

Study Data Reviewer's Guide

Philip Morris International
Study ZRHM-REXA-07-JP

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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-07-JP

Protocol Title: Reduced exposure study using THS 2.2 Menthol with 5 days in a confinement setting and 85 days in an ambulatory setting

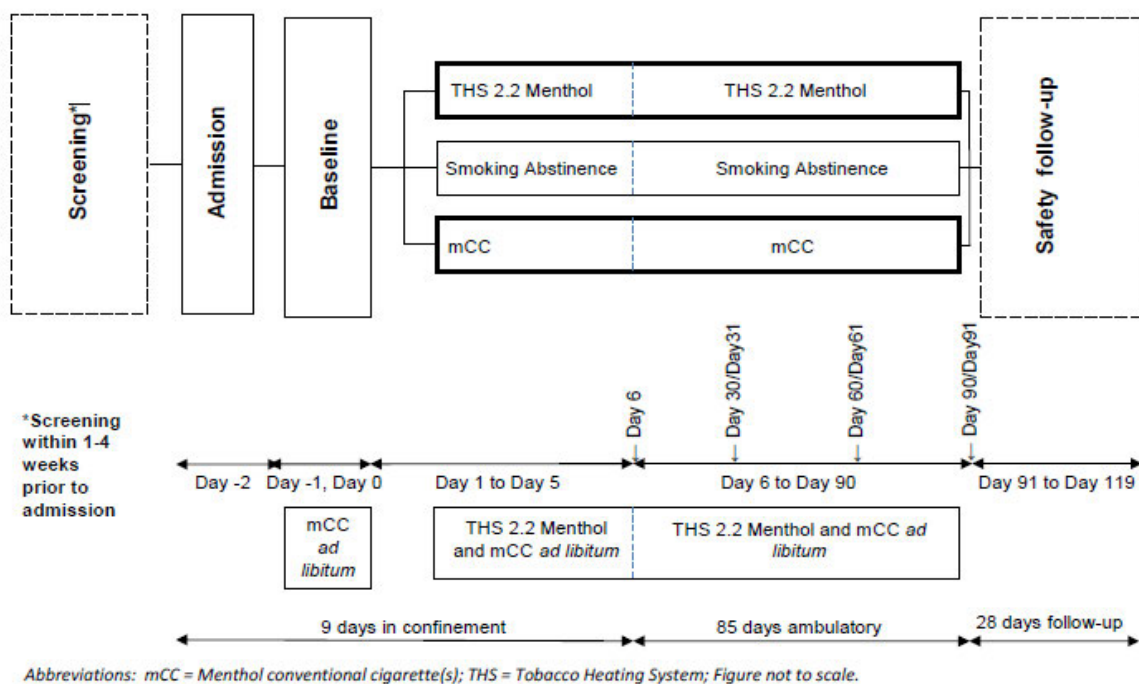
Protocol Versions: Final 3.0 (07 April 2014)

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 between 06:30 AM and 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 08:00 AM to 23:00 PM on Day 30, Day 60, and Day 90. Smoking/product use before 08:00 AM on Day 30, Day 60 and Day 90 are not restricted. On Day 31, Day 61, product use will be allowed from 06:30 AM onwards.

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

Dataset	Dataset Label
TV	Trial Visits
TI	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?

AE

CM

DM

DS

DV

FA

IE

SE

SV

LB

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, PE, CM, MH, XP and DE.

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.

<i>Domain</i>	<i>Datasets</i>	<i>Description</i>	<i>Class</i>	<i>Information captured</i>
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 - 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?
 - 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):
 - 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 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 (BU): In the LB, dates are all from sample taken data instead of external files

- Blood Sample time(BU): In the LB, dates are all from sample taken data instead of external files
- Urine Sample time(BU): In the LB, dates are all from sample taken data instead of external files
- The data of Lab_BU_CCLS form and Lab_BU Risk marker form are both 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
AE – Adverse Events		X		X	CM	Events
CM – Concomitant Medications		X		X	AE, MH	Interventions
CO - Comments			X			Special Purpose
DA – Drug Accountability			X	X		Findings
DE – Device Events		X		X	DT	Events
DI - Device Identifiers			X			Special Purpose Domains
DM – Demographics			X	X		Special Purpose Domains
DR - Device Subject Relationship			X			Special Purpose Domains
DS – Disposition			X	X		Events
DT - Device Tracking and Disposition			X		DE	Events
DV – Protocol Deviations			X	X		Events
DX – Device Exposure			X	X		Interventions
EG – ECG Test Results		X		X		Findings
EX – Exposure			X	X	FA	Interventions
FA – Findings About Events or Interventions			X	X	EX	Findings About

Dataset – Dataset Label	Efficacy	Safety	Other	SUPP-	Related Using RELREC	Observation Class
IE - Inclusion/Exclusion Criterion Not Met			X			Findings
LB – Laboratory Test Results		X		X		Findings
MH - Medical History		X			CM	Events
PC - pharmacokinetic Concentrations			X			Findings
PE – Physical Examination		X		X		Findings
PP – Pharmacokinetic Parameters			X			Findings
QS - Questionnaire		X				Findings
SE - Subject Elements			X			Special Purpose Domains
SU – Substance Use			X			Interventions
SV - Subject Visits			X			Special Purpose
VS – Vital Signs		X		X		Findings
XP – Pulmonary Function		X		X		Findings
XT – HST Assessments			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
AEACNP1	Action Taken with Study Product 1
AEEXPEC	AE Expectedness to Study Product 1
AERELSP	Relationship to Study Procedure
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
AENUM	AE Number
ATCCD1	ATCCD1
ATCCD2	ATCCD2
ATCCD3	ATCCD3
ATCCD4	ATCCD4
ATCTXT1	ATCTXT1
ATCTXT2	ATCTXT2
ATCTXT3	ATCTXT3
ATCTXT4	ATCTXT4
CMPTCD	Preferred Term Code
CMSYCD	Trade Name Code
CMSYN	Trade Name
MHNUM	Concomitant Disease Number
OTHER	Other

3.3.3. DA – Drug Accountability

The following variables have been mapped into SUPPDA

QNAM	Description
BEXPDTC	Batch Expiration Date
PCKRCVD	number of packs received

UNUSPKRT	Number of unused packs returned
UNUSSTRT	Number of unused sticks returned

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
AENUM	AE Number
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 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
DVSIG	Deviation Type
DVTIMEPT	Deviation Timepoint
EVALCAT	Evaluation Category
RESOL	Deviation Resolution
SOURCE	Deviation Source

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
MENTHOL CONVENTIONAL CIGARETTES	PRODUCT USE DIARY - PAPER

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
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	
URINALYSIS	24H URINE SAMPLE

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
BACTUB	Back Up Tubes
LB_FLG	Flag
LBCLSIG	Clinically Significant
LBCONC	Conventional Text Result
LBCONN	Conventional Numeric Result
LBCONRHI	Conventional Reference Range High
LBCONRLO	Conventional Reference Range Low

