

Study Data Reviewer's Guide

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Study ZRHM-PK-05-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 Study Data Standards and Dictionary Inventory

Standard or Dictionary	Versions Used
SDTM	SDTM Version 1.3 / SDTM Implementation Guide version 3.1.3 SDTM Draft Implementation Guide for Medical Devices (SDTMIG-MD)
Controlled Terminology	2014-06-27
Data Definitions	Define.xml version 2.0
Medications Dictionary	WHO DDE Version Q1 2013 – Coded to indication
Medical Events Dictionary	MedDRA Version 16.0
Device Events Dictionary	C54451/Medical_Device_Problem_Codes_FDA_CDRH

2. Protocol Description

2.1 Protocol Number and Title

Protocol Number: ZRHM-PK-05-JP

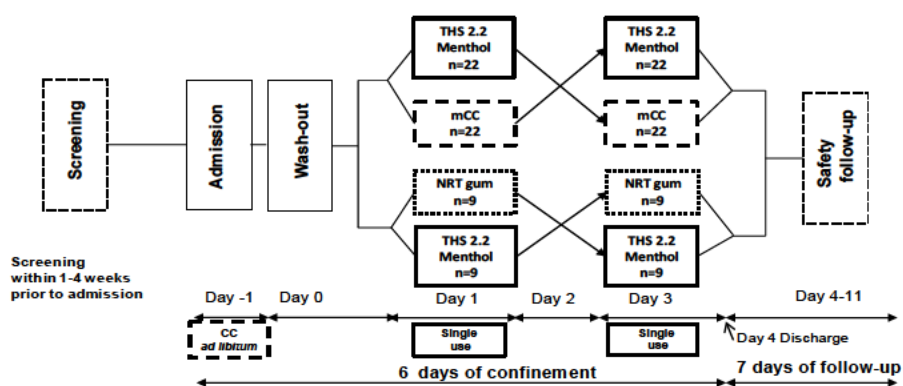
Protocol Title: A single-center, open-label, randomized, controlled, crossover study to investigate the nicotine pharmacokinetic profile and safety of Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) following single use in smoking, healthy subjects compared to menthol conventional cigarettes and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

Protocol Versions: Final 1.0 / 21 June 2013

2.2 Protocol Design

Figure S1: Study Design

- Cross over with incomplete block design, 4 sequences
- 62 smokers to be randomized



Abbreviations: THS: Tobacco Heating System; mCC = menthol conventional cigarette; NRT = Nicotine Replacement Therapy

2.3 Trial Design Datasets

Are Trial Design datasets included in the submission?

(If no, delete the remainder of this section. If yes, refer to SDRG Completion Guidelines Section 2.3 and provide additional information below.)

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

2.3.1. TV – Trial Visits

Subjects who withdrew from the study were required to perform withdrawal early termination procedures which are the same as the discharge assessments performed at Day 4. The protocol did not require these procedures to be performed at a separate withdrawal visit but, rather, to perform them at

the scheduled visit at which the subject was withdrawn. Therefore, a combined Day 4/ Withdrawal Discharge visit was created to account for the timings of the procedures performed for withdrawn subjects.

2.3.2. TI – Trial Inclusion/Exclusion Criteria

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

3. Subject Data Description

3.1 Overview

Are the submitted data taken from an ongoing study? No

If yes, describe the data cut or database status:

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

If no, what were the sources of analysis datasets?

Do the submission datasets include screen failures? Yes

If yes, which datasets include screen failure data?

DM

DS

DV

FA

IE

SE

SV

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

If yes, list domains not submitted:

CM

DE

MH

Are the submitted data a subset of collected data?

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

(Text here)

Additional Content of Interest

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

The primary endpoint data can be found in PC.

A new domain, XP, has been created for the spirometry 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 device.
DI	DI	Device Identifiers	Special Purpose Domains	Details of the THS 2.2 device holders and chargers used in the study.
DE	DE	Device Events	Events	Details events associated with the THS 2.2 device holders and chargers used in the study.
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

<i>Domain</i>	<i>Datasets</i>	<i>Description</i>	<i>Class</i>	<i>Information captured</i>
EX	EX	Exposure	Interventions	Methanol conventional cigarettes smoked by the subjects.
FA	FA	Findings About Events or Interventions	Findings	Smoking history information, cigarette brand and the standardize brand name.
LB	LB	Laboratory Test Results	Findings	This domain was used to capture the following lab data: - ALCOHOL TEST - BIOBANKING - BIOMARKERS - CLINICAL CHEMISTRY - COTININE SCREENING - DRUG SCREEN - ENZYME ACTIVITY - HAEMATOLOGY - PREGNANCY - SEROLOGY - URINALYSIS
XP	XP	Pulmonary Function	Findings	Captures the Spirometry (lung capacity)

