STATISTICAL ANALYSIS PLAN:

A multi-center, multi-region smoking cessation study to understand the biological and functional changes related to smoking cessation in healthy smokers who are continuously abstinent from smoking for one year

Study Product: Not Applicable

Sponsor Reference No.: SA-SCR-01
[redacted] Project No.: 217920

Sponsor:
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1 STATISTICAL ANALYSIS PLAN APPROVAL

By signing this page the Statistical Analysis Plan (SAP) is considered final, the signatories agree to the statistical analyses to be performed for this study, and to the basic format of the tables, figures, and listings (TFLs).

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3 INTRODUCTION

This clinical study aims at understanding the clinical, biological and functional changes after one year of smoking cessation in healthy subjects. Healthy subjects will be included in this study, since the impact of potential diseases on the study endpoints is difficult to evaluate.

This SAP has been developed to supplement the statistical analysis described in the clinical study protocols ("SA-SCR-01" final version 8.0 dated 18 May 2017, and "SA-SCR-01" for [redacted] final version 6.0 dated 18 May 2017).

This SAP describes the methodology and considerations of the planned analyses and lists the Tables, Figures and Listings (TFLs) for this study. A detailed description of the TFLs will be provided in a separate TFLs shell document. Any changes to the TFL shell numbering or to the title of a TFL will not require an amendment to this SAP.

This SAP and any amendments will be finalized prior to the lock of the clinical database. Any changes to the analyses described in this document or additional analyses performed to supplement the planned analyses, will be documented and described in the clinical study report (CSR).

The preparation of this SAP is based on the following documents:

- International Conference on Harmonisation (ICH) E9 guideline entitled, "Guidance for Industry: Statistical Principles for Clinical Trials" [1]
- ICH E3 guideline entitled, "Guidance for Industry: Structure and Content of Clinical Study Reports" [2]
- Case report forms (eCRF) final version 10.0 (dated 06 December 2016)
- Study Manual about Smoking Cessation Support and Enrollment Plan final version 1.0 (dated 17 July 2015)
- Data Review Plan final version 3.0 (dated 11 October 2017)
- Data Cut-off Process version 4.0 (dated 30 March 2017)
- Vitalograph Customer Requirements Specification version 5.0 (dated 29 April 2016) [3]
- Safety Management Plan (SMP) for UK version 4.4 (dated 15May 2017)
- SMP for Poland version 4.5 (dated 15 May 2017)
- SMP for US version 4.6 (dated 15 May 2017)
- SMP for Germany version 4.7 (dated 15 May 2017)
- SMP for Japan version 4.8 (dated 15 May 2017).

3.1 Revision History

Version	Date of Revision	Description
1.0	22 Apr 2016	• Original version
2.0	27 Jul 2016	• Added Safety Follow-up visit, • Updated End of Study definition and study duration • Added subsection about assessments at V17 to be performed if Total NNAL is above the cut-off at V11 • Update of handling of missing data for compliance assessments • Added subsection about handling of early termination assessment data • Added exclusion of subjects from Site 515 from Enrolled population • Clarified that AE with missing intensity will not be counted as "severe" but reported as missing. • Added Kaplan-Meier approach for the estimation of the continuous smoking cessation rate • Clarified in Section 9 additional derived endpoints for lung function, spirometry and apolipoprotein not listed in Section 3 "Study Objectives and Endpoints" of the study protocol. • Change of Biostatistician and Statistical Programmer in [redacted] team for review and approval of the SAP
3.0	19 June 2017	• Section 1 – Updated to latest reviewers names. • Section 3 – Updated to latest version of study documentation • Section 4.1 - Added VI (Inspired volume) and VA (Alveolar volume) abbreviations, and added that KCO is equal to DLCO/VA. • Sections 4.2 and 6.1 - Deleted 'EOS of the entire study' definition because this does not impact the analysis. • Section 4.2 – Added 'Lost to follow-up (date)' to be consistent with latest protocol. • Section 7.2.6 - Added 'total weekly time exercise (minutes/week)' derivation and rule. • Section 9 – Added the change from protocol about definition of Full Safety Population and Quitters Population. • Section 10 – Updated Full Safety Population and Quitters Population definition. Removed to perform the analysis on both Abstinence3m and Abstinence6m only if the two populations differ by e.g at least. 2%, and on both Abstinence6m and Abstinence12m only if the two populations differ, so kept all summaries to simplify the analysis. • Section 11.1.1 – Added major PD in case of 24 hour urine collection covering less than 20 hours or more than 28 hours. Added major PD in case of visit conducted out of window for more than 30 days. • Section 11.1.2 - Updated PD description for the 'duration of 24 hour collection' PD category. Updated PD description for the 'Visit window deviation' PD category. • Section 12.1.3 – Added 'Relative Change' statistics. • Section 12.1.4.1 – Added a 'Normal' category for the COPD staging variable. • Section 12.1.4.2 Table 20 – Added 'LDL-C' (because both LDL-C

Version	Date of Revision	Description
		and HDL-C were planned to be analysed in Section 12.5.1.1), and added 'Age' as general evaluated covariate for all endpoints because generally considered an adjustment factor. • Section 12.1.5 – Deleted sentence 'Descriptive summaries will be provided for the evaluable data with no imputation.' • Section 12.1.5 – Minor changes in the missing or partial date table header. • Section 12.1.6 – Added this Section about 'Handling of 24 Hour Urine Collection'. • Section 12.1.7 - Added this Section about '12.1.7 Handling of Assessments Prior TQD or AQD' • Section 12.1.8 - Added this Section about 'Handling of Scheduled Assessments Conducted out of Window for more Than 30 Days'. • Section 12.1.8 – Updated rules for early termination assessments, and added mapping rules for unscheduled assessments. • Section 12.3.1.1 - Added 'smoking duration' display. • Section 12.5.1 – Added that predicted values for Lung function parameters will be derived by a central provider. • Section 12.5.1 – Suppressed WBC differential counts from the list of parameters to be analyzed, they will be part of the safety outputs. Renamed 'WBC' into 'WBC total count'. Suppressed Stethographics and Stethos parameters, xenobiotics and genotoxicity markers (i.e. CYP2A6 and Total NNAL) from the list of parameters to be analyzed in real scale. Updated for nasal and buccal epithelium scrapes, and transcriptomics and lipidomics, samples (only the reasons when the assessments were not collected will be listed). • Section 12.5.1.1 – Expanded list of covariance structure to include simpler covariance structures. • Sections 12.5.1.1 and 16.7 – Deleted Table 15.2.2.3.3 because no [redacted] parameters are part of the Endpoint Analysis Modelling. • Section 12.5.2.1 – Added 'and the quantity excreted' for more clarity. • Section 12.5.3 – Added the Proc Lifetest SAS code to be used. • Section 12.5.4.4 – Added Vital Signs at V1 to be listed and summarized. • Sections 16.2 to 16.5 – Specified when the parameters are to be log-transformed accordingly to the planned statistical analyses (see Section 12.5). • Section 16.2 – Added FEV_1/FVC and Reversibility in FEV_1. Corrected MPO into 'Percent reduction', Apo B into 'Absolute decrease', and added 'Apo B/Apo A1'. • Sections 16.4 and 16.5 – Added the 'Effect Measure' column. • Section 16.5 – Suppressed DLCO [Hb] because not available with lung diffusion data, and rename VI [BTPS] to VI accordingly to data to be received.
4.0	27 February 2018	• Section 1 – Updated to latest reviewers names. • Section 7.1.4 –Added formulas for FEV_1/FVC and reversibility in FEV_1. • Section 7.1.5 – Added the Stethographics and Stethos data