LBCONU	Conventional Reference Range Units
PRIMTUB	Primary tubes

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
TOBACCO HEATING SYSTEM 2.2	COTININE
TOBACCO HEATING SYSTEM 2.2	NICOTINE
CONVENTIONAL CIGARETTE	COTININE
CONVENTIONAL CIGARETTE	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
TOB_USE	PRODUCT USE DIARY - PAPER
NRT_USE	PRODUCT USE DIARY - PAPER

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
LUNG CAPACITY	WITHOUT SHORT ACTING BRONCHODILATOR
LUNG CAPACITY	WITH SHORT ACTING BRONCHODILATOR

The following variable has been mapped into SUPPXP

QNAM	Description
XPCLSIG	Clinically Significant

3.3.18. XT – HST Assessments

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

The following variables have been mapped into SUPPXT

QNAM	Description
ANALYDTC	Date of Analysis
ATMPCORR	Atm. Pressure Correction
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
RTDBTHD	RTD Base Threshold
RUNNUM	Run Numero
SMOKNB	Smoker Smoking Number
SMPLAQ	Sample Acquisition
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 table shows notable extensions to CDISC terminology for this study.

Domains	Variable (Codelist)	Value
CM	C66729	AURICULAR (OTIC)
CM	C66729	OTHER
CM	C71620	per filter
CM	C71620	BOLUS
CM	C71620	Capsule
CM	C71620	Not Applicable
CM	C71620	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	C66790	JAPANESE
DM	C66790	DISCHARGE
DM	C66790	DISCONTINUED FROM ENROLLMENT
DM	C66790	INFORMED CONSENT OBTAINED
DM	C66790	RANDOMIZED
DM	C66790	PROTOCOL VIOLATION
DT	C112037	COLLECTION
DT	C112037	DISTRIBUTION
DT	C112037	REPLACED
DX	C71620	STICK
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	C101832	WILLABL
FA	C101833	Number of Sticks
FA	C101833	ISO Nicotine Yield
FA	C101833	ISO Tar Yield
FA	C101833	Plan to Quit Smoking Next 3 Months
FA	C101833	Smoke for at Least 3 Consecutive Years
FA	C101833	Cigarettes per Day Last 4 Weeks
FA	C101833	Smoke Menthol Cigarettes Last 4 Weeks
FA	C101833	Nicotine-Containing Products
FA	C101833	Was the THS 2.2M Product Trial Performed
FA	C101833	Willing to Use the Product
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-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	Follical Stimulating Hormone
LB	C67154	Monohydroxybutenyl Mercapturic Acid

LB	C67154	Nicotine-Glucuronide
LB	C67154	O-Toluidine
LB	C67154	Paraxanthine
LB	C67154	Pregnancy Test
LB	C67154	S-Benzylmercapturic Acid
LB	C67154	Intercellular Adhesion Molecule 1
LB	C67154	3-hydroxypropylmercapturic Acid
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	C65047	_1_NA
LB	C65047	_1_OHP
LB	C65047	_2_NA
LB	C65047	_3_HPMA
LB	C65047	_4_ABP
LB	C65047	AMES
LB	C65047	BIOBANK
LB	C65047	CEMA
LB	C65047	CO
LB	C65047	COTG
LB	C65047	FCOT
LB	C65047	FNIC
LB	C65047	FTRANSY
LB	C65047	HEMA
LB	C65047	HMPMA
LB	C65047	LBALL

LB	C65047	MHBMA
LB	C65047	NICG
LB	C65047	NNAL
LB	C65047	O_TOL
LB	C65047	PREGTEST
LB	C65047	PX
LB	C65047	S_BMA
LB	C65047	S_PMA
LB	C65047	ICAM1
LB	C65047	_BAP
LB	C65047	TRANS3H
LB	C65047	TRANSHYG
LB	C65047	TRANS3H
LB	C65047	TRANSHYG
LB	C65047	UVOL
LB	C85492	LC-MS/MS
LB	C85492	SPECTROPHOTOMETRIC
LB	C85492	BREATH TEST
LB	C78733	INVALID/FIBRIN CLOTS
LB	C78733	MICROCLOTS
LB	C78733	HEMOLYSIS
LB	C78733	SPECIMEN RECEIVED BEYOND STABILITY
LB	C78733	NO SPECIMEN RECEIVED
LB	C78733	GROUP ORDERED TO COMPLETE VISIT REQUIREMENTS
LB	C71620	10 ⁴ /UI
LB	C71620	10 ⁶ /UI
LB	C71620	fg/MI
LB	C71620	GI/L
LB	C71620	mg/filter

LB	C71620	mg/Ml
LB	C71620	ng/Ml
LB	C71620	pg/Ml
LB	C71620	REV/Ml
LB	C71620	T/L
PP	C85493	Average Conc
SE	C99079	ADMI
SE	C99079	BASELINE
SE	C99079	FOLLOWUP
SE	C99079	PRODUCT USE AMBULATORY
SE	C99079	PRODUCT USE CONFINEMENT
SU	C71620	GUM
XP	C85492	SPIROMETRY
XT	C85492	SNF
XT	C78735	ANTHONY BRUCHET
XT	C85492	TOPOGRAPHY
XT	C85492	UV
XT	C78735	THIERRY BACHMANN
XT	C78735	VALERIE POUX
XT	C78734	TOBACCO PLUG
XT	C78734	mJ
XT	C78734	mL/sec
XT	C78734	mmWG
XT	C78734	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 2014-12-19 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	DR and DI are unrecognized domain. Because DR/DI are not recognized by OpenCDISC.
ALL	Variable length is too long for actual data.	Error	1	Reduction to the length were not done for 07.
AE	AEENDTC date is after RFPENDTC	Error	1	RFPENDTC is the end of study date from raw

				for treatment subject and screen failed date for screen failed subject.
AE	SDTM Expected variable not found	Warning	1	Follow the spec, action information stored in suppaе.АЕACNP1
AE	No Treatment Emergent info for Adverse Event	Warning	2	When SUPPAE.AETRTEM = 'N', delete these records in the SUPPAE according to the PMI comments.
CM	Value for CMDOSU not found in (Unit) user-defined codelist	Error	1	'CAPSULE' is not in the UNIT codelist, follow the spec.
CO	Variable appears in dataset, but is not in SDTM standard	Error	1	Follow the spec
CO	Inappropriate usage of variables in CO domain	Warning	5527	Follow the spec
DA	Variable is in wrong order within domain	Warning	1	Follow the spec
DA	Duplicate records	Warning	28	DAGRPID is different.
DE	Value for VISIT not found in (VISIT) user-defined codelist	Error	7	UNSCHEDULED 160.01 and UNSCHEDULED 160.02 are not in the codelist VISIT
DE	Value for VISITNUM not found in (VISITCD) user-defined codelist	Error	7	160.01 and 160.02 are not in the codelist VISITCD
DE	Variable appears in dataset, but is not in SDTM standard	Error	2	Be consistent with SPEC, adding SPDEVID/DEACNDEV to DE.
DE	DEENDTC date is after RFPENDTC	Error	5	RFPENDTC is the end of study date from raw for treatment subject and screen failed date for screen failed subject.
DE	Duplicate records	Warning	22	DESPID is different.

DM	No records for 'SCRFAIL' subject are found in IE domain	Warning	135	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.
DS	DSCAT is not 'DISPOSITION EVENT', when EPOCH is provided	Warning	405	It is 'OTHER EVENT'
DS	Duplicate records	Warning	201	DSTERM is different.
DT	Value for VISIT not found in (VISIT) user-defined codelist	Error	18	UNSCHEDULED 160.01 and UNSCHEDULED 160.02 are not in the codelist VISIT
DT	Value for VISITNUM not found in (VISITCD) user-defined codelist	Error	18	160.01 and 160.02 are not in the codelist VISITCD
DT	Variable appears in dataset, but is not in SDTM standard	Error	3	Follow the spec and add SPDEVID/DTPARTY/DTPRTYID
DT	DTSTDTC date is after RFPENDTC	Error	3	RFPENDTC is the end of study date from raw for treatment subject and screen failed date for screen failed subject.
DT	Duplicate records	Warning	243	DTSPID is different.
DV	DVSTDTC date is after RFPENDTC	Error	30	RFPENDTC is the end of study date from raw for treatment subject and screen failed date for screen failed subject.
DV	DVENDTC date is after RFPENDTC	Error	423	RFPENDTC is the end of study date from raw for treatment subject and screen failed date for screen failed subject.
DV	USUBJID/VISIT/VISITNUM values do not match SV domain data	Warning	1	Assign VISIT='DAY 6/DISCHARGE CONFINEMENT' when

				PDVIS='DISCHARGE', and source.PD derived DV is not used to derive SV.
DV	High risk of truncated value for DVTERM variable	Warning	2	DVTERM is not truncated and the length is 200.
DV	Duplicate records	Warning	69	DVSPID is different.
DX	Value for DXSCAT not found in (DXSCAT) user-defined codelist	Error	7326	The value in codelist are 'PRODUCT USE DIARY-ELECTRONIC' and 'PRODUCT USE DIARY- PAPER' while in data are 'PRODUCT USE DIARY - ELECTRONIC' and 'PRODUCT USE DIARY - PAPER'
EG	Missing value for EGREASND, when EGSTAT is 'NOT DONE'	Warning	2	Assigned "NOT DONE" when EGORRES was blank
EX	Value for EXSCAT not found in (EXSCAT) user-defined codelist	Error	14991	The value in codelist are 'PRODUCT USE DIARY-ELECTRONIC' and 'PRODUCT USE DIARY- PAPER' while in data are 'PRODUCT USE DIARY - ELECTRONIC' and 'PRODUCT USE DIARY - PAPER'
EX	EXSTDTC date is after RFXENDTC	Error	14420	RFPENDTC is the end of study date from raw for treatment subject and screen failed date for screen failed subject.
EX	EXENDTC date is after RFXENDTC	Error	14420	RFPENDTC is the end of study date from raw for treatment subject and screen failed date for screen failed subject.
EX	EX record is present, when subject is not assigned to an arm	Warning	201	CT version is 20141229, the latest version in opencdisc1.5 is 20150328
EX	Variable not recommended for use	Warning	2	Follow the spec and add 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.
FA	Variable is in wrong order within domain	Warning	1	Follow the spec
IE	Value for IETEST not found in (IETEST) user-defined codelist	Error	49	The value in codlist is 'Current smoker, who has smoked at least 10 menthol mCCs per day for 4 weeks with a yield of 1 mg nicotine ISO/mCC per cigarette, and has smoked for the past 3 years. Status verified with cotinine test.', while in data is 'Current smoker, who has smoked at least 10 menthol mCCs per day for 4 weeks with a yield of 1 mg nicotine ISO/mCC per cigarette, and has smoked for the past 3 years. Status verified with cotinine test'
LB	Inconsistent value for Standard Units	Error	1036	When LBTESTCD = 'MCHC', LBCAT = 'HAEMATOLOGY', LBSTRESU has two values "g/dL" and "%".
LB	Missing value for LBORRESU, when LBORRES is provided	Warning	84	Protein no need unit.
LB	Duplicate records	Warning	1	LBORRES is different
LB	Missing value for LBREASND, when LBSTAT is 'NOT DONE'	Warning	14	Assigned "NOT DONE" when EGORRES was blank
MH	Value for MHSOC not found in MedDRA dictionary	Error	10	The length too short and caused truncation.
PE	Duplicate records	Warning	5128	PESPID is different.

PE	Missing value for PEREASND, when PESTAT is 'NOT DONE'	Warning	37	Assigned "NOT DONE" when PEORRES was blank
QS	Value for QSCAT not found in (QSCAT) user-defined codelist	Error	231	QSCAT='PRODUCT PREFERENCE' in data not appeared in codelist QSCAT
SE	SDTM/dataset variable label mismatch	Warning	2	Follow the spec
SE	Variable is in wrong order within domain	Warning	2	Be consistent with SPEC but the order of SESTDY/SEENDY are not from CDISC.
SU	Missing value for SUDOSU, when SUDOSE, SUDOSTXT or SUDOSTOT is provided	Error	104923	There is no unit for CHWSMKLS
SU	Value for SUSCAT not found in (SUSCAT) user-defined codelist	Error	164879	SAME WITH EX AND DX
SU	Redundancy in paired variables values	Warning	584	SUCAT=SUTRT=CAFFEINE, follow the crf
SV	Value for VISIT not found in (VISIT) user-defined codelist	Error	11	UNSCHEDULED 160.01 and UNSCHEDULED 160.02 are not in the codelist VISIT
SV	Value for VISITNUM not found in (VISITCD) user-defined codelist	Error	11	160.01 and 160.02 are not in the codelist VISITCD
SV	SVSTDTC date is after RFPENDTC	Error	2	RFPENDTC is the end of study date from raw for treatment subject and screen failed date for screen failed subject.
SV	SVENDTC date is after RFPENDTC	Error	2	RFPENDTC is the end of study date from raw for treatment subject and screen failed date for screen failed subject.
TI	Value for IETEST not found in (IETEST) user-defined codelist	Error	1	The value in codlist is 'Current smoker, who has smoked at least 10 menthol mCCs per day for 4

				weeks with a yield of 1 mg nicotine ISO/mCC per cigarette, and has smoked for the past 3 years. Status verified with cotinine test.', while indata is 'Current smoker, who has smoked at least 10 menthol mCCs per day for 4 weeks with a yield of 1 mg nicotine ISO/mCC per cigarette, and has smoked for the past 3 years. Status verified with cotinine test'
TS	SDTM/dataset variable label mismatch	Warning	1	Follow the spec
XT	Value for XTREASND not found in (XTREAS) user-defined codelist	Error	49	The value in codelist is 'TOBACCO PLUG DESTROYED, ANALYSIS IMPOSSIBLE' while in data is 'TOBACCO PLUG DESTROYED, ANALYSIS IMPOSSIBLE'
XT	Missing value for XTORRESU, when XTORRES is provided	Warning	145885	When XTTESTCD = 'ABUVTABS', there is no unit.
XT	Missing value for XTSTRESU, when XTSTRESC is provided	Warning	145885	When XTTESTCD = 'ABUVTABS', there is no unit.
XT	Duplicate records	Warning	1088237	XTSPID is different.

4.3 Additional Conformance Details

Dataset	Diagnostic Message	Severity	Count	Explanation
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	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

Protocol/ Amendment Version	Category	IETESTCD	Full Text of Criterion
07 April 2014	INCLUSION	INC01	Subject has signed the ICF and is able to understand the information provided in the Subject Information Sheet and ICF.
07 April 2014	INCLUSION	INC02	Subject is aged from 23 to 65 years (inclusive).
07 April 2014	INCLUSION	INC03	Subject is Japanese.
07 April 2014	INCLUSION	INC04	Smoking, healthy subject as judged by the Investigator based on all available assessments from the Screening period/day of Admission (e.g. safety laboratory, spirometry [FEV1/FVC >0.7 at post-bronchodilator spirometry, post-bronchodilator FEV1 >80% predicted value, and post-bronchodilator FVC >80% predicted value], vital signs, physical examination, ECG, chest X-ray and medical history).
07 April 2014	INCLUSION	INC05	Subject smokes at least 10 commercially available menthol mCCs per day (no brand restrictions) with a maximum yield of 1 mg nicotine ISO/mCC, as labelled on the cigarette package, for the last 4 weeks, based on self-reporting. Furthermore, the subject has been smoking for at least the last three consecutive years. The smoking status will be verified based on a urinary cotinine test (cotinine \geq 200 ng/mL).
07 April 2014	INCLUSION	INC06	The subject does not plan to quit smoking in the next 3 months.
07 April 2014	INCLUSION	INC07	The subject is ready to accept interruptions of smoking for up to 90 days.
07 April 2014	INCLUSION	INC08	The subject is ready to accept using the THS 2.2 Menthol.

Protocol/ Amendment Version	Category	IETESTCD	Full Text of Criterion
07 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).
07 April 2014	EXCLUSION	EXC02	A subject who is legally incompetent, physically or mentally incapable of giving consent (e.g. emergency situation, under guardianship, prisoners or subjects who are involuntarily incarcerated).
07 April 2014	EXCLUSION	EXC03	The subject has 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.
07 April 2014	EXCLUSION	EXC04	The subject has a body mass index (BMI) <18.5 or ≥ 32 kg/m ² .
07 April 2014	EXCLUSION	EXC05	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.
07 April 2014	EXCLUSION	EXC06	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.
07 April 2014	EXCLUSION	EXC07	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	IETESTCD	Full Text of Criterion
07 April 2014	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 if these can potentially interfere with the study objectives or subject's safety.
07 April 2014	EXCLUSION	EXC09	Concomitant use of NSAIDs or acetylsalicylic acid.
07 April 2014	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.
07 April 2014	EXCLUSION	EXC11	The subject has a positive urine drug test.
07 April 2014	EXCLUSION	EXC12	Positive serology test for HIV1/2, hepatitis B or hepatitis C.
07 April 2014	EXCLUSION	EXC13	Donation or receipt of whole blood or blood products within 3 months prior to Admission.
07 April 2014	EXCLUSION	EXC14	The subject is a current or former employee of the tobacco industry or of their first-degree relatives (parent, sibling, child).
07 April 2014	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, child).
07 April 2014	EXCLUSION	EXC16	The subject has participated in a clinical study within 3 months prior to the Screening Visit.
07 April 2014	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).
07 April 2014	EXCLUSION	EXC18	For women only: Subject is pregnant (does not have negative pregnancy tests at Screening and at Admission) or is breast feeding.

Protocol/ Amendment Version	Category	IETESTCD	Full Text of Criterion
07 April 2014	EXCLUSION	EXC19	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-07_CDARO Filenote 3_Final 1.0_2014_10_01

Due to an inconsistency between formats of the supplementary comment field in RAVE and the vendor system, a "Test Not Performed" comment for subject 49 at SEI site is truncated during the import process to RAVE.

The original comment in the vendor file is:

Test could not be performed by clumps of platelets.

This comment is 51 characters long.

In RAVE, the length of this field has been set up to contain a maximum of 40 characters, therefore rather than amend the database via migration at this stage in the study, we plan to programmatically replace the original comment with shortened text that keeps the original meaning.

The new comment will read:

Not performed by clumps of platelets.

REXA-07_CDARO Filenote 4_Final 1.0_2014_10_09

Due to different coding used by the vendor system and Rave, files received from Celerion cannot be processed by Rave Batch Uploader. To facilitate loading the data into Rave, a change in coding is required and can be done outside the vendor system, before integration with Rave. For the files to be properly uploaded into Rave, the following actions will be taken:

1. Merging numerous vendor data files into just two – one for blood and one for urine analysis (as specified in DTA document) with an exception for BIOMK file containing Ames records which will be delivered from Celerion to Covance later.
2. SiteID will be set to "TOK".
3. Blank rows and blank columns will be removed
4. Visit "Early Termination" will be recoded to "DISCHARGE_1"
5. Visit "DAY91" will be recoded to "DAY90"
6. Blank space will be removed from Visit records and record will be changed to uppercase, for example "Day 1" will be recoded to "DAY1".

Changes to the source files received from Celerion will be done using R software version 3.0.3.

The following code will be used (timestamps of the file may differ for final program run):

```
# Reading files sent from vendor

BIOMA <- read.csv("1:/8278007/Pharmacometrics/Datafiles/Batch Upload/Celerion/QA-ZRHM-REXA-07-
JP_PROD_CELERION_BIOMA_FULL_2014OCT03140000.csv", sep="|", strip.white=TRUE,
colClasses=("character"))

BIOMB <- read.csv("1:/8278007/Pharmacometrics/Datafiles/Batch Upload/Celerion/QA-ZRHM-REXA-07-
JP_PROD_CELERION_BIOMB_FULL_2014SEP25150000.csv", sep="|", strip.white=TRUE,
colClasses=("character"))

BIOMC <- read.csv("1:/8278007/Pharmacometrics/Datafiles/Batch Upload/Celerion/QA-ZRHM-REXA-07-
JP_PROD_CELERION_BIOMC_FULL_2014SEP26130000.csv", sep="|", strip.white=TRUE,
colClasses=("character"))

BIOMD <- read.csv("1:/8278007/Pharmacometrics/Datafiles/Batch Upload/Celerion/QA-ZRHM-REXA-07-
JP_PROD_CELERION_BIOMD_FULL_2014SEP26110000.csv", sep="|", strip.white=TRUE,
colClasses=("character"))

BIOME <- read.csv("1:/8278007/Pharmacometrics/Datafiles/Batch Upload/Celerion/QA-ZRHM-REXA-07-
JP_PROD_CELERION_BIOME_FULL_2014SEP26130000.csv", sep="|", strip.white=TRUE,
colClasses=("character"))

BIOMF <- read.csv("1:/8278007/Pharmacometrics/Datafiles/Batch Upload/Celerion/QA-ZRHM-REXA-07-
JP_PROD_CELERION_BIOMF_FULL_2014OCT03140000.csv", sep="|", strip.white=TRUE,
colClasses=("character"))

BIOMG <- read.csv("1:/8278007/Pharmacometrics/Datafiles/Batch Upload/Celerion/QA-ZRHM-REXA-07-
JP_PROD_CELERION_BIOMG_FULL_2014SEP25130000.csv", sep="|", strip.white=TRUE,
colClasses=("character"))
```

```

BIOMH <- read.csv("1:/8278007/Pharmacometrics/Datafiles/Batch Upload/Celerion/QA-ZRHM-REXA-07-
JP_PROD_CELERION_BIOMH_FULL_2014SEP26140000.csv", sep="|", strip.white=TRUE,
colClasses=("character"))

BIOMI <- read.csv("1:/8278007/Pharmacometrics/Datafiles/Batch Upload/Celerion/QA-ZRHM-REXA-07-
JP_PROD_CELERION_BIOMI_FULL_2014SEP25170000.csv", sep="|", strip.white=TRUE,
colClasses=("character"))

BIOMJ <- read.csv("1:/8278007/Pharmacometrics/Datafiles/Batch Upload/Celerion/QA-ZRHM-REXA-07-
JP_PROD_CELERION_BIOMJ_FULL_2014SEP29080000.csv", sep="|", strip.white=TRUE,
colClasses=("character"))

# BIOMK not included

# BIOMK <- read.csv("1:/8278007/Pharmacometrics/Datafiles/Batch Upload/Celerion/TEST-ZRHM-REXA-
07-JP_PROD_CELERION_BIOMK_FULL_2014SEP15110000.csv", sep="|", strip.white=TRUE,
colClasses=("character"))

BIOML <- read.csv("1:/8278007/Pharmacometrics/Datafiles/Batch Upload/Celerion/QA-ZRHM-REXA-07-
JP_PROD_CELERION_BIOML_FULL_2014SEP26150000.csv", sep="|", strip.white=TRUE,
colClasses=("character"))

BIOMM <- read.csv("1:/8278007/Pharmacometrics/Datafiles/Batch Upload/Celerion/QA-ZRHM-REXA-07-
JP_PROD_CELERION_BIOMM_FULL_2014SEP26160000.csv", sep="|", strip.white=TRUE,
colClasses=("character"))

BIOMN <- read.csv("1:/8278007/Pharmacometrics/Datafiles/Batch Upload/Celerion/QA-ZRHM-REXA-07-
JP_PROD_CELERION_BIOMN_FULL_2014OCT03140000.csv", sep="|", strip.white=TRUE,
colClasses=("character"))

BIOMO <- read.csv("1:/8278007/Pharmacometrics/Datafiles/Batch Upload/Celerion/QA-ZRHM-REXA-07-
JP_PROD_CELERION_BIOMO_FULL_2014SEP29080000.csv", sep="|", strip.white=TRUE,
colClasses=("character"))

# Merging files for blood analysis

BLOOD <- rbind(BIOMA,BIOMG)

# Keeping only relevant columns in BIOMO, removing blank column

BIOMO <-
BIOMO[c("STUDYID","USUBJID","PCREFID","PCTEST","PCSPEC","PCORRES","PCORRESU","PCSTAT","PCREASND",
"PCMETHOD","PCLOQ","PCTPTNUM","PCVSTNUM","STUDYNM","PCACTNUM","SITEID","PCTPMNUM","PCTPSNUM","PCT
PENUM","VISIT")]

# Merging files for urine analysis

URINE <- rbind(BIOMB,BIOMC,BIOMD,BIOME,BIOMF,BIOMH,BIOMI,BIOMJ,BIOML,BIOMM,BIOMN,BIOMO)

# Removing empty rows

BLOOD <- BLOOD[!BLOOD$STUDYID=="",]
URINE <- URINE[!URINE$STUDYID=="",]

# Changing SiteID to TOK

BLOOD$SITEID <- "TOK"
URINE$SITEID <- "TOK"

```



```
# Changing Early Termination to DISCHARGE_1
BLOOD$VISIT <- ifelse(BLOOD$VISIT=="ET",paste("DISCHARGE_1"),paste(BLOOD$VISIT))
URINE$VISIT <- ifelse(URINE$VISIT=="ET",paste("DISCHARGE_1"),paste(URINE$VISIT))

# Changing DAY91 to DAY90
BLOOD$VISIT <- ifelse(BLOOD$VISIT=="DAY91",paste("DAY90"),paste(BLOOD$VISIT))
URINE$VISIT <- ifelse(URINE$VISIT=="DAY91",paste("DAY90"),paste(URINE$VISIT))

# Removing blanks from Visit and changing it to UPPERCASE
BLOOD$VISIT <- toupper(gsub(" ","",BLOOD$VISIT))
URINE$VISIT <- toupper(gsub(" ","",URINE$VISIT))

# Saving files
write.table(BLOOD, file="1:/8278007/Pharmacometrics/Datafiles/Batch Upload/Celerion/ZRHM-REXA-07-
JP_PROD_CELERION_BIOM_XXXX_2014OCT08013100.csv", sep="|", row.names=FALSE, quote=FALSE)
write.table(URINE, file="1:/8278007/Pharmacometrics/Datafiles/Batch Upload/Celerion/ZRHM-REXA-07-
JP_PROD_CELERION_BIOMU_XXXX_2014OCT08013100.csv", sep="|", row.names=FALSE, quote=FALSE)
```

REXA-07_CDARO Filenote 5_Final 1.0_2014_10_28

1. In order to maintain consistency with previous studies, the test named “HBMA” (as transferred to Covance in the BIOMU dataset from Celerion) will be renamed to “HMPMA” in the study SDTM datasets.
2. In the Spirometry form in the eCRF, the data fields for “Bronchodilator Name”, “Dose” and “Unit” were free-text fields (PT dataset). It was confirmed by the CRA that all devices used in the study are SULTANOL INHALERS with a dose of either 100ug or 200ug (microgram). Therefore the following changes will be made:
 - 2.1. For the field “Bronchodilator Name” (PTBD) values SULTANOL, SALTANOL INHALER, SALUTANOL INHALER, SOLTANOL INHALER and SULTANOL INHALER 100MG will be replaced by SULTANOL INHALER.
 - 2.2. The field “Dose” (PTDOSE) will only include numerical values.
 - 2.3. The field “Unit” (PTDOSEU) will have UG as the unit if PTDOSE is not missing.
 - 2.4. The P.I. signatures below confirm that the changes outlined in point 2 are true representations of the data recorded in source documentation for their respective sites.

SEI Site, P.I. Signature:_____ Date:_____

TOK Site, P.I. Signature:_____ Date:_____

REXA-07_CDARO Filenote 6_Final 1.0_2014_10_31

Due to site data completion errors on the Laboratory Requisition Forms (as confirmed subsequently via data queries) and also due to different coding used by the vendor system and Rave, the data received from Celerion contains errors in visit dates and visit names for several subjects. To have correct data loaded in Rave, a change in coding is required and can be done outside the vendor system, before integration with Rave. For the files to contain corrected data, the following actions will be taken:

For Celerion "BIOM" file:

1. For SubjectID 30, Visit "DAY6" will be recoded to "BASELINE"
2. For SubjectID 36, Visit "DAY5" date will be changed from "2013-Sep-11" to "2013-Sep-12"
3. For SubjectID 259, Visit "DAY60" date will be changed from "2014-Mar-23" to "2014-Mar-25"
4. For SubjectID 121, Visit "DAY6" date will be changed from "2013-Nov-14" to "2013-Oct-17"
5. For SubjectID 168, Visit "DAY6" will be recoded to "DISCHARGE"
6. For SubjectID 64, Visit "DAY6" will be recoded to "DISCHARGE"
7. For all the following SubjectID: 205, 207, 214, 216, 227, 228, 229, 233, 237, 238, 240, 241, 242, 245, 246, 248, 250, 254, 259, 266, 269, 272, 273, 278, 279, 283, 287 and 292, Visit "DAY90", for PCTEST="Cot" and PCTEST="tHCot" and PCTPENUM="91" date will be changed from "2014-Apr-24" to "2014-Apr-25"

For Celerion "BIOMU" file:

1. For SubjectID 36, Visit "DAY5" date will be changed from "2013-Sep-11" to "2013-Sep-12"
2. For SubjectID 259, Visit "DAY60" date will be changed from "2014-Mar-23" to "2014-Mar-25"
3. For SubjectID 81, Visit "BASELINE" date will be changed from "2013-Sep-09" to "2013-Sep-20"

All subject numbers referred to above are from the Tokyo Heart Centre site (TOK).

REXA-07_CDARO Filenote 7_Final 1.0_2014_11_07

The Data Management Plan (DMP), version Final 3.0, dated 06NOV14, only covers the Protocol Deviations recorded by the CRA in the Site Protocol Deviation Form (N.B. - this is not part of the CRF – it is a separate site level form in the database).

At the point of locking the database, only the protocol deviations identified through this mechanism have been reviewed and categorized.

During the Data Review held on 28-OCT-2014 it was determined that in order to identify all of the protocol deviations systematically;

- Additional protocol deviations will be programmatically identified and categorized during the ADaM programming using the SDTM data. All rules will be defined in the ADaM Specification including the Deviation Type; Category; and Evaluability.
- Rules to define the protocol deviations are in the study Protocol – and therefore to ensure that all protocol deviations are in accordance with the protocol each rule will reference the corresponding section of the protocol.
- Because the Systematic Protocol Deviations are being programmed after lock, Subjects with Non-Evaluable Protocol Deviations will be excluded from the PP Population in addition to the subjects being excluded per the CRA reported protocol deviations.

REXA-07_CDARO Filenote 8_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".

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

BIOM and BIOMU.

REXA-07_CDARO Filenote 9_Final 1.0_2015_06_03

During programming of the SDTM data sets for the study, which has taken place post-database lock, two instances of incorrect visit dates were observed in the locked data.

1) For subject TOK-0190, there is a visit date entered as 20 OCT 2010 which is clearly incorrect based on the time period that the study was conducted.

The incorrect date is found within the CRF raw data file WH, which contains the vital signs. Further identifiers are copied below:

PROJECT	SUBJECT	SITENUMBER	FOLDERNAME	VSSTAT_WH	VSDAT_RAW
ZRHM-REXA-07-JP	0190	TOK	Admission (Day -2)	Yes	20 OCT 2010

The correct date has been confirmed as 20 OCT 2013 and will be amended programmatically (hard-coded) within the SDTM datasets.

2) For subject TOK-0012, there is a visit date entered as 11 AUG 2013 for the Day 4 visit which is clearly incorrect based on the sequence of visits and dates for this subject as shown in full below:

PROJECT	SUBJECT	SITENUMBER	FOLDER	PCBDAT_RAW	PCBTIM
ZRHM-REXA-07-JP	0012	TOK	DAY0	07 SEP 2013	20:21
ZRHM-REXA-07-JP	0012	TOK	DAY1	08 SEP 2013	20:26
ZRHM-REXA-07-JP	0012	TOK	DAY2	9 SEP 2013	20:27
ZRHM-REXA-07-JP	0012	TOK	DAY3	10 SEP 2013	20:27
ZRHM-REXA-07-JP	0012	TOK	DAY4	11 SEP 2013	20:29
ZRHM-REXA-07-JP	0012	TOK	DAY5	12 SEP 2013	6:42
ZRHM-REXA-07-JP	0012	TOK	DAY6	13 SEP 2013	2:42
ZRHM-REXA-07-JP	0012	TOK	DAY6	13 SEP 2013	6:42
ZRHM-REXA-07-JP	0012	TOK	DAY30	04 OCT 2013	10:34
ZRHM-REXA-07-JP	0012	TOK	DAY60	05 NOV 2013	10:18
ZRHM-REXA-07-JP	0012	TOK	DAY90	05 DEC 2013	10:15

The incorrect date is found within the raw PCB_COT data file. The correct date has been confirmed as 11 SEP 2013 and will be amended programmatically (hard-coded) within the SDTM datasets.

REXA-07_CDARO Filenote 10_Final 1.0_2015_06_16

During programming of the SDTM data sets for the study, which has taken place post-database lock, further instances of incorrect visit dates were observed in the locked data (subsequent to the finalisation of file note CDARO 9).

The details are copied below:

usubjid	visit	visitnum	ds	datevar	Incorrect Raw Data Value	Correct Data Value to Hard Code
ZRHM-REXA-07-JP-TOK-0094	DAY 30	130	PC	PCDTC	PCB_COT.pcbdat_raw : 07 OCT 2013	07 NOV 2013
ZRHM-REXA-07-JP-TOK-0094	DAY 30	130	SV	SVSTDTC	PCB_COT.pcbdat_raw : 07 OCT 2013	07 NOV 2013
ZRHM-REXA-07-JP-	DAY 90	190	QS	QSDTC	QS_COUGH_PAPER.qsdat_raw: 10 JAN	10 JAN 2014

TOK-0111					2013	
ZRHM-REXA-07-JP-TOK-0111	DAY 90	190	SV	SVSTDTC	QS_COUGH_PAPER. qsdats_raw: 10 JAN 2013	10 JAN 2014
ZRHM-REXA-07-JP-TOK-0037	DAY 5	105	SV	SVSTDTC	PCB_COT.pcbdat_raw : 12 AUG 2013	12 SEP 2013

The incorrect date is shown under the column entitled “Incorrect Raw Data Value” and these dates will be replaced with those shown in the column entitled “Correct Data Value to Hard Code”. All these dates will be amended programmatically (hard-coded) within the SDTM datasets.

Note: for Subject JP-TOK-0111, the Day 90 visit was performed on 09 JAN2014, however the QS_COUGH_PAPER is performed on the second day of this 2 day visit (i.e. Day 91) and so the correct date for this particular assessment is 10 JAN 2014.

REXA-07_CDARO Filenote 11_Final 1.0_2015_06_25

During the programming and QC of the ADBX analysis dataset for REXA-07, Covance programmers noted that one result for the biomarker 3-OH BaP had no VISIT assigned. The full list of 3-OH BaP results for the one affected subject (TOK0054) are shown below (dark grey rows, the yellow highlight indicates the missing visit):

DD_CELERION_BIOMF_FULL_2014OCT03140000.csv									
0050	05112230000519	3-OH BaP Urine BLQ<(25.0) fg/mL OK	LC-MS/MS 25.0	60	AA99127-07 2013-Nov-19	TOK	60 61	DAY60	
0050	05112230000520	3-OH BaP Urine 35.4 fg/mL OK	LC-MS/MS 25.0	90	AA99127-07 2013-Dec-17	TOK	90 91	DAY90	
0053	05112230000531	3-OH BaP Urine BLQ<(25.0) fg/mL OK	LC-MS/MS 25.0	1	AA99127-07 2013-Sep-20	TOK	1 0	BASELIN	
0053	05112230000532	3-OH BaP Urine BLQ<(25.0) fg/mL OK	LC-MS/MS 25.0	0	AA99127-07 2013-Sep-21	TOK	0 1	DAY0	
0053	05112230000533	3-OH BaP Urine BLQ<(25.0) fg/mL OK	LC-MS/MS 25.0	1	AA99127-07 2013-Sep-22	TOK	1 2	DAY1	
0053	05112230000534	3-OH BaP Urine BLQ<(25.0) fg/mL OK	LC-MS/MS 25.0	2	AA99127-07 2013-Sep-23	TOK	2 3	DAY2	
0053	05112230000535	3-OH BaP Urine BLQ<(25.0) fg/mL OK	LC-MS/MS 25.0	3	AA99127-07 2013-Sep-24	TOK	3 4	DAY3	
0053	05112230000536	3-OH BaP Urine BLQ<(25.0) fg/mL OK	LC-MS/MS 25.0	4	AA99127-07 2013-Sep-25	TOK	4 5	DAY4	
0053	05112230000537	3-OH BaP Urine BLQ<(25.0) fg/mL OK	LC-MS/MS 25.0	5	AA99127-07 2013-Sep-26	TOK	5 6	DAY5	
0053	05112230000538	3-OH BaP Urine BLQ<(25.0) fg/mL OK	LC-MS/MS 25.0	30	AA99127-07 2013-Oct-18	TOK	30 31	DAY30	
0053	05112230000539	3-OH BaP Urine BLQ<(25.0) fg/mL OK	LC-MS/MS 25.0	60	AA99127-07 2013-Nov-19	TOK	60 61	DAY60	
0053	05112230000540	3-OH BaP Urine BLQ<(25.0) fg/mL OK	LC-MS/MS 25.0	90	AA99127-07 2013-Dec-17	TOK	90 91	DAY90	
0054	05112200001084	3-OH BaP Urine 207 fg/mL OK	LC-MS/MS 25.0		AA99127-07	TOK			
0054	05112230000551	3-OH BaP Urine 420 fg/mL OK	LC-MS/MS 25.0	1	AA99127-07 2013-Sep-20	TOK	1 0	BASELINE	
0054	05112230000552	3-OH BaP Urine 228 fg/mL OK	LC-MS/MS 25.0	0	AA99127-07 2013-Sep-21	TOK	0 1	DAY0	
0054	05112230000553	3-OH BaP Urine 147 fg/mL OK	LC-MS/MS 25.0	1	AA99127-07 2013-Sep-22	TOK	1 2	DAY1	
0054	05112230000554	3-OH BaP Urine 80.4 fg/mL OK	LC-MS/MS 25.0	2	AA99127-07 2013-Sep-23	TOK	2 3	DAY2	
0054	05112230000555	3-OH BaP Urine 130 fg/mL OK	LC-MS/MS 25.0	3	AA99127-07 2013-Sep-24	TOK	3 4	DAY3	
0054	05112230000556	3-OH BaP Urine 181 fg/mL OK	LC-MS/MS 25.0	4	AA99127-07 2013-Sep-25	TOK	4 5	DAY4	
0054	05112230000557	3-OH BaP Urine 129 fg/mL OK	LC-MS/MS 25.0	5	AA99127-07 2013-Sep-26	TOK	5 6	DAY5	
0054	05112230000558	3-OH BaP Urine 139 fg/mL OK	LC-MS/MS 25.0	30	AA99127-07 2013-Oct-18	TOK	30 31	DAY30	
0054	05112230000559	3-OH BaP Urine 157 fg/mL OK	LC-MS/MS 25.0	60	AA99127-07 2013-Nov-19	TOK	60 61	DAY60	
0054	05112230000560	3-OH BaP Urine 134 fg/mL OK	LC-MS/MS 25.0	90	AA99127-07 2013-Dec-17	TOK	90 91	DAY90	
0058	05112230000571	3-OH BaP Urine 47.6 fg/mL OK	LC-MS/MS 25.0	1	AA99127-07 2013-Sep-20	TOK	1 0	BASELINE	
0058	05112230000572	3-OH BaP Urine 54.0 fg/mL OK	LC-MS/MS 25.0	0	AA99127-07 2013-Sep-21	TOK	0 1	DAY0	
0058	05112230000573	3-OH BaP Urine BLQ<(25.0) fg/mL OK	LC-MS/MS 25.0	1	AA99127-07 2013-Sep-22	TOK	1 2	DAY1	
0058	05112230000574	3-OH BaP Urine BLQ<(25.0) fg/mL OK	LC-MS/MS 25.0	2	AA99127-07 2013-Sep-23	TOK	2 3	DAY2	
0058	05112230000575	3-OH BaP Urine BLQ<(25.0) fg/mL OK	LC-MS/MS 25.0	3	AA99127-07 2013-Sep-24	TOK	3 4	DAY3	
0058	05112230000576	3-OH BaP Urine BLQ<(25.0) fg/mL OK	LC-MS/MS 25.0	4	AA99127-07 2013-Sep-25	TOK	4 5	DAY4	
0058	05112230000577	3-OH BaP Urine BLQ<(25.0) fg/mL OK	LC-MS/MS 25.0	5	AA99127-07 2013-Sep-26	TOK	5 6	DAY5	
0058	05112230000578	3-OH BaP Urine 45.4 fg/mL OK	LC-MS/MS 25.0	30	AA99127-07 2013-Oct-18	TOK	30 31	DAY30	

Covance Data Management confirmed that this “extra” record was present both in the file received from the vendor (Celerion) and in the RAVE database. The subject already had all the expected scheduled records present in the database, so the vendor was requested to confirm the identity of this record.

On 22-JUN-2015, Kirk Newland (Technical Director, Tobacco Science, Celerion) confirmed that the “extra” record with value of 207 fg/mL should be recorded as the DAY2 visit and that the value currently present at DAY2 (80.4 fg/mL) should be removed. The “extra” record was in fact the correct result to include in the DAY2 visit and should have over-written the previous value.

Upon review and approval of this file note, the Covance programming team will hard-code the 3-OH BaP result at DAY2 for subject TOK0054 to 207 fg/mL (all other variables for this record stay the same) and remove the “extra” record with no VISIT assigned.

REXA-07 CDARO Filenote 12 Final 1.0 2015-07-13

At the point of approval of the final post-lock SDTM datasets for the study, a final approval form was produced listing the latest version of the study SDTM Specification, aCRF (Main) and aCRF (Site) along with the list of final datasets and their associated production dates.

The version numbering for the SDTM Specification, aCRF (Main) and aCRF (Site) were questioned due to apparent missing approvals for previous version numbers.

The summary table below identifies all versions of the SDTM Specification, aCRF (Main) and aCRF (Site) that have been produced to date. It also shows the prior versions that have written approvals. This does not follow the document naming convention as the plan was to only version with signatures. However due the existence and reference to these documents the decision was to leave the version numbering as, include all version in the SMF and explain the lack of approvals.

Version Naming Convention:

Unapproved version exchanged between PMI and Covance would increment in the decimal numbering to indicate that they are not approved, and only once both Covance and PMI agree that the document is OK for sign off should the version number been incremented to the next whole number. Therefore the version numbering should have been as follows:

SDTM Specification	Given Version	Intended Version
ZRHR_REXA-07-JP SDTM Dataset specification Final V3.0 30Mar2015	V3.0	V2.1
ZRHR_REXA-07-JP SDTM Dataset specification Final V3.0 30Mar2015 updated	V3.0	V2.2
ZRHM_REXA-07-JP SDTM Dataset specification Final V3.1 08May2015	V3.1	V2.3
ZRHM_REXA-07-JP SDTM Dataset specification Final V4.0 08Jun2015	V4.0	V2.4
ZRHM_REXA-07-JP SDTM Dataset specification Final V5.0 17Jun2015	V5.0	V3.0

It is considered inappropriate at this stage to go back and change the version numbers as there are documents previously circulated with versioning as shown below. In order to clarify for future reference, this file note serves to confirm which versions have and have not been finalized through

formal written approval.

Summary of approval received for Data Management Deliverables			
SDTM Specification	Version	Date	Approval Signature
ZRHM-REXA-07-US SDTM Dataset specification Final V1.0	V1.0	26-Nov-14	Yes
ZRHM-REXA-07-US SDTM Dataset specification Final V2.0	V2.0	13-Feb-15	Yes
ZRHR_REXA-07-JP SDTM Dataset specification Final V3.0 30Mar2015	V3.0	30-Mar-15	No
ZRHR_REXA-07-JP SDTM Dataset specification Final V3.0 30Mar2015 updated	V3.0	07-Apr-15	No
ZRHM_REXA-07-JP SDTM Dataset specification Final V3.1 08May2015	V3.1	08-May-15	N/A
ZRHM_REXA-07-JP SDTM Dataset specification Final V4.0 08Jun2015	V4.0	08-Jun-15	No
ZRHM_REXA-07-JP SDTM Dataset specification Final V5.0 17Jun2015	V5.0	02-Jul-15	Pending
aCRF (Main)			
ZRHM-REXA-07-JP-SDTM-crf_Final_v1.0	V1.0	26-Nov-14	Yes
ZRHM-REXA-07-JP-SDTM-crf Final v2.0	V2.0	16-Feb-15	Yes
ZRHM-REXA-07-JP-SDTM-crf Final v3.0	V3.0	13-Jul-15	Pending
aCRF (Site)			
ZRHM-REXA-07-sdtm-site-crf Final v1.0	V1.0	26-Nov-14	Yes
ZRHM-REXA-07-sdtm-site-crf Final v2.0	V2.0	13-Feb-15	Yes
ZRHM-REXA-07-sdtm-site-crf Final v3.0	V3.0	13-Jul-15	Pending

REXA-07 CDARO Filenote 13 Final 1.0 2015-07-17

At the point of approval of the final post-lock SDTM datasets for the study one date issue was identified by Covance programmers - subject SEI-0049 has "Day 5" visit date 19-~~09~~-2013 (September). Correct date is 19-~~08~~-2013 (August).

Change will be implemented by hard-coding the correct date.

REXA-07 CDARO Filenote 13 Final 2.0 2015-07-19

This file note will serve to document the issue identified post database lock, and prior to approval of SDTM data. An erroneous date was identified by the Covance programmers. The erroneous date was identified in the nicotine sample collection form as defined below.

Subject SEI-0049 is present in the Celerion (pcb_nic) raw data file and reports a “Day 5” visit date of 19-~~09~~-2013 (19 September 2013). The correct date for this visit is 19-~~08~~-2013 (19 August 2013). At the time the date issue was identified the Final SDTM and ADaM data had already been run and submitted to PMI for final approval. Therefore the data could have been corrected programmatically. The decision though was taken not to correct the data at this point in time, but to document the discrepancy in the Reviewer's Guide to accompany the data. The reasoning for this decision was because:

- (1) Programmatic corrections are not recommended;
- (2) the subjects from the SEI site would not be included in the summaries or analyses;
- (3) the error impacted a single data point and was not a systematic issue
- (4) the error would have no impact on the interpretation of the study data or results

Therefore this note documents the issue including the correction for the issues which is to note the issue in the Reviewer's Guide portion of the DEFINE.xml.