3.2 Annotated CRFs

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

- Responses to the screen failure question ‘Is there a pregnancy event?’, as this is captured in the exclusion criteria (IE) dataset.
- The Y/N responses to the questions prompting the entry of data and used by data management solely for data validation purposes:
 - Has the subject given written informed consent for Bio-banking for Biomarkers of Exposure and Risk Markers?
 - Has the subject given written informed consent for Bio-banking for Transcriptomics (Pharmacogenomics)?
 - Has the subject experienced any past and/ or concomitant diseases?
 - Was there any Adverse Event for this subject?
 - Has the subject taken previous or concomitant medication?

- Were there any events with the device?
 - Inclusion Criteria Result and Number
 - Exclusion Criteria Result and Number
-
- The medical history category was derived in the SDTMs, based on the start of medical event
 - Responses to the questions relating to THS 2.2 Product demonstration and Advice on the risks on smoking and debriefing was not submitted as this data is for data management and site monitoring. If these questions were answered 'no' then the data would be presented as a protocol deviation in the DV dataset
 - The subject date of birth from the questionnaires was not captured since this information is already presented in the DM domain. The global assessment status was not captured as the individual question responses were provided for this study
 - The variable 'H_NOW' was not submitted as this is a derived variable used to validate information in the database
 - In Plasma Nicotine or Cotinine forms: Not Done
 - Subject (Site level)
 - In site Accountability form: Category, Date of batch dispensed, Number of unused packs returned, Number of unused sticks returned, Number of packs received
 - In LABSTAT result form: Day Number
 - In LAB-BU form: Data Type unique identifier and Random number, Sex, Date of Birth, Visit ID, Site Number, Derived Form name
 - 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 and CYP2A6 activity) were entered by the site.
- The submitted annotated CRF (blankcrf.pdf) includes the final version of the eCRF (main study CRF version 5.0).

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.

3.3 SDTM Subject Domains

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

Dataset – Dataset Label	Efficacy	Safety	Other	SUPP-	Related Using RELREC	Observation Class
SU - Substance Use			X			Interventions
SV - Subject Visits			X			Special Purpose Domains
VS - Vital Signs		X		X		Findings
XP - Pulmonary Function		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.

QNAM	Description
AERELSP	Relationship to Study Procedure
AEREL1	Causality to Product 1
AEREL2	Causality to Product 2
AEEXPEC	AE Expectedness to product 1
AEEXPEC1	AE Expectedness to product 2
AEACNP1	Action Taken With Study Product 1
AETRTEM	Treatment Emergent Flag

3.3.2. DA - Drug Accountability

The following variables have been mapped into SUPPDA

QNAM	Description
BEXPDTC	Batch Expiration Date

3.3.3. DM - Demographics

The following variables have been mapped into SUPPDM

QNAM	Description
DMRANDNO	Randomization Number

3.3.4. DS – Disposition

The following variables have been mapped into SUPPDS

QNAM	Description
OTHER	Other Reason for Screen Failure

3.3.5. 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
DVREPDTC	Date Deviation Reported
RESOL	Deviation Resolution
SOURCE	Deviation Source
DVSIG	Deviation Type
DVTIMEPT	Deviation Timepoint

3.3.6. DX - Device Exposure

This dataset captures the THS 2.2 exposure data.

The following variables have been mapped into SUPPDX

QNAM	Description
DISDTC	Time of distribution

3.3.7. EX – Exposure

This dataset captures the cigarette exposure data.

The following variables have been mapped into SUPPEX

QNAM	Description
DISDTC	Time of product distribution
RETDTC	Time of product return

3.3.8. FA - Findings About Events or Interventions

The following variables have been mapped into SUPPFA

QNAM	Description
BRAND	Standardised Brand Name

3.3.9. LB - Laboratory Test Results

Toxicity grading of the laboratory safety data, as outlined in Appendix 5 of the study protocol, is presented in the variables LBTOX and LBTOXGR.

The following variables have been mapped into SUPPLB

QNAM	Description
LBCLSIG	Clinically Significant
LB_FLG	Flag

3.3.10. PP - Pharmacokinetic Parameters

The following variables have been mapped into SUPPPP

QNAM	Description
PPSTINT	Planned Start of Assessment Interval
PPENINT	Planned End of Assessment Interval
HLFLG	t1/2 calculated over period<2x t1/2
PCTCMAX	Percentage of T0 relative to Cmax
FLGCMAX	Flag where T0 >5% of Cmax

3.3.11. VS - Vital Signs

The following variables have been mapped into SUPPVS

QNAM	Description
SMOK15P	Smoked within 15 min prior to assessment

Notable extensions to CDISC terminology

Domain	Variable Codelist	Value
LB	C67154	Carbon Monoxide
LB	C67154	HIV-1 HIV-2 Antigen Measurement
LB	C67154	Pregnancy Test
LB	C67154	Trans-3 Hydroxycotinine
LB	C65047	CO
LB	C65047	HIV12AG
LB	C65047	PREGTEST
LB	C65047	TRANS3H
LB	C71620	10⁴/uL
EX, FA	C71620	GUM
DA, DX	C71620	STICK
LB	C71620	ng/mL

4. Data Conformance Summary

4.1 Conformance Inputs

Was OpenCDISC used to evaluate conformance?	Yes
If yes, specify the versions of OpenCDISC and the OpenCDISC validation rules:	
OpenCDISC v1.5, SDTM 3.1.3, Controlled Terminology version 2014-06-27 and MedDRA 16.0	
Were sponsor-defined validation rules used to evaluate conformance?	No
If yes, describe any significant sponsor-defined validation rules:	
(Text here)	
Were the SDTM datasets evaluated in relation to define.xml?	No
Was define.xml evaluated?	Yes
Provide any additional compliance evaluation information:	
OpenCDISC v1.5	

4.2 Issues Summary

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

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

Dataset	Diagnostic Message	Severity	Count	Explanation
AE	SDTM Expected variable not found	Error	1	AEACN was not used in this study due to the variable's association with a treatment. The data was captured in a SUPPAE variable, AEACNP1, with a codelist specific to the investigational product.
AE	Permissible AESCONG variable with missing value for all records	Notice	1	Variable required for the production of the ADaM dataset
AE	Permissible AESDISAB variable with missing value for all records	Notice	1	Variable required for the production of the ADaM dataset
AE	Permissible AESDTH variable with missing value for all records	Notice	1	Variable required for the production of the ADaM dataset
AE	Permissible AESHOSP variable with missing value for all records	Notice	1	Variable required for the production of the ADaM dataset
AE	Permissible AESLIFE variable with missing value for all records	Notice	1	Variable required for the production of the ADaM dataset
DA	Value for DASTRESU not found in (UNIT) CT codelist	Warning	270	The codelist is extensible. The unit is 'STICK'
DA	Value for DAORRESU not found in (UNIT) CT codelist	Notice	270	The codelist is extensible. The unit is 'STICK'
DA	Permissible DAREASND variable with missing value for all records	Notice	1	Variable required for the production of the ADaM dataset
DA	Permissible DASTAT variable with missing value for all records	Notice	1	Variable required for the production of the ADaM dataset

Dataset	Diagnostic Message	Severity	Count	Explanation
DI	Unrecognized domain	Warning	1	This version of OpenCDISC has an issue with device domains
DM	No records for 'SCRFAIL' subject are found in IE domain	Warning	47	Subjects discontinued for reasons other than I/E failure
DM	Value for ETHNIC not found in (ETHNIC) CT codelist	Notice	147	Mapped to sponsor's standard. The value is 'Japanese'
DR	Unrecognized domain	Warning	1	This version of OpenCDISC has an issue with device domains
DS	Missing DSDY variable, when DSDTC variable is present	Warning	1	Not in the sponsor's standard
DS	Value for DSDECOD not found in (NCOMPLT) CT codelist	Notice	11	Codelist is extensible. The values are 'DISPOSITION EVENT' and 'DISCONTINUED FROM ENROLLMENT'
DT	Variable appears in dataset, but is not in SDTM standard	Error	3	SPDEVID, DTPARTY and DTPRTYID are part of the standard
DT	SDTM Expected variable not found	Warning	1	This domain is not a subject –level domain. Consequently, USUBJID is missing.
DV	DVENDTC date is after RFPENDTC	Warning	164	The end date of the deviation can be after the end of study for a subject
DV	Model permissible variable added into standard domain	Notice	5	FDA preferred variables added (VISIT, DVENDY, DVSTDY, VISITDY, VISITNUM)

Dataset	Diagnostic Message	Severity	Count	Explanation
DX	Value for DXDOSU not found in (UNIT) CT codelist	Notice	135	The codelist is extensible. The unit is 'STICK'
EG	Value for EGSTRESC not found in (EGSTRESC) CT codelist	Notice	196	ECG interpretations. The codelist is extensible
EG	Permissible EGREASND variable with missing value for all records	Notice	1	Needed for ADaM production
EG	Permissible EGSTAT variable with missing value for all records	Notice	1	Needed for ADaM production
EX	EX record is present, when subject is not assigned to an arm	Warning	102	Subjects discontinued from enrollment
EX	Value for EXDOSU not found in (UNIT) CT codelist	Notice	91	Codelist is extensible. The unit is 'cigarettes'
EX	Model permissible variable added into standard domain	Notice	2	Addition of visit variables
FA	Value for FASTRESU not found in (UNIT) CT codelist	Warning	146	The codelist is extensible The units are 'GUM' and 'STICK'
FA	USUBJID/VISIT/VISITNUM values do not match SV domain data	Warning	148	Subjects have information recorded at this visit even though they discontinued The

Dataset	Diagnostic Message	Severity	Count	Explanation
				subjects are screening failures and did not perform any other assessments for Day -2.
FA	Value for FAORRESU not found in (UNIT) CT codelist	Notice	146	The codelist is extensible. The units are 'STICK' and 'GUM'
IE	Missing IEDY variable, when IEDTC variable is present	Warning	1	IEDY variable would be null if added since IEDTC is null.
IE	Model permissible variable added into standard domain	Notice	1	FDA preferred variable added (EPOCH).
LB	Value for LBSTRESU not found in (UNIT) CT codelist	Warning	581	The codelist is extensible. The units are: '10 ⁴ /uL' and 'ng/mL'
LB	Missing LBSTRESC value for Baseline record	Warning	35	Issue relates to missing biomarker assessments
LB	Value for LBTEST not found in (LBTEST) CT codelist	Notice	1412	The codelist is extensible. The tests are biomarkers and the 'All laboratory tests' indicator test.
LB	Value for LBTESTCD not found in (LBTESTCD) CT codelist	Notice	1412	The codelist is extensible. The testcds are biomarkers and the 'All laboratory tests' indicator test.
LB	Value for LBORRESU not found in (UNIT) CT codelist	Notice	581	The codelist is extensible. The units are: '10 ⁴ /uL' and 'ng/mL'
PE	Missing PESTRESC value for Baseline record	Warning	73	'Other' body system assessments not always performed/relevant.

Dataset	Diagnostic Message	Severity	Count	Explanation
PE	Model permissible variable added into standard domain	Notice	1	Relates to the addition of baseline flag variable (PEBLFL)
PE	Model permissible variable added into standard domain	Notice	1	FDA preferred variable added (PEBLFL).
PP	Missing value for PPORRESU, when PPORRES is provided	Warning	481	Not every parameter has a unit
PP	Missing value for PPSTRESU, when PPSTRESC is provided	Warning	481	Not every parameter has a unit
PP	PPORRES variable length is too long for actual data	Warning	1	Variable length reflects the longest value
PP	PPSTRESC variable length is too long for actual data	Warning	1	Variable length reflects the longest value
PP	Duplicate records	Warning	860	The interval variables in the supppp dataset show these are not duplicates
QS	Permissible QSREASND variable with missing value for all records	Notice	1	Needed for ADaM production
QS	Permissible QSSTAT variable with missing value for all records	Notice	1	Needed for ADaM production
SE	Variable is in wrong order within domain	Warning	2	FDA preferred variables added. (SESTDY and SEENDY)
SE	Model permissible variable added into standard	Notice	3	FDA preferred variables added. (SESTDY

Dataset	Diagnostic Message	Severity	Count	Explanation
	domain			and SEENDY)
SUPPPP	QVAL variable length is too long for actual data	Warning	1	Variable length reflects longest value
SV	Model permissible variable added into standard domain	Notice	1	The variable Epoch added
SV	Permissible SVUPDES variable with missing value for all records	Notice	1	Required for the production of the ADaM datasets
TS	TSPARM and TSPARMCD values do not have the same Code in CDISC CT	Error	1	Maps to the SDTM IG. TSPARM=' Clinical Study Sponsor' and TSPARMCD=' SPONSOR'
TS	TSPARM and TSPARMCD values do not have the same Code in CDISC CT	Error	1	Maps to the SDTM IG. . TSPARM=' Clinical Study Sponsor' and TSPARMCD=' SPONSOR'
TS	SDTM/dataset variable label mismatch	Warning	2	Maps to the SDTM IG. The variables in question are TSVAL1 and TSVAL2.
VS	Value for VSTEST not found in (VSTEST) CT codelist	Notice	5	The codelist is extensible. The test is 'All Vital Signs'.
VS	Value for VSTESTCD not found in (VSTESTCD) CT codelist	Notice	5	The codelist is extensible. The tested is 'VSALL'.

Appendix I: Inclusion/Exclusion Criteria

Protocol/ Amendment Version	Category	IETESTCD	Full Text of Criterion
1.0	INCLUSION	INC01	Subject has signed the ICF and is able to understand the information provided in the Subject Information Sheet and ICF.
1.0	INCLUSION	INC02	Subject is aged from 23 to 65 years (inclusive).
1.0	INCLUSION	INC03	Subject is Japanese.
1.0	INCLUSION	INC04	Smoking, healthy subject as judged by the Investigator based on all available assessments in the Screening period/day of Admission (e.g., safety laboratory, spirometry* [forced expiratory volume in 1 second {FEV1}/forced vital capacity {FVC} >0.7 at post-bronchodilator basal spirometry, post-bronchodilator FEV1 >80% predicted value, and post-bronchodilator FVC >0.8], vital signs, physical examination, ECG, chest X-ray and medical history).
1.0	INCLUSION	INC05	Subject smokes at least 10 commercially available menthol CCs 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 3 consecutive years. The smoking status will be verified based on a urinary cotinine test (cotinine \geq 200 ng/mL).
1.0	INCLUSION	INC06	The subject does not plan to quit smoking in the next 3 months.
1.0	INCLUSION	INC07	The subject is ready to accept interruptions of smoking for up to 4 days.
1.0	INCLUSION	INC08	The subject is ready to accept using both the THS 2.2 Menthol and NRT gum products.
1.0	EXCLUSION	EXC01	As per Investigator judgment, the subject cannot participate in the study for any reason (e.g., medical, psychiatric, and/or social reason).
1.0	EXCLUSION	EXC02	A subject who is legally incompetent, physically or mentally incapable of giving consent (e.g., emergency situation, under guardianship, prisoners or subjects who are involuntarily incarcerated).

Protocol/ Amendment Version	Category	IETESTCD	Full Text of Criterion
1.0	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.
1.0	EXCLUSION	EXC04	The subject has a body mass index (BMI) <18.5 or ≥ 32.0 kg/m ² .
1.0	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.
1.0	EXCLUSION	EXC06	The subject has used nicotine-containing products other than commercially available mCC (either tobacco-based products or nicotine-replacement therapy) as well as electronic cigarettes and similar devices, within 4 weeks prior to assessment.
1.0	EXCLUSION	EXC07	The subject has received medication (prescription or over-the-counter) within 14 days or within 5 half-lives of the drug prior to the Admission Day (Day -1; whichever is longer) that has an impact on CYP2A6 activity.
1.0	EXCLUSION	EXC08	In case the subject received any medication (prescribed or over-the-counter) within 14 days prior to Screening or prior to the Admission Day (Day -1) it will be decided at the discretion of the Investigator if these can potentially interfere with the study objectives and subject's safety.
1.0	EXCLUSION	EXC09	The subject has a positive alcohol test and/or the subject has a history of alcohol abuse that could interfere with subject's participation in study.
1.0	EXCLUSION	EXC10	The subject has a positive urine drug test.
1.0	EXCLUSION	EXC11	Positive serology test for human immunodeficiency virus (HIV) 1/2, Hepatitis B or Hepatitis C.
1.0	EXCLUSION	EXC12	Donation or receipt of whole blood or blood products within 3 months prior to Admission.
1.0	EXCLUSION	EXC13	The subject is a current or former employee of the tobacco industry or of their first-degree relatives (parent, sibling, child).
1.0	EXCLUSION	EXC14	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).

Protocol/ Amendment Version	Category	IETESTCD	Full Text of Criterion
1.0	EXCLUSION	EXC15	The subject has participated in a clinical study within 3 months prior to the Screening Visit.
1.0	EXCLUSION	EXC16	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).
1.0	EXCLUSION	EXC17	For women only: Subject is pregnant (does not have negative pregnancy tests at Screening and at Admission) or is breast feeding.
1.0	EXCLUSION	EXC18	For women only: Subject does not agree to use an acceptable method of effective contraception.