Version	Date of Revision	Description
		section. • Section 9 – Added that Stethographics and Stethos data will be analysed separately. Added COPD scores to be listed. • Section 12.1.3 – Updated the rounding rule for summary statistics. • Section 12.1.4.2 - Clarified that the endpoint FEV1 means pre-bronchodilator %pred FEV1 and post-bronchodilator %pred FEV1. • Section 12.4 – Added that 3 months will be considered as 90 days for criterion about NRT. • Section 12.5.1 – Added that Stethographics and Stethos data will be analysed separately. • Section 12.5.1.1 – Added that in case of computational issue, the clinical risk endpoint may not be analyzed. • Section 12.5.1.1 _ Added wording on handling of the covariate Caucasian Origin. • Appendices 16.3 to 16.5 – Updated the Appendix order to follow core SAP order. • Appendix 16.3 – Added the COPD scores derived from Stethographics. • Appendix 16.5 – Added that CO is not to be log-transformed. • Appendix 16.5 – Changed 'Crotonaldehyde [gas]' to Reduced List. • Appendix 16.7 – Updated titles from 'Subjects' into 'Population'. Table 15.2.1.3.2 - Updated title from 'Enrolled' into 'All Subjects'. Tables 15.2.5.1.2, 15.2.5.2.2 and 15.2.5.3.2 - Updated titles for AE tables from "at 6 months" into "in 6 months".

4 ABBREVIATION OF TERMS AND DEFINITIONS

4.1 Abbreviations

The following abbreviations are used within this SAP.

1-NA	1-aminonaphthalene
1-OHP	1-hydroxypyrene
2-NA	2-aminonaphthalene
3-HMPMA	3-hydroxy-1-methylpropylmercapturic acid
3-HPMA	3-hydroxypropylmercapturic acid
4-ABP	4-aminobiphenyl
8-epi-PGF2α	8-epi-prostaglandin F2α
11-DTX-B2	11-dehydro-thromboxane B2
AE/SAE	Adverse Event/ Serious Adverse Event
AIC	Akaike's Information Criterion
Apo A1	Apolipoprotein A1
Apo B	Apolipoprotein B
AQD	Actual quit date
ATC	Anatomical Therapeutic and Chemical
B[a]P	3-hydroxybenzo(a)pyrene
BMI	Body Mass Index
BoExp	Biomarkers of exposure
CC	Conventional cigarette
CEMA	2-cyanoethylmercapturic acid
CI	Confidence interval
CO	Carbon monoxide
COHb	Carboxyhaemoglobin
COPD	Chronic obstructive pulmonary disease
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events and Common Toxicity Criteria
CV	Coefficient of variation

CVD	Cardiovascular disease
CYP2A6	Cytochrome P450 2A6
DLCO	Diffusion capacity for lung CO
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EOS	End of Study
FEF 25-75	Forced expiratory flow 25-75
FEV_1	Forced Expiratory Volume in 1 second
FRC	Functional residual capacity
FTND	Fagerström Test for Nicotine Dependence
FVC	Forced Vital Capacity
HbA1c	Glycosylated hemoglobin
HDL-C	High density lipoprotein cholesterol
HEMA	2-hydroxyethylmercapturic acid
HIV	Human Immunodeficiency Virus
HMPMA	3-hydroxy-1-methylpropyl-mercapturic acid
HPHC	Harmful and potentially harmful constituent
HR	Heart rate
hs-CRP	High sensitive C-reactive protein
IC	Inspiratory capacity
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
KCO	Rate constant of CO, equal to DLCO/VA
KM	Kaplan-Meier
LDL-C	Low density lipoprotein cholesterol
LLOQ	Lower Limit of Quantification
LOQ	Limit of quantification
LS	Least Squares
MedDRA	Medical Dictionary for Regulatory Activities
MHBMA	Monohydroxybutenyl mercapturic acid

MPO	Myeloperoxidase
MRTP	Modified risk tabacco product
Neq	Nicotine equivalents
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
NNK	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
NNN	Total N-nitrosonornicotine
NRT	Nicotine replacement therapy
o-tol	o-toluidine
PD	Protocol Deviation
PI	Principal investigator
PMI	Philip Morris International
PT	Preferred Term
[redacted]	[redacted]
QTcB	QT Interval Corrected using Bazett's Formula
QTcF	QT Interval Corrected using Fridericia's Formula
RC	Relative Change
RV	Residual Volume
SA	Smoking abstinence
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
S-BMA	S-benzyl-mercapturic acid
SC	Smoking cessation
SD	Standard Deviation
SES	Socio-economic status/situation
sICAM-1	Soluble intercellular adhesion molecule-1
SMP	Safety Management Plan
SOC	System Organ Class
SOP	Standard Operating Procedure
S-PMA	S-phenylmercapturic acid
TFL	Tables, Figures, and Listings
TLC	Total lung capacity

TQD	Target Quit Date
ULOQ	Upper Limit of Quantification
VA	Alveolar volume
VAS	Visual Analogue Scale
VC	Vital capacity
VI	Inspired Volume
WBC	White blood cell
WHO	World Health Organisation
WHO-DDE	World Health Organization-Drug Dictionary Enhanced

4.2 Definition of Special Terms

The following special terms are used in this SAP:

Actual quit date (AQD)	The AQD is the date recorded in the source document on which the subject actually quits smoking and from which onwards total smoking abstinence (SA) is expected. AQD corresponds to the first day without any tobacco/nicotine use (except NRT).
Baseline	Baseline Visit is defined as V2.
Baseline value	Unless specified, baseline value is defined as the last available value prior to Target quit date (TQD) or AQD, whichever comes first.
Conventional cigarette (CC)	The term 'conventional cigarette' refers to commercially available cigarettes (manufactured and hand-rolled) and excludes cigars, pipes, bidis, and other nicotine-containing products.
End of study (EOS)	The individual EOS for a subject who has previously completed V17 is defined as V18, unless the subject is lost to safety follow-up. The individual EOS for a subject who has been discontinued from the study prematurely (early termination) is defined as the date of the early termination of the subject plus 28 days of the Safety Follow-Up Period. For withdrawn subjects the individual EOS is equal to the date of discontinuation.
Lost to follow-up (date)	When the PI(s) or designee(s) declare(s) a subject is lost to follow-up, the lost to follow-up date will be recorded and will correspond to the date of the end of study of the subject. If the site has lost track of the subject but the subject has reached the maximum number of study days (465 days), then the PI(s) or designee(s) will declare the subject lost to follow-up at this date.
Nicotine replacement therapy (NRT)	The NRT consists of nicotine-containing products such as nicotine gum, lozenge, patches, inhaler or nasal spray. The NRT should be used as per country label for up to 3 months (+2 weeks) after the start date of NRT. NRT may be started at any time between the TQD and 1 week after the AQD.

Screening	Screening Visit is defined as V1
Study completion	The study will be completed once the last successful quitter has reached V18.
Successful quitter	A successful quitter is defined as a subject that was continuously abstinent from smoking from AQD to V17, as assessed by the four criteria described in Section 12.4 "Measurements of Compliance".
Target quit date (TQD)	Date from which the smoker intends to quit smoking and may start treatment with his/her preferred NRT as per country label, if any and where applicable.
Unsuccessful quitter	An unsuccessful quitter is defined as a subject that was not continuously abstinent from smoking from AQD to V17, as assessed by the four criteria described in Section 12.4 "Measurements of Compliance".

5 STUDY OBJECTIVES AND ENDPOINTS

The objectives and endpoints of this study are:

1. To describe the clinical, biological and functional changes in smokers who are continuously abstinent from smoking.

   Clinical risk endpoints associated with cardiovascular disease (CVD) at week 13 (V8), week 26 (V11) and week 52 (V17):

   - White blood cell count (WBC), platelet count, glycosylated hemoglobin (HbA1c), and carboxyhemoglobin (COHb) in blood.
   - High and low density lipoprotein cholesterol (HDL-C, and LDL-C), myeloperoxidase (MPO), soluble intercellular adhesion molecule-1 (sICAM-1), apolipoprotein A1 and B (Apo A1 and Apo B), and high sensitivity C-reactive protein (hs-CRP) in serum.
   - Fibrinogen and homocysteine in plasma.
   - Albumin, 11-dehydrothromboxane B2 (11-DTX-B2) and 8-epi-prostaglandin-alpha (8-epi-$PGF_{2\alpha}$) in urine (expressed as concentration adjusted to creatinine).

   Clinical risk endpoints associated with respiratory diseases at week 13 (V8), week 26 (V11) and week 52 (V17):

   - Spirometry (pre- and post-bronchodilator): Forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), FEV_1/FVC, and forced expiratory flow (FEF 25-75).
   - Lung volume: vital capacity (VC), total lung capacity (TLC), functional residual capacity (FRC), inspiratory capacity (IC), at selected sites specialized for lung function testing.
   - Cough symptoms (intensity and frequency), amount of sputum production and bothersomeness of cough symptom from the cough-visual analog scale (cough-VAS) questionnaire.

   Clinical risk endpoints associated with respiratory diseases which will be assessed/collected at the Heart Lung Centre at the [redacted] only are:

   - Computerized multichannel lung sounds analysis (Stethographics and Stethos) at week 13 (V8), week 26 (V11) and week 52 (V17).
   - Gas transfer: diffusion capacity for lung carbon monoxide (CO) (DLCO) and rate constant of CO (KCO) at week 2 (V5), week 4 (V6), week 9 (V7), week 13 (V8), week 26 (V11) and week 52 (V17).

- Samples from nasal and buccal epithelium will be collected at Baseline Visit (V2), week 13 (V8), week 26 (V11) and week 52 (V17)

Clinical risk endpoint associated with xenobiotic metabolism at week 13 (V8), week 26 (V11), and week 52 (V17):

- Cytochrome P450 2A6 (CYP2A6) activity: molar metabolic ratio of *trans*-3-hydroxycotinine/cotinine in plasma.

Clinical risk endpoint associated with genotoxicity at week 13 (V8), week 26 (V11), and week 52 (V17):

- Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (Total NNAL) in urine (expressed as concentration adjusted to creatinine).

2. To describe the changes in biomarkers of exposure (BoExp) to harmful and potentially harmful constituents (HPHCs) in smokers who are continuously abstinent from smoking.

   BoExp to HPHCs at week 13 (V8), week 26 (V11), and week 52 (V17):

   - BoExp to carbon monoxide (CO): CO in exhaled breath (expressed as ppm).*
   - BoExp to nicotine: cotinine and nicotine in plasma and nicotine equivalents (Neq) in urine[1] *
   - BoExp to 1,3-butadiene: monohydroxybutenylmercapturic acid (MHBMA).*
   - BoExp to acrolein: 3-hydroxypropylmercapturic acid (3-HPMA).*
   - BoExp to acrylonitrile: 2-cyanoethylmercapturic acid (CEMA).*
   - BoExp to benzo(a)pyrene: 3-hydroxybenzo(a)pyrene (B[a]P).*
   - BoExp to pyrene: Total 1-hydroxypyrene (Total 1-OHP).*
   - BoExp to crotonaldehyde: 3-hydroxy-1-methylpropylmercapturic acid (3-HMPMA).*
   - BoExp to N-nitrosonornicotine: total N-nitrosonornicotine (Total NNN).*
   - BoExp to 4-aminobiphenyl: 4-aminobiphenyl (4-ABP).
   - BoExp to benzene: S-phenylmercapturic acid (S-PMA).
   - BoExp to 1-aminonaphthalene: 1-aminonaphthalene (1-NA).
   - BoExp to 2-aminonaphthalene: 2-aminonaphthalene (2-NA).

[1] Nicotine equivalents (Neq) are defined as molar sum of free nicotine, nicotine-glucuronide, free cotinine, cotinine-glucuronide, free *trans*-3'-hydroxycotinine, *trans*-3'- hydroxycotinine-glucuronide.

- BoExp to o-toluidine: o-toluidine (o-tol).
- BoExp to ethylene oxide: 2-hydroxyethylmercapturic acid (HEMA).
- BoExp to toluene: S-benzylmercapturic acid (S-BMA).

All BoExp measured in urine, will be expressed as concentrations adjusted for creatinine. Only BoExp marked with " * " will be assessed at week 26 (V11) and week 52 (V17).

3. To describe the rate of continuous smoking abstinence at each visit following the actual quit date (AQD) of smoking cessation.

4. To monitor the safety:
   - Adverse events (AEs) / serious adverse events (SAEs).
   - Body weight.
   - Vital signs.
   - Spirometry.
   - Electrocardiogram (ECG).
   - Clinical chemistry, hematology and urine analysis safety panel.
   - Physical examination.
   - Concomitant medications.

5. Additional study assessments:

- Prochaska "Stage of change" questionnaire.
- Fagerström test for nicotine dependence (FTND, revised version).
- Socio-economic status (SES) in the following countries: US, UK, Poland, Germany and Japan).
- Lifestyle assessments.

6 INVESTIGATIONAL PLAN

6.1 Study Design

This is an ambulatory, single arm, smoking cessation study in healthy smokers. This multi-regional study will be conducted in centers located in the United States (US), Japan (JP) and Europe (EU). Additional objectives/endpoints which will be assessed /collected only at the Heart Lung Centre at the [redacted] include: computerized multichannel lung sounds analysis, gas transfer assessment, and nasal and buccal epithelium scrapes. The maximum total duration of the study for a subject will be 66 weeks.

Smokers who are motivated to quit smoking within the next 30 days at Screening (V1) will be enrolled in order to reach approximately 950 subjects who have been continuously abstinent from smoking from the AQD onwards at week 2 (V5), and to reach at least 190 successful quitters at week 52 (V17) to complete the study.

Screening Period

The Screening Visit (V1) will take place within 1-42 days prior to enrollment at Baseline Visit (V2). Eligibility of the subjects to participate in the study will be assessed at V1. Eligible subjects will be provided with urine containers at V1.

Baseline Visit – V2

Twenty-four-hour urine collection will start in the morning of the day prior to V2 and end 24 hours later in the morning of V2. Enrollment of the subject will take place at V2. All subjects will continue smoking their preferred brand of conventional cigarettes (CC). Before check-out at V2, subjects will be asked to define their TQD, the date from which the subject will stop smoking. The TQD must be within 14 days after V2. At TQD or thereafter, NRT use will be allowed as per label for up to 3 months (+2 weeks) to support the subject to remain abstinent from smoking. NRT may be started at any time between the TQD and 1 week after the AQD. The start day of NRT will be counted as Day 1 of NRT use. From that day on, the duration of NRT use must not exceed 3 months + 2 weeks.

From Check-out of V2 to AQD

The subject will be asked to come to the clinic for V3 within 24 to 48 hours after their defined TQD. The goal of this visit will be to ensure that the subject has actually quit smoking and to provide him/her with the necessary support. From V3 onwards, smoking cessation (SC) counseling and behavioral support will be provided to the subject according to the SC support plan. Additional SC support will be offered at any time as requested by the subject.

A Grace Period of a maximum of 14 days will be allowed after the TQD, during which occasional slips of smoking (defined as occasional use of nicotine and/or tobacco-containing products day) will be accepted. From the AQD onwards, strict abstinence from any tobacco- or nicotine-containing product (including electronic cigarettes) other than Nicotine replacement therapy (NRT) is required. Subjects will be asked to record their AQD. The latest possible day for the AQD is defined as the last day of the Grace Period (*i.e.*, TQD + 14 days).

Therefore, the period from check-out of V2 to AQD (Day 1) might last up to 28 days. This period aims to identify subjects who are more motivated and more likely to quit as well as to remain continuously abstinent from smoking for the whole duration of the study.

Smoking Abstinence Period (from the AQD up to the check-out of V17 [Week 52])

The Smoking Abstinence Period will start on AQD, which will serve as the starting point for all subsequent visits. From the AQD, subjects will be asked to come on site at week 1 (V4), week 2 (V5) and then on a monthly basis at week 4 (V6), week 9 (V7), week 13 (V8), week 17 (V9), week 22 (V10), week 26 (V11), week 30 (V12), week 35 (V13), week 39 (V14), week 43 (V15), week 48 (V16), and week 52 (V17). Visits will be scheduled based on the AQD. A time window of ± 8 days is allowed for the visits, except V4 (± 3 days) and V5 (± 3 days).

V8, V11, and V17 will correspond to full assessment visits at site(s) where 24-hour urine and blood samples will be collected for analysis of BoExp and clinical risk endpoints. The collection of the 24-hour urine which has to be done for these visits will start at home in the morning of the day before the visit and will end 24 hours later in the morning of the day of the visit to the clinic.

The Safety Follow-Up Period and Phone Contact (28 days after the check-out of V17 [V18 (±3 days); week 56])

A subject who has completed week 52 (V17), or a subject who has been discontinued from the study prematurely (early termination), will enter a 28-day Safety Follow-Up Period during which spontaneously reported new AEs/SAEs will be recorded, and the active follow-up of ongoing AEs/SAEs will be done by the site. All AEs will be followed-up until resolved, stabilized (*i.e.*, no worsening of the event), or a plausible explanation for the event has been found until the end of the Safety Follow-Up Period.

At the end of the Safety Follow-Up Period in week 56 (V18 [±3 days]), the investigator will attempt to contact only the subject who has previously completed V17 by phone to check if all AEs/SAEs potentially occurring during the Safety Follow-Up period are fully reported and for self-reporting by the subject on continuous smoking abstinence. At the end of the Safety Follow-Up Period, all ongoing AEs will be documented as “ongoing” and will not be followed-up by the investigator. At the discretion of the investigator, the subject will be referred to his/her General Practitioner for follow up on ongoing AEs.

If the investigator can reach the subject who has previously completed V17 by phone at the end of the Safety Follow-Up Period in Week 56, the date of this phone call with the subject will be recorded as the date of the EOS of the subject.

If the investigator cannot reach the subject who has previously completed V17 by phone at the end of the Safety Follow-Up Period in Week 56 after a reasonable number of attempts, the date of the last contact (e.g., last visit of the subject, last phone call with the subject) will be recorded as the date of the EOS of the subject.

End of Study

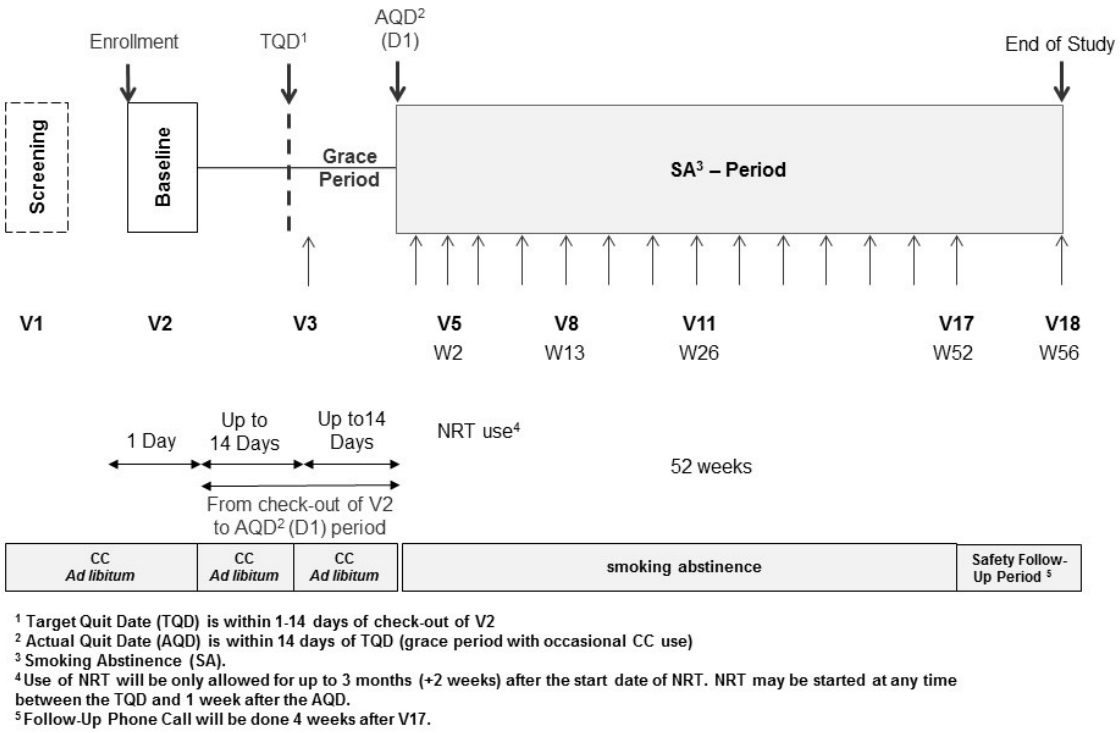
The individual EOS for a subject who has previously completed V17 is defined as V18, unless the subject is lost to safety follow-up.

The individual EOS for a subject who has been discontinued from the study prematurely (early termination) is defined as the date of the early termination of the subject plus 28 days of the Safety Follow-Up Period. For withdrawn subjects the individual EOS is equal to the date of discontinuation.

In subjects lost to follow-up, the EOS is defined as the date of lost to follow-up; it will be the date when the PI(s) or designee(s) declare(s) a subject is lost to follow-up.

Study design and visit schedule are provided in Figure 1.

Figure 1 Study Flowchart



[1] Target Quit Date (TQD) is within 1-14 days of check-out of V2
[2] Actual Quit Date (AQD) is within 14 days of TQD (grace period with occasional CC use)
[3] Smoking Abstinence (SA).
[4] Use of NRT will be only allowed for up to 3 months (+2 weeks) after the start date of NRT. NRT may be started at any time between the TQD and 1 week after the AQD.
[5] Follow-Up Phone Call will be done 4 weeks after V17.

Abbreviations: CC = Conventional cigarettes; NRT = Nicotine replacement therapy; SA = Smoking abstinence; V = Visit; W = week

6.2 Selection of Study Population

Healthy smoking adult subjects (female or male), with no restriction on race and ethnicities, who have smoked at least 10 CCs per day on average for the last 12 months and who have been smoking for at least the last 10 years will be enrolled in this study.

The study will be a multi-center study, with approximately 50 sites located in Europe, Japan and US.

6.2.1 Inclusion Criteria

Each subject enrolled at Baseline Visit (V2) must meet the following criteria:

Inclusion Criteria	Screening (V1)	Baseline (V2)
1. Subject has signed the ICF(s) and is able to understand the information provided in the ICF(s).	X	
2. Subject is aged from 30 to 65 years old (inclusive).	X	
3. Smoking, healthy subject as judged by the investigator based on all available assessments from the Screening Period (e.g., safety laboratory, spirometry, vital signs, physical examination, ECG, concomitant medications and medical history).	X	
4. Subject smokes at least 10 commercially available CCs per day on average (no brand restrictions), for the last 12 months, based on self-reporting. Furthermore, the subject has been smoking for at least the last 10 years prior to screening. The smoking status will be verified based on an urinary cotinine test (cotinine ≥ 200 ng/mL).	X	X
5. The subject is willing to quit smoking within the next 30 days, as assessed by the Prochaska's 'Stage of Change' questionnaire.	X	
6. The subject is ready to comply with the study protocol (e.g., readiness to accept continuous smoking abstinence for 52 weeks).	X	X

6.2.2 Exclusion Criteria

Subjects who meet any of the following exclusion criteria must not be enrolled into the study:

Exclusion Criteria	Screening (V1)	Baseline (V2)
1. As per the investigator (or designee) judgment, the subject cannot participate in the study for any reason (e.g., medical, psychiatric and/or social reason).	X	
2. The subject is legally incompetent, or physically or mentally incapable of giving consent (e.g., emergency situation, under guardianship, in a social or psychiatric establishment, prisoner or involuntarily incarcerated).	X	
3. Clinically relevant gastrointestinal, renal, hepatic, neurological, hematological, endocrine, oncological, urological, pulmonary, immunological, psychiatric or cardiovascular disorders or any other conditions that in	X	

Exclusion Criteria	Screening (V1)	Baseline (V2)
the opinion of the investigators would jeopardize the safety of the participant or affect the validity of the study results.		
4. Abnormal findings on physical examination, in the medical history, or in clinical laboratory results deemed clinically relevant by investigators (as per the common terminology criteria for adverse events [CTCAE]).	X	
5. Acute illness (e.g., upper-respiratory-tract infection, viral infection etc.) requiring treatment within 42 days prior to enrollment in the study.		X
6. Use of any prescribed or over-the-counter systemic medication listed in Table 1* of Section 6.4 of study protocol (except for vitamins) within the last 42 days prior to enrollment in the study (except for hormonal contraceptives and hormone-replacement therapy).		X
7. The subject has $FEV_1/FVC < 0.7$ and $FEV_1 < 80\%$ predicted value at post-bronchodilator spirometry.	X	
8. The subject has $FEV_1/FVC < 0.75$ (post-bronchodilator) and reversibility in FEV_1 (that is both > 12% and > 200 mL from pre- to post-bronchodilator values).	X	
9. The subject has a body mass index (BMI) < 18.5 or ≥ 35 kg/m2.	X	
10. As per the investigator's or designee's 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.	X	
11. The subject has a positive alcohol test and/or he/she has a history of alcohol abuse that could interfere with his/her participation in the study.	X	
12. The subject has a positive urine drug test.	X	
13. The subject has positive serology test for human immunodeficiency virus (HIV)1/2, Hepatitis B or Hepatitis C.	X	

Exclusion Criteria	Screening (V1)	Baseline (V2)
14. The subject has donated or received whole blood or blood products within 3 months prior to V1.	X	
15. The subject has been previously screened for this study.	X	
16. The subject is a current or former employee of the tobacco industry or their first-degree relatives (parent, sibling and child).	X	
17. The subject is an employee of the investigational site or any other parties involved in the study or their first-degree relatives (parent, sibling and child).	X	
18. The subject has participated in a clinical study within 3 months prior to V1.	X	
19. For women only: subject is pregnant (does have positive pregnancy test) or is breast feeding.	X	X

* Concomitant Medication with potential impact on Clinical Risk Endpoints (Section 6.4 of study protocol). Subjects using salbutamol for post-bronchodilator spirometry testing at screening will not be excluded from the study.

6.3 Product Allocation and Blinding

No randomization and no blinding are required in this ambulatory single arm smoking cessation study. However an adequate representation of subjects by sex (*i.e.*, to have at least 40% of each sex at enrollment) will be monitored during the study. The Study Manual about Smoking Cessation Support and Enrollment Plan details how the capping will be handled.

6.4 Clinical, Laboratory, Biomarkers and Safety Variables

Clinical, laboratory, biomarkers and safety variables will be assessed as detailed in Appendix 16.1 "Study Assessments". The endpoints are detailed in section 5 "STUDY OBJECTIVES AND ENDPOINTS".

6.4.1 Assessments at Visit 17 to be performed if Total NNAL is above the cut-off at Visit 11

Analysis of Total NNAL will be performed by a central laboratory to determine which assessments will be performed at Visit 17. The concentration of Total NNAL will be determined in 24-hour urine collected at Visit 11 (cut-off < 75.9 pg/mL) [4]. If the concentration of Total NNAL is ≥ 75.9 pg/mL, the subject will remain in and continue with

the study, unless the subject is discontinued for other reasons. However, for this subject, only the following assessments at Visit 17 will be performed:

- Smoking cessation support
- Prior/Concomitant medication
- Pregnancy test (all female subjects)
- Vital signs
- CO Breath test
- Cotinine test in spot urine (cut-off < 100 ng/mL)
- AE/SAE recording.

7 DERIVED AND COMPUTED VARIABLES

For each timepoint, the change from Baseline will be calculated by subtracting the individual subject's Baseline value from the value at the given timepoint. Mean change from Baseline (Baseline is defined in Section 4.2 "Definition of Special Terms") is the mean of all individual subjects' change from Baseline values.

For each timepoint, the percent change from Baseline will be calculated by subtracting the individual subject's Baseline value from the value at the given timepoint and then dividing this calculated value by the individual subject's Baseline value and multiplying by 100. Mean percent change from Baseline is the mean of all individual subjects' percent change from Baseline values.

When the Baseline values is 0, the percent change from baseline will not be calculated and the number of such cases will be tabulated as "Not Calculated" in the descriptive summaries.

The Caucasian origin will include the subjects with a race equal to white, excluding subjects with ethnicity Hispanic or Latino, or Japanese.

Age, BMI, QTcB and QTcF will be calculated in database for all subjects as defined below. Weight and height will also be converted to standard units for analysis.

Age will be calculated as the number of complete years between a subject's birth date and the date the subject signed informed consent. In case the birth day is missing (and the month is present), it will be imputed to 1st of the month for the age calculation. In case both the birth day and month are missing, they will be imputed to the 1st January of the year. For countries (e.g. Germany) where, according to local regulation, only the birth year can be recorded, age will be entered on eCRF. When age is both reported and derived in eCRF, only the age reported will be included in the summaries.

Weight will be summarized in kg, so weight in lb will be multiplied by 0.45359237, and rounded to one decimal place. Height will be summarized in cm, so height in inch will multiplied by 2.54, and rounded to nearest integer.

BMI will be calculated at site and derived in database from the body weight and height using the following formula:

$$\text{BMI } [\text{kg/m}^2] = \frac{\text{weight in kilograms}}{\text{height in meters}^2}$$

The QT interval corrected using Bazett's formula (QTcB) will be calculated on site as follows:

$$\text{QTcB} = \frac{\text{QT}}{\sqrt[2]{\left(60/_{\text{HR}}\right)}}$$

with HR = Heart rate.

The QT interval corrected using Fridericia's formula (QTcF) will be calculated on site as follows:

$$\text{QTcF} = \frac{\text{QT}}{\sqrt[3]{\left(60/_{\text{HR}}\right)}}$$

The indirect bilirubin will be derived as below.

$$\text{Indirect bilirubin} = \text{Total Bilirubin} - \text{Direct Bilirubin}$$

The apo B/apo A1 ratio will be derived.

The geometric coefficient of variation (CV) will be calculated using the following formula:

$$\text{CV} = 100\sqrt{e^{\text{var}} - 1}$$

where var = the variance from the log transformed data.

The geometric percent Relative Change (RC) from baseline will be calculated using the following formula:

$$\text{RC} = 100 * (\exp\big(\text{mean}(\ln(x) - \ln(\text{base}))\big) - 1)$$

where ln(x) are the natural logarithm of the values at the timepoint and ln(base) are the natural logarithm of the baseline values.

7.1 Clinical Risk Endpoints and Biomarkers of Exposure

7.1.1 Clinical Risk Endpoints and Biomarkers of Exposure in Urine

The adjustment for creatinine for the urinary clinical risk endpoints and biomarkers will be calculated as:

$$\text{Clinical Risk Endpoint or Biomarker (creatinine adjusted)} = \frac{[\text{Clinical Risk Endpoint or Biomarker}]}{[\text{Creatinine}]}$$

where the [ ] indicated concentrations measured from the same 24 hour urine collection.

7.1.2 Nicotine Equivalents

The concentration of Neq in 24 hours will be derived according to the formula below. The concentrations reported for free nicotine and its five major metabolites will not be used individually as analysis variables.

$$\begin{aligned}\text{Neq [mg/L]} = {} & (\text{free nicotine[µmol/L]} + \text{nicotine-glucuronide [µmol/L]} \\ & + \text{free cotinine [µmol/L]} + \text{cotinine-glucuronide [µmol/L]} \\ & + \text{free } \textit{trans}\text{-3'-hydroxycotinine [µmol/L]} \\ & + \textit{trans}\text{-3'-hydroxycotinine-glucuronide [µmol/L])} \\ & *162.2[\mu g/\mu mol] / 1000 [\mu g/mg]\end{aligned}$$

Since all concentrations must be in µmol/L before applying the above formula, the conversion factors will be applied as described in Table 1 below:

Table 1. Conversion factors from ng/ml into µmol/L

	Molecular weight (g/mol)	Conversion factor from ng/mL to µmol/L
Free Nicotine	162.232 [5]	0.006164
Nicotine glucuronide	338.356 [6]	0.002955
Cotinine	176.218 [7]	0.005675
Cotinine-glucuronide	352.341 [8]	0.002838
Trans-3'hydroxycotinine	192.217 [9]	0.005202
Trans-3'hydroxycotinine-glucuronide	368.34 [10]	0.002715

7.1.3 CYP2A6

CYP2A6 activity is calculated in plasma as the metabolic ratio of *trans*-3' hydroxycotinine to cotinine, both expressed in molar equivalent (nmol/L) [11].

The conversion factor will be applied as in Table 2 below:

Table 2. Conversion factors from ng/ml into nmol/L

	Molecular weight (g/mol)	Conversion factor from ng/mL to nmol/L
Cotinine	176.218 [7]	5.675
Trans-3'hydroxycotinine	192.217 [9]	5.202

The converted results will be calculated to three decimal places and the ratio will be reported as a percentage with two decimal places.

If either the cotinine or the *trans*-3'hydroxycotinine concentration is below LLOQ then the ratio will not be calculated. It will be coded as NC for "Not Calculated", and will be excluded from analysis, but will be included in the descriptive statistics as a separate category NC.

7.1.4 Spirometry

Results from the scheduled assessment and for a repeat asssessment can be collected. Each assessment will be listed. Only validated spirometry data will be available. If data are not available, the assessment is either missing (*i.e.*, assessment not done) or not valid/accepted (*i.e.*, assessment not performed correctly). Spirometry will be selected for their inclusion in the analysis as Baseline value, V8, V11, and V17 endpoints across available scheduled and repeat assessments, as described below. The assessements selected for analysis will be flagged in the listings accordingly.

For each spirometry endpoint:

Table 3. Spirometry Data Included in Analysis

Scheduled Assessment	Repeat Assessment	Included in Analysis
Pre- and Post-available	Pre- and Post-available Only Pre-available Only Post-available None available	Pre- and Post from scheduled assessment
Only Pre-available Only Post-available None available	Pre- and Post-available	Pre- and Post- from repeat assessment
Only Pre-available	Only Post-available	Merge Pre- and Post- from the two assessments
Only Post-available	Only Pre-available	Merge Pre- and Post- from the two assessments
Only Pre-available Only Post-available	None available	Pre- or Post- data at scheduled assessment
None available	Only Pre-available Only Post-available	Pre- or Post- data at repeat assessment
Only Pre-available	Only Pre-available	Pre- from scheduled assessment
Only Post-available	Only Post-available	Post- from scheduled assessment

Pre- and Post- refer to spirometry data collected at pre- and post-bronchodilator session

Results for the reversibility will be available for analysis purposes only in case both pre- and post-bronchodilator data are available for the same assessment i.e. Pre- and Post- are both from scheduled assessment, or Pre- and Post are both from repeat assessment.

There will be no need to merge information about salbutamol, this will be available in listings only.

The FEV_1/FVC ratio will be derived and uploaded into database.

The reversibility in FEV_1 in mL and % will also be derived as below, and uploaded into database.

$$\text{Reversibility in FEV1 [mL]} = (\text{Post FEV1 [L]} - \text{Pre FEV1 [L]}) \times 1000$$

$$\text{Reversibility in FEV1 [\%]} = \frac{\text{Post FEV1 [L]} - \text{Pre FEV1[L]}}{\text{Pre FEV1 [L]}} \text{ x } 100$$

Residual volume (RV) will be calculated as TLC minus VC.

7.1.5 Stethographics and Stethos data

The Stethographics parameters listed in Appendix 16.3 will be derived from the Stethographics software after input of recorded lung sounds captured by the Stethographics device.

The Stethos parameters will also be derived from the Stethographics software.

All received Stethographics data will be listed, but the analysis of both Stethographics and Stethos data will be described in a separate SAP.

7.2 Questionnaires

7.2.1 Questions on Smoking History/Habits

At V1 and V2, subjects will be asked 5 questions on Smoking History/Habits related to their current and past smoking behavior.

The questions on Smoking History/Habits are self-administrated, to be answered by subjects. Questions 5, 5a and 5b are about the e-cigarette use. No imputation for missing data will be performed.

The questions on Smoking History/Habits are shown in Table 4.

Table 4. Questions on Smoking History/Habits

	Question	Answer
1	Have you smoked for at least the past 10 consecutive years?	Yes / No
2	How many years have you smoked?	Numeric response, 2 digits
3	On average, how many cigarettes per day have you smoked over the last year?	Numeric response, 2 digits
4	On average, how many cigarettes per day have you smoked since you started	Numeric response, 2 digits

Table 4. Questions on Smoking History/Habits

	Question	Answer
	smoking?	
5	On average, how would you describe your e-cigarette use over the last year?	a. Daily. b. Weekly. c. Sporadically. (less than once per week) d. Tried e-cigarettes. (between 1 – 10 uses) e. Never tried e-cigarettes.
5.a	If daily - How much use per day?	Numeric response, 2 digits
5.b	If weekly - How much use per week?	Numeric response, 2 digits

The average daily number of conventional cigarettes (CC) smoked over the last year will be obtained from the self-reported subjects' answer to item 3 at Baseline.

The smoking history intensity at Baseline evaluating the amount a person has smoked over his/her life, expressed as number of pack-years, will be derived as: [item 2] x [item 4]/20 and will be rounded to one decimal place. One pack year is defined as twenty cigarettes smoked every day for one year.

7.2.2 Prochaska 'Stage of Change' Questionnaire: Intention to Quit Smoking

Subjects will complete the Prochaska 'Stage of Change' questionnaire at V1.

This questionnaire will be used to assess the stage of smokers' intention to quit smoking (Non-smoker, Precontemplation, Contemplation, Preparation, Action, and Maintenance Stage). The details of the staging algorithm [12, 13] are provided in the Appendix 3 of the study protocol.

The smokers' stage will be derived. No imputation of missing data will be performed.

The questions are shown in Table 5.

Table 5. Prochaska 'Stage of Change' Questionnaire

	Question	Answer	Stage
1	Are you currently a smoker?	Yes, I currently smoke	
		No, I quit within the last 6 months	ACTION STAGE
		No, I quit more than 6 months ago	MAINTENANCE STAGE
		No, I have never smoked	NON-SMOKER
Smokers only			
2	In the last year, how many times have you quit smoking for at least 24 hours?	Numeric response, 2 digits	
3	Are you seriously considering quitting smoking?	Yes, within the next 30 days	And if they have one 24-hour quit attempt in the past year: PREPARATION STAGE And if there was no quit attempt in the past year: CONTEMPLATION STAGE
		Yes, within the next 6 months	CONTEMPLATION
		No, not thinking of quitting	PRECONTEMPLATION

7.2.3 Fagerström Test for Nicotine Dependence (FTND)

The FTND will be used in its revised version, as updated in 2012 [14]. These questions are to be answered by the subjects themselves. It is conducted at V2 to determine subject's dependence on nicotine.

Table 6 below details the six questions of the questionnaire, and the scores associated with each question.

The FTND total score will be derived by summing the individual item scores. If any item is missing the total score will be set to missing. No missing data imputation will be performed. For the FTND total score, descriptive statistics and frequency tables according to the following classification will be provided [14]:

Mild	Total score from 0 to 3
Moderate	Total score from 4 to 6
Severe	Total score from 7 to 10

Table 6. Fagerström Test for Nicotine Dependence

	FTND Question	Answer	Score
1	How soon after you wake up do you smoke your first cigarette?	After 60 minutes	0
		31 to 60 minutes	1
		6 to 30 minutes	2
		Within 5 minutes	3
2	Do you find it difficult to refrain from smoking in places where it is prohibited?	No	0
		Yes	1
3	Which cigarette would you hate most to give up?	The first one in the morning	1
		Any other one	0
4	How many cigarettes per day do you smoke?	10 or less	0
		11 to 20	1
		21 to 30	2
		31 or more	3
5	Do you smoke more frequently during the first hours after waking than during the rest of the day?	No	0
		Yes	1
6	Do you smoke if you are so sick that you are in bed most of the day?	No	0
		Yes	1

7.2.4 Cough-VAS Questionnaire

Subjects will self-report the respiratory symptom ‘cough’ using a VAS, three Likert scale questions, and one open ended question at V2, V8, V11 and V17.

Subjects will be asked if they have experienced a regular need to cough, (*i.e.*, Question 1: whether they have coughed several times in the previous 24 hours prior to assessment). If the answer is ‘yes’, subjects will be asked to complete questionnaire (*i.e.*, Questions 2, 3 and 4), and will also be asked to assess the intensity and frequency of cough and the amount of sputum production on Likert scales.

Table 7 below provides details to these Questions 2, 3 and 4.

The VAS will assess how bothersome cough is to the subject ranging from ‘not bothering me at all’ to ‘extremely bothersome’, and this will be given a numeric value between 0 and 100, measured on a 100 mm scale (“100” being “extremly bothersome”).

Then the subjects will report via an open question any other important observations that they would like to mention about their coughing. The observations from this field will only be reported in a listing.

The questions will be analyzed separately by frequency summaries, no missing data imputation will be performed.

Table 7. Cough Assessment Likert Scales

	Question	Likert Scale
2	The intensity of cough	1 = very mild 2 = mild 3 = moderate 4 = severe 5 = very severe
3	The frequency of cough	1 = rarely 2 = sometimes 3 = fairly often 4 = often 5 = almost always
4	The amount of sputum production	0 = no sputum 1 = a moderate amount of sputum 2 = a larger amount of sputum 3 = a very large amount of sputum

7.2.5 Socio-Economic Status Questionnaires

At V2, subjects will complete a series of questions related to their education, occupational status, size and annual income of their household. Different SES questionnaires will be used depending on the region.

For US subjects, a categorization for the education and the income will be derived, as well as a composite measure combining both, as described in Section 7.2.5.1.

For UK subjects, a categorization will be entered in database. This categorization (a social grade) will be based on external vendor input.

For subjects in Japan, Poland and Germany, no categorization will be derived.

7.2.5.1 SES Questionnaire in US

The questionnaire by King and Hyland will be administered in the US subjects.

These data will be used to create measures of educational attainment (Low / Moderate / High) and annual household income (Low / Moderate/ High), as detailed in Table 8 below (see [15]).

Table 8. Classification for the Socio-Economic Status Questionnaire in US

Question	Answer	Category
Question 1. What is the highest level of education you have completed?	1 Less than High School	Low
	2 Some High school or general education development (GED)	Moderate
	3 High School Graduate	Moderate
	4 Some College	High
	5 College Graduate	High
	6 Advanced Degree	High
Question 2. What is your current occupational status?	1 Working now	
	2 Only temporarily laid off, sick leave or maternity leave	
	3 Looking for work, unemployed	
	4 Retired	
	5 Disabled, permanently or temporarily	
	6 Keeping house	
	7 Student	
	8 Other (SPECIFY):_____	
Question 3. How many people are currently living in your household, including yourself?		
Question 4. Of these people, how many are children?		
Question 5. Of these people, how many are adults?		
Question 6. Of the adults, how many bring income into the household?		

Table 8. Classification for the Socio-Economic Status Questionnaire in US

Question		Answer	Category
Question 7. Which of these categories best describes your total combined family income for the past 12 months? This should include income (before taxes) from all sources, wages, rent from properties, social security, disability and/or veteran's benefits, unemployment benefits, workman's compensation, help from relatives (including child payments and alimony), and so on	1	Less than $10,000	Low
	2	$10,000 to $29,999	Low
	3	$30,000 through $44,999	Moderate
	4	$45,000 through $59,999	Moderate
	5	$60,000 through $74,999	High
	6	$75,000 through $99,999	High
	7	$100,000 through $149,999	High
	8	$150,000 and over	High
	9	I do not know	< Missing>
	10	No response	< Missing>

For Question 1 (Education) and Question 7 (Annual household income), if multiple answers are obtained the higher degree or income will be chosen; the subject cannot be classified if the answer is missing.

Education and income categories will be combined to create a composite measure for SES with categories defined as in Table 9 below:

Table 9. Composite measure for SES

	Income		
Education	**Low**	**Moderate**	**High**
Low	LOW	MODERATE	MODERATE
Moderate	MODERATE	HIGH	HIGH
High	MODERATE	HIGH	HIGH

Subjects who do not report either income or education will be excluded from the analysis of the composite SES.

7.2.5.2 SES Questionnaire in Japan

The questionnaire in Table 10 below will be administered to subjects in Japan.

Table 10. Classification for the Socio-Economic Status Questionnaire in Japan

Question	Answer
Question 1. In total, including yourself, how many people live in your household?	
Question 2. What is the highest level of education you have attained or are currently attending?	1 Elementary school / Junior High School 2 Senior High school 3 College 4 University / Postgraduate 5 Prefer not to say
Question 3. How many income earners are in your household?	1 None – all are unemployed 2 Just one income earner 3 Two or more income earners 4 Prefer not to say
<Those who have one or more income earners>	
Question 4. What is your occupation?	1 General white collar 2 Professional/ technical worker 3 General blue collar 4 Working in service industry 5 Manager (kacho or above) 6 Director/president (30 employees or more) 7 Proprietor (29 employees or less) 8 Professional/technical worker (Lawyer, Accountant, Professor etc.) 9 Farming/forestry/fishing 10 Shop keeper 11 Part-time worker (more than one day per week) 12 Student 13 Housewife (Including part-time less than one day per week) 14 Unemployed 15 Others 16 Prefer not to say

Table 10. Classification for the Socio-Economic Status Questionnaire in Japan

Question	Answer
Question 5a. What is your approximate MONTHLY household income from all sources before tax?	1 Below 100,000 yen 2 100,000 yen－199,999 yen 3 200,000 yen－299,999 yen 4 300,000 yen－399,999 yen 5 400,000 yen－499,999 yen 6 500,000 yen－599,999 yen 7 600,000 yen－699,999 yen 8 700,000 yen－799,999 yen 9 800,000 yen－899,999 yen 10 900,000 yen－999,999 yen 11 1,000,000 yen or above 12 Don’t know 13 Prefer not to say
<Those who don't know / prefer not to say about household income>	
Question 5b. Would your MONTHLY household income be over or under 800,000 yen?	1 Under 800,000 yen 2 800,000 yen or more 3 Don’t know 4 Prefer not to say

7.2.5.3 SES Questionnaire in Europe (UK, Poland, Germany)

SES QUESTIONNAIRE IN UK

The questionnaire in Table 11 below will be administered in the UK subjects. A grading based on the interview to be performed will be entered in the database.

Table 11. Classification for the Socio-Economic Status Questionnaire in UK

Question		Answer
Question 1. What is your current occupational status?	1	Full-time paid work (30+ hours per week)
	2	Part- time paid work (8-29 hours per week)
	3	Part- time paid work (under 8 hours per week)
	4	Retired
	5	Still at school
	6	In full time higher education
	7	Unemployed (seeking work)
	8	Not in paid employment (no seeking work)
	9	Prefer not to say
Question 2. What is your marital status?	1	Married/Living as married
	2	Single
	3	Widowed/Divorced/Separated
	4	Prefer not to say
Question 3. How many people are there in your household altogether, including any children and yourself? (including partner)		
Question Q4. Only asked, if [Q3 > 1]		
Question 4. And how many children under the age of 16 are there in the household?		
Question 5. State gender and age of your children starting with the eldest		
Question 6. Is the home where you live	1	Own outright
	2	Own with a mortgage
	3	Rent from council
	4	Rent privately
	5	Other
	6	Prefer not to say
Question 7. Which member of your household is the Chief Income Earner, that is the person with the largest income, whether from employment, pensions, state benefits, investments or any other sources?	1	Respondent
	2	Respondent’s spouse/partner
	3	Other adult

Table 11. Classification for the Socio-Economic Status Questionnaire in UK

Question		Answer
Question 8. Working status of Chief Income Earner (CIE)	1	Employed
	2	Self- Employed
	4	Not working, dependent on state benefit
	5	Not working, other income
	6	Prefer not to say
If [Q8 = 4] stop questionnaire		
Question 9. What is the type of firm where the CIE works?		
Question 10. What is the job actually done by the CIE?		
Question 11. What is the title, rank, grade, etc. of the CIE?		
Question 12. How many people work there altogether?		
Question 13. How many people at work is the CIE responsible for?		
Question 14. Does the CIE have any qualifications (such as apprenticeships, professional qualifications, university degrees, diplomas, etc…)?	1	Yes
	2	No
Question Q15 only asked if [Q14 = 1]		
Question 15. What are the qualifications of CIE? Enter qualifications.		
Social Grade	1	upper middle class
	2	middle class
	3	lower middle class
	4	skilled working class
	5	working class
	6	Those at the lowest levels of subsistence

SES QUESTIONNAIRE IN POLAND

The questionnaire in Table 12 below will be administered in the subjects in Poland.

Table 12. Classification for the Socio-Economic Status Questionnaire in Poland

Question	Answer
Question 1. What is the city size you live in? Is it	1 Village 2 City with 10,000-49,999 residents 3 City with 50,000-99,999 residents 4 City with 100,000-200,000 residents 5 City over 200,000 residents 6 City, but I don't know how many residents does it have 7 I don't know 8 Prefer not to say
Question 2. What is your education?	1 Primary/ gymnasium 2 Vocational 3 High school w/o certificate 4 High school with certificate 5 Higher (bachelor, engineer, master or higher) 6 Prefer not to say GO TO Question 2_2
Question 2.2. Could you than please tell me if your education is:	1 Below secondary level 2 Secondary and higher 3 Prefer not to say
Question 3. What is your current occupational status? MULTIPLE ANSWER. READ OUT.	1 Work full-time GO TO Question 4 2 Work part-time GO TO Question 4 3 Student 4 Housewife/ taking care of home 5 Pensioner/ retired 6 Unemployed/ sick leave/