG
CM	C66728	U
LB	C78733	INVALID/FIBRIN CLOTS
LB	C78733	SPECIMEN RECEIVED BEYOND STABILITY
LB	C78733	MICROCLOTS
LB	C78733	ERROR IN SPECIMEN ID ASSIGNMENT
LB	C78733	HEMOLYSIS-TEST NOT PERFORMED
LB	C78733	BEYOND STABILITY
LB	C78733	SPECIMEN SEVERELY HEMOLYZED - UNABLE TO PERFORM TEST
LB	C78733	NOT ORDERED W/IN STABILITY
LB	C78733	TEST CANCELED; HCT>55%
LB	C85492	LC-MS/MS
LB	C85492	SNF
LB	C85492	SPIROMETRY

LB	C85492	TOPOGRAPHY
LB	C85492	SINGLE BREATH TECHNIQUE
LB	C85492	SPECTROPHOTOMETRIC
LB	C85492	BREATH TEST
LB	C85492	HELIUM DILUTION TECHNIQUE
LB	C85492	URINE SAMPLE
LB	C71620	Manufactured Cigarettes
LB	C71620	Hand-rolled Cigarettes
LB	C71620	STICK
LB	C71620	10 <sup>3</sup> /uL
LB	C71620	10 <sup>6</sup> /uL
LB	C71620	fg/mL
LB	C71620	S/CO RATIO
LB	C71620	GI/L
LB	C71620	T/L
LB	C71620	mg/mL
LB	C71620	ng/mL
LB	C71620	OTHER
LB	C71620	pg/mL
LB	C71620	REV/mL
LB	C71620	Not Applicable
LB	C71620	Other Dosing Unit
MH	C66728	U
SE	C99079	ADMI
SE	C99079	BASELINE
SE	C99079	FOLLOWUP
SE	C99079	PRODUCT USE CONFINEMENT
SE	C99079	PRODUCT USE AMBULATORY
SU	C71620	GUM

XT	C78735	ANTHONY BRUCHET
XT	C78735	THIERRY BACHMANN
XT	C78735	VALERIE POUX
XT	C78734	TOBACCO PLUG
XT	C71620	mJ
XT	C71620	mmWg
XT	C71620	mmWg/mL/sec

## 4. Data Conformance Summary

### 4.1 Conformance Inputs

Was OpenCDISC used to evaluate conformance? Yes

If yes, specify the version of the OpenCDISC validation rules:

OpenCDISC v1.5, SDTM 3.1.3, Controlled Terminology version 2014-03-28 and MedDRA 16.0

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

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

Were the SDTM datasets evaluated in relation to define.xml? Yes

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
ALL	Domain referenced in define.xml but dataset is missing	Warning	2	No need to update. Because DR/DI are not recognized by OpenCDISC.

ALL	Variable length is too long for actual data.	Error		In some cases, when the max length of the value of a variable is less than the length defined in the data, this error will appear. Just ignore the error.
AE	SDTM Expected variable not found	Warning	1	SDTM.AE.AEACN is deleted in the spec and corresponding value goes into SUPPAE.AEACNP1.
AE	Duplicate records	Warning	2	AETERM is different.
AE	No Treatment Emergent info for Adverse Event	Warning	16	When SUPPAE.AETRTEM = 'N', delete these records in the SUPPAE according to the PMI comments.
CO	Variable appears in dataset, but is not in SDTM model	Error	1	Added EPOCH according to the SPEC.
CO	Missing CODY variable, when CODTC variable is present	Warning	1	Be consistent with SPEC.
CO	Inappropriate usage of variables in CO domain	Warning	342	Be consistent with SPEC.
DE	Variable appears in dataset, but is not in SDTM model	Error	2	Be consistent with SPEC, adding SPDEVID/DEACNDEV to DE.
DE	Duplicate USUBJID/--TERM/--STDTC record	Warning	11	Other variables like SPDEVID was different for records with same USUBJID/DEDECOD/DESTDTC.
DI	Unrecognized domain	Warning	1	No need to update. Because DI is not recognized by OpenCDISC.
DM	No baseline result in EG for subject	Warning	1	There is no record for subject ="1042" in the EG.
DM	No baseline result in VS for subject	Warning	1	There is no record for subject ="1042" in the VS.
DM	No records for 'SCRFAIL' subject are found in IE domain	Warning	48	It may be a raw data issue. Raw data.PRESCREEN was used to derive the value of DM.ARMCD, but the subject did not appear

				in raw data of SDTM.IE.
DR	Unrecognized domain	Warning	1	No need to update. Because DR is not recognized by OpenCDISC.
DS	DSCAT is not 'DISPOSITION EVENT', when EPOCH is provided	Warning	294	According to IG, EPOCH needs populating when DSCAT ='OTHER'
DS	Duplicate records	Warning	138	DSTERM is different.
DT	Variable appears in dataset, but is not in SDTM model	Error	3	Be consistent with SPEC, adding SPDEVID/DTPARTY/DTPRTYID to DT.
DT	Duplicate USUBJID/--TERM/--STDTC record	Warning	205	DTCAT/DTSPID/SPDEVID are different for records with same USUBJID/DTDECOD/DTSTDTC.
DV	Value for DVSCAT not found in (DVSCAT) user-defined codelist	Error	1	DVSCAT="ALL" is missing in the codelists "DVSCAT", resulting in opencdisc issue.
DV	DVSTDTC date is after RFPENDTC	Error	78	DVSTDTC is not consistent with the date in other domains. So the date is not used to derive RFPENDTC.
DV	DVENDTC date is after RFPENDTC	Error	105	DVENDTC is not consistent with the date in other domains. So the date is not used to derive RFPENDTC.
DV	USUBJID/VISIT/VISITNUM values do not match SV domain data	Warning	31	RAW.PD1 is not used to derive SV because the difference of the date in the pd1 and that in the other rawdata for the same visit is more than 2 days or 1 month.
DV	Duplicate USUBJID/--TERM/--STDTC record	Warning	469	DVSPID was different for records with same USUBJID/DVDECOD/DVSTDTC record.
EX	NULL value in EXTRT variable marked as Required	Error	35	For subject ="1042", EXTRT is missing.

EX	Value for EXSCAT not found in (EXSCAT) user-defined codelist	Error	11743	There are a space before/after "-" for the EXSCAT="PRODUCT USE DIARY - ELECTRONIC" in the data and CRF annotation which is not consistent with spec "PRODUCT USE DIARY-ELECTRONIC"
EX	EXSTDTC date is after RFXENDTC	Error	10683	Handle this case per PMI requirement. RFXENDTCs are from SDTM.DX regardless of EX.
EX	EXENDTC date is after RFXENDTC	Error	10683	Handle this case per PMI requirement. RFXENDTCs are from SDTM.DX regardless of EX.
EX	EX record is present, when subject is not assigned to an arm	Warning	54	On Day 0, subjects would be randomized to 1 of 3 arms, but in the raw.ex_cc there were some records on day -1, because of smoking on day -1.
EX	Variable not recommended for use	Warning	2	Be consistent with SPEC, adding EXSTAT/EXREASND.
EX	Variable is in wrong order within domain	Warning	1	Be consistent with SPEC. But the order of EPOCH is not same as specified by CDISC standard.
IE	Missing IEDY variable, when IEDTC variable is present	Warning	1	Be consistent with SPEC.
LB	Value for LBTPTNUM not found in (RLBTPTCD)	Error	96286	The codelists values are not correct. They are all numeric values and should be 1, 1.5 instead of

	user-defined codelist			1.00, 1.50, resulting opencdisc issues.
LB	Missing value for LBORRESU, when LBORRES is provided	Warning	69	Some LBTESTCD do not need a unit, for example, when LBCAT = 'URINALYSIS' and LBTESTCD = 'PROT', the unit is null.
LB	Missing value for LBSTRESU, when LBSTRESC is provided	Warning	6	Some LBTESTCD do not need a unit, for example, when LBCAT = 'URINALYSIS' and LBTESTCD = 'PROT', the unit is null.
LB	Duplicate records	Warning	5	LBTPPT was different for records.
LB	Missing value for LBREASND, when LBSTAT is 'NOT DONE'	Warning	80	Raw data issue. When LBSTAT = 'NOT DONE', some LBREASND is null.
MH	Value for MHSOC not found in MedDRA dictionary	Error	133	The length of MHSOC is less than the length of actual value, resulting in value truncated.
MH	Duplicate records.	Warning	2	MHTERM is different.
PE	Duplicate records	Warning	3644	PESPID is different to distinguish records.
PE	Missing value for PEREASND, when PESTAT is 'NOT DONE'	Warning	7	Raw data issue.
QS	Inconsistent value for Standard Units	Error	5743	These records are consistent with the CRF mapping.
QS	Duplicate records	Warning	5520	QSORRESU was different.
SE	Variable is in wrong order within domain	Warning	2	Be consistent with SPEC.



SU	Missing value for SUDOSU, when SUDOSE, SUDOSTXT or SUDOSTOT is provided	Error	82183	Some Doses don't need a unit.
SU	Value for SUSCAT not found in (SUSCAT) user-defined codelist	Error	129144	There are a space before/after "-" for the SUSCAT="PRODUCT USE DIARY - ELECTRONIC" in the data and CRF annotation which is not consistent with spec "PRODUCT USE DIARY-ELECTRONIC"
SU	Redundancy in paired variables values	Warning	451	According to the spec, SUTRT is equal to SUCAT.
SUPPDV	QVAL variable length is too long for actual data	Warning	1	QEVAL is missing with \$1.
TS	Value for TSVAL not found in (TSVAL) user-defined codelist	Error	1	2015-08-19 is missing in the codelists, resulting opendisc issues: Value for TSVAL not found in (TSVAL) user-defined codelist
VS	EPOCH value not found in 'Epoch' extensible codelist	Warning	9430	Be consistent with spec.
VS	Duplicate records	Warning	3	VSORRES was different.
XT	Value for XTORRESU not found in (UNIT) user-defined codelist	Error	243790	In the spec codeslists sheet, the value "mmWg" and "mmWg/mL/sec" are not consistent with that in the data "mmWG" and "mmWG/mL/sec"
XT	Value for XTSTRESU not found in (UNIT) user-defined codelist	Error	243790	In the spec codeslists sheet, the value "mmWg" and "mmWg/mL/sec" are not consistent with that in the data "mmWG" and "mmWG/mL/sec"
XT	Missing value for XTORRESU, when XTORRES is	Warning	97569	It is not necessary to have a unit.

	provided			
XT	Missing value for XTSTRESU, when XTSTRESC is provided	Warning	97569	It is not necessary to have a unit.
XT	Permissible variable with missing value for all records	Warning	1	XTSCAT is missing.
XT	Duplicate records	Warning	732063	XTXFN was different.

### 4.3 Additional Conformance Details

Dataset	Diagnostic Message	Severity	Count	Explanation
LB	NA	Minor	1	During the reconciliation process of the biobanking samples, performed after the database lock, a discrepancy has been noticed for subject DAL 2072. Indeed, in the CRF it was reported that the sample was not taken while this sample has been received by the laboratory in charge of the analysis. Since the biobanking analysis are not part of the study protocol assessment, this findings is considered minor and was not corrected in the database.
TS	NA	Minor	1	The value --2014-10-06--- in the TS.TSVCDVER is not correct. And update it in the SDRG and OpenCDISC report using 2014-12-19.
DT	NA	Minor	1	<p>The REXA-08 DT domain contains a missing value for the required SDTM variable SPDEVID (device id). This finding was queried and there is a valid reason that the field is blank. What the reason the Clinical Data Management has provided is:</p> <p>This was queried on May of this year (during re-review performed under PMI's supervision). Missing value is the New Device Serial Number for replacement of device 1245448. Sites had a</p>

				lot of missing values for device logs, and this is one of these cases. They reported a new device 12492819 on Device Events page, but this was not available in site's inventory log. Also all device numbers should be 7 digit rather than 8. Since they were not able to verify the number and provide correct new device number, they were queried to remove it from Device Events page (Inventory and Events pages should match). The query note was: "Please note that according to query response on device inventory page this serial number is incorrect and cannot be verified. In that case this field should be left blank."
DT	NA	Minor	1	REXA-08 DT domain reports the USUBJID when this data column should not have been included per SDTM IG. Keep this variable for validating and tracing records

**Appendix I: Inclusion/Exclusion Criteria**

<b>Protocol/ Amendment Version</b>	<b>Category</b>	<b>IETESTC D</b>	<b>Full Text of Criterion</b>
14 April 2014	INCLUSION	INC01	Subject has signed the ICF and is able to understand the information provided in the Subject Information Sheet and ICF.
14 April 2014	INCLUSION	INC02	Subject is at a minimum 22 years of age(inclusive).
14 April 2014	INCLUSION	INC03	Smoking, apparently healthy subject as judged by the Investigator based on all available assessments from the Screening period/Day of Admission (e.g., safety laboratory, spirometry, vital signs, physical examination, ECG, chest X-ray, and medical history).
14 April 2014	INCLUSION	INC04	Subject smokes at least 10 commercially available mCCs per day (no brand restrictions), for the last 4 weeks, based on self-reporting. Furthermore, the subject has been smoking for at least the last 3 consecutive years. The smoking status will be verified based on a urinary cotinine test (cotinine $\geq$ 200 ng/mL).
14 April 2014	INCLUSION	INC05	The subject does not plan to quit smoking within the next 6 months as assessed by the Prochaska 'Stage of Change' questionnaire.
14 April 2014	INCLUSION	INC06	The subject is ready to comply with study protocol (e.g. readiness to accept interruptions of smoking for up to 91 days and to use THS 2.2 Menthol *).
14 April 2014	EXCLUSION	EXC01	As per Investigator judgment, the subject cannot participate in the study for any reason (e.g., medical, psychiatric and/or social reason).
14 April 2014	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).

Protocol/ Amendment Version	Category	IETESTC D	Full Text of Criterion
14 April 2014	EXCLUSION	EXC03	The subject has clinically relevant diseases which required medications (including but not limited to gastrointestinal, renal, hepatic, neurological, hematological, endocrine, oncological, urological, immunological, pulmonary, and cardiovascular disease or any other medical condition (including safety laboratory as per CTCAE), which in the opinion of the Investigator would jeopardize the safety of the subject.
14 April 2014	EXCLUSION	EXC04	Subject who has forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) <0.7 and FEV1 <80% predicted value at post-bronchodilator spirometry (GOLD, 2013).
14 April 2014	EXCLUSION	EXC05	Subject with asthma condition (FEV1/FVC < 0.75 and reversibility in FEV1 > 12% (or > 200 mL) from pre to post-bronchodilator values).
14 April 2014	EXCLUSION	EXC06	Subjects with renal insufficiency as defined by serum creatinine levels of >1.3 mg/dL for females and >1.5 mg/dL for males.
14 April 2014	EXCLUSION	EXC07	The subject has a body mass index (BMI) <18.5 or $\geq 35$ kg/m <sup>2</sup> .
14 April 2014	EXCLUSION	EXC08	As per Investigator 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.
14 April 2014	EXCLUSION	EXC09	Any subject with an history of adverse events linked to caffeine or caffeine containing drugs (e.g., Vivarin), such as but not limited to hypersensitivity or allergy.
14 April 2014	EXCLUSION	EXC10	The subject has used nicotine-containing products other than commercially available mCC (either tobacco-based products or NRT), as well as electronic cigarettes and similar devices, within 4 weeks prior to assessment.
14 April 2014	EXCLUSION	EXC11	The subject has received medication (prescription or over-the-counter) within 14 days or within five 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	IETESTC D	Full Text of Criterion
14 April 2014	EXCLUSION	EXC12	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 if these can potentially interfere with the study objectives or subject's safety.
14 April 2014	EXCLUSION	EXC13	Concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) or acetylsalicylic acid.
14 April 2014	EXCLUSION	EXC14	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.
14 April 2014	EXCLUSION	EXC15	The subject has a positive urine drug test.
14 April 2014	EXCLUSION	EXC16	Positive serology test for human immunodeficiency virus (HIV)1/2, hepatitis B or hepatitis C.
14 April 2014	EXCLUSION	EXC17	Donation or receipt of whole blood or blood products within 3 months prior to Admission.
14 April 2014	EXCLUSION	EXC18	The subject is a current or former employee of the tobacco industry or of their first-degree relatives (parent, sibling, child).
14 April 2014	EXCLUSION	EXC19	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, and child).
14 April 2014	EXCLUSION	EXC20	The subject has participated in a clinical study within 3 months prior to the Screening Visit.
14 April 2014	EXCLUSION	EXC21	For women only: Subject is pregnant (does not have negative pregnancy tests at Screening and at Admission) or is breast feeding.
14 April 2014	EXCLUSION	EXC22	For women only : Subject does not agree to use an acceptable method of effective contraception*

## Appendix II: Conformance Issues Details

Per the sponsor's request, some permitted variables which are empty are included in the SDTM output. Below is a list of the empty permitted variables:

Permitted Variable	Domains
AESCONG	AE
AESDISAB	AE
AESDTH	AE
AESLIFE	AE
CODTC	CO
DXSTAT	DX
DXREASND	DX
EXREASND	EX
XTSCAT	XT

These filenotes below are to describe and summarize actions taken regarding post-lock use which have influence on the analysis.

### **REXA-08\_CDARO\_Filenote 3\_Final 1.0\_2015\_05\_29**

During a Covance review of the final QA'd data files provided by Celerion, many discrepancies related to the sample collection date were discovered relative to those already entered in the Rave database. A subsequent physical review of the sample collection containers held at the Celerion site revealed that many samples were incorrectly annotated by site (dates were hand-written on the tubes and were either incorrect per source notes or confirmed to have been updated after samples had been shipped). All samples were however pre-labelled with VISIT ID and these identifiers were confirmed to be correct and could therefore be used reliably as the source for reconciliation.

The correction of the discrepant sample collection dates within the Celerion system would require a substantial amount of time to implement due to the process that would have to be followed and as such the decision was made that they would not be amended.

As a result, the data from variable "PACTNUM" (Date of Collection) in the Celerion files will be discarded. Instead the VISIT ID in the Celerion data files will be matched to that in Rave database and the correct date of sample collection will be considered to be the Rave "date of visit" or "date of visit +1 day" (for samples collected at Day 91 only).

This change will be implemented programmatically at the SDTM data set level and is required for the following source datasets as received from Celerion:



BIOMA, BIOMB, BIOMC, BIOMD, BIOME, BIOMF, BIOMG, BIOMH, BIOMI, BIOMJ, BIOMK, BIOML, BIOMM, BIOMN, BIOMO, BIOMPU.

Datasets BIOM and BIOMU that were also received from Celerion are empty/null datasets that can be ignored

#### **REXA-08\_CDARO Filenote 4\_Final 1.0\_2015\_06\_22**

This file note describes and summarizes the actions taken, with respect to the data in the RAVE eCRF for Subject 1042 who withdrew their HIPAA Authorization, in writing to the Site, on 26-FEB-2014.

Per review of the audit trail in the RAVE eCRF, it was apparent that data had been entered and source verified within the subjects' eCRF after the withdrawal of HIPAA Authorization.

Further to discussion with Covance QA through Triage and the PMI management team, the following actions were agreed as a result of PMI's statement on the withdrawal of HIPAA Authorization; *no* subject data should be either entered [from the patient's source records] or SDV'd at Site after the date *that* Subject 1042 withdrew consent, even if the data had been acquired prior to that date. The exception being data related to adverse event follow-up.

1. All data entered by the Site into RAVE after withdrawal of HIPAA authorization that required access to patient's source records should not have been entered into the eCRF and must not be present in any downstream analysis, with the following specific exceptions:

- a. Adverse events and medications related to AEs – the subject specifically provided consent for AE follow up.
- b. End of Study and Withdrawal pages
- c. Pages integrated from vendor, as they are de-identified data and are loaded into RAVE without access to the patient's source records.
- d. Documented and agreed self-evident corrections that do not require access to the patient's source records.

2. All data that was entered prior to, but updated after withdrawal of HIPAA authorization (with exception of SEC) must be rolled-back to the values that were present in the system on 26-FEB-2014. It was accepted for Covance Data Management to query site to ask them to enter the appropriate specific value that was identified by audit trial review.

3. If the whole eCRF page was data entered after withdrawal of HIPAA authorization, such pages were inactivated by Covance Data Management to serve the purpose of such data not being available for extraction from the database.

4. It was decided that for all SDV (with the exception of several log lines on two pages) that was done after withdrawal of HIPAA authorization the data status would not be rolled-back to "un-SDV", however, no further SDV is allowed.

5. Due to missing SDV, pages could not be DM reviewed, frozen and signed by the PI prior to Locking the database. Covance Data Management will use the Medidata RWS-role that overrides these system requirements to lock the eCRF without SDV, DM review or PI signature being in place. It is a deviation from standard process to which both PMI and Covance agree for this Subject only.

6 . Due to missing SDV at the time of withdrawal of HIPAA authorization, all data for this subject that was not SDV'd would be excluded from the study datasets (SDTM) and therefore not included in the statistical analysis. The exceptions are the data covered by points 1a-d above.

#### **REXA-08\_CDARO\_Filenote 5\_Final 1.0\_2015\_07\_14**

Prior to locking the RAVE database, it was identified that the Celerion data for 5 subjects that were lost-to-follow-up was not correctly reported. The 5 subjects affected were: 1159, 1181, 1194, 1235 and 1252.

During the course of the study Celerion had been informed by Covance that the samples for these five subjects should not be analysed (based on the status of these subjects and Covance's interpretation of the protocol requirements) and so Celerion had reported according to those instructions.

For all of the 5 subjects, the 16 data files received from Celerion (and loaded into Rave correctly), had the following 2 data scenarios:

- A result present, but a comment saying "Analyzed in Error"
- No result present, with a comment saying "Analysis not Required"

Later, upon discussions between Covance, Celerion and PMI, it was determined that these results should have been reported and as such, Celerion was requested to update their data files.

- Report the results, where possible, and remove the comments
- For samples where results were not possible, the results were to remain blank and the comment to be updated from "Analysis not Required" to "Not Analyzed in Error".

Celerion unlocked their database, made the updates requested and the 16 updated data files were transferred to Covance to load into RAVE. Covance reviewed the updated files and confirmed that the changes had been made as required prior to loading the updated file into the RAVE database. The files were loaded into RAVE using Medidata Batch Uploader and the reconciliation reports run, checked and it was confirmed that the identified records had been updated. The actual data changes were not however further verified by manual review of the data in the RAVE database.

The RAVE database was subsequently locked on 23-JUN-2015 and then the post-lock data extract was taken and incorporated into the SDTM datasets. At this point the Covance SDTM programmers reported that for these 5 subjects, the comments were still present in the "Reason for Not Done" field, even though they were blank in the updated Celerion files.

Upon investigation by Covance Data Management, it was confirmed that although the Celerion files were correct and the reconciliation report identified that at the record level the changes had occurred, Batch Uploader had failed to execute certain data field updates; when the updated files contained entries that were blank values in the PCREASND field the RAVE database had not changed to blank. All other changes had been executed correctly.

This problem only affected the five subjects that were amended by Celerion in the last data transfer, but this still meant that 957 records were not identical in the Celerion files and the locked RAVE database.

To remediate the issue, the following programmatic change to the data must be done at the SDTM

level:

For the 16 Celerion datasets BIOMA, BIOMB, BIOMC, BIOMD, BIOME, BIOMF, BIOMG, BIOMH, BIOMI, BIOMJ, BIOMK, BIOML, BIOMM, BIOMN, BIOMO, BIOMPU and for Subjects 1159, 1181, 1194, 1235, 1252 if the result (PCORRES) is not missing (. or blank) then "Reason for Not Done" (PCREASND) must be blank.

By following the above instruction (logic), the Covance programmers will remove the 'NOT DONE' reason comments that should not be present, resulting in a match between the actual data result reported in the SDTMs and the final files received from Celerion.

#### **REXA-08\_CDARO\_Filenote 6\_Final 1.0\_2015\_07\_13**

During SDTM programming it was noted that two Protocol Deviations had incorrect (impossible) dates. The issue was raised to Covance CRA, Amy Rainey.

#### **REXA-08\_CDARO\_Filenote 7\_Final 1.0\_2015\_07\_24**

Data errors relating to protocol deviation start and stop dates were found post database lock. These data points have been verified by Covance Clinical Research Associates (CRAs)/ Monitors. It has been agreed between PMI and Covance that all of the erroneous dates will be present in the Rave data extract and the corrections will be hard coded by the SDTM programmer when creating the SDTM DV domain.

#### **REXA-08\_CDARO\_Filenote 7\_Final 2.0\_2015\_07\_27**

In the NTF: REXA-08\_CDARO\_Filenote 7\_Final 1.0\_2015\_07\_24.pdf, there are some incorrect date. So REXA-08\_CDARO\_Filenote 7\_Final 2.0\_2015\_07\_27.pdf is needed.

#### **8278008 CDARO NTF8 ePRO Final 1.0**

Purpose of this filenote is to describe and summarize actions taken regarding post-lock data change to questionnaire data.

During SDTM programming it was noticed that some questionnaires are present while they are not required per protocol:

1. For subject 2029 and 2285 mCEQ questionnaire was performed on visits from Day 1 to Day 6
2. mCEQ and QSU questionnaires were performed on Day 6

It was agreed between PMI and Covance that this data will be present in Rave data extract but will be removed at SDTM level.

#### **REXA-08\_CDARO\_Filenote 9\_Final 1.0\_2015\_07\_24**

Purpose of this filenote is to describe and summarize actions taken regarding post-lock use of data related to Inclusion/Exclusion criteria.

During TFL programming it was noticed that for subjects 1108 and 1109 Inclusion and Exclusion criteria are available in two data sets: IE\_I and IE\_I\_SF for Inclusion and also IE\_E and IE\_E\_SF for Exclusion. For both subjects their status changed during the study from incorrectly assigned Discontinued from Enrollment to Screen Failure.

It was agreed between PMI and Covance that all of this data will be present in Rave data extract, but only criteria from data sets corresponding to Screen Failures data (IE\_I\_SF and IE\_E\_SF) will be used.

Covance programmers will be required to hard code the exclusion of subject 1108 and 1109 when reporting data from the Criteria files IE\_I and IE\_E.

#### **REXA-08\_CDARO\_Filenote 10\_Final 1.0\_2015\_07\_30**

Data errors relating to incorrect start and end dates were found post database lock. These data points have been verified by Covance Clinical Research Associates (CRAs)/ Monitors. It has been agreed between PMI and Covance that all of the erroneous dates will be present in the Rave data extract and the corrections will be hard coded by the SDTM programmer when creating the SDTM SV, QS, LB/SUPPLB and XP domains.

#### **REXA-08\_CDARO\_Filenote 10\_Final 2.0\_2015\_07\_30**

In the NTF: REXA-08\_CDARO\_Filenote 10\_Final 1.0\_2015\_07\_30.pdf, there are some incorrect date. So REXA-08\_CDARO\_Filenote 10\_Final 2.0\_2015\_07\_30.pdf is needed.

#### **REXA-08\_CDARO\_Filenote 11\_Final 1.0\_2015\_07\_27**

The time for subject 2299's Day 5 Nicotine/Cotinine is 00:48 which is 29Apr2015. The date was incorrectly entered into the database as 28Apr2015. This error was identified and clarified post database lock. The data point has been verified by a Covance Clinical Research Associates (CRA)/ Monitor. It has been agreed between PMI and Covance that all of the erroneous date will be present in the Rave data extract and the correction will be hard coded by the SDTM programmer when creating the PK SDTM domain. The date/time value is read in from the raw data PCB\_NIC\_D5 and PCB\_COT\_D5.

#### **REXA-08\_CDARO\_Filenote 12\_Final 1.0\_2015\_07\_29**

This file note serves to retrospectively document the transition activities that took place following the PMI request to move the CDARO activities for this study from the Covance Early Clinical team to the Covance Late Stage team.

The transition activities between the two CDARO groups were not formally documented during the period in which they occurred, specifically the 3 month period from late May 2014 through to completion of the official handover of the database on 22-Aug-2014 (as communicated in email correspondence only).

During this transition period, various joint team meetings were held to share historic knowledge,

provide current status of the activities and train on the processes that the Early Clinical team had been following for the conduct of this study to date and/or other studies in this program previously.

All the functional groups met directly with their counterparts to discuss role specific requirements as well as all the functional groups being represented on the broader internal handover meetings covering the logistics of the transition (e.g. access to specific share drives, the database, timings for next steps).

Client Teleconferences were also attended by both the Early and Late Stage CDARO Project Managers (Alex Wilkinson and Jo Taylor respectively) during this period to ensure that there was maximum coverage in study support, with both teams giving and receiving updates directly with colleagues from Clinical and the Client.

Since the completion of the handover on 22-Aug-2014, discussion and email communication between the Early and Late Stage teams has continued as needed either directly between functional counterparts or in the team setting, facilitated by the CDARO Project Manager. This ongoing collaboration has ensured that any topics not covered up front in the transition process (as not known or not deemed relevant at that point in time) have been handled appropriately at the relevant point of the study life cycle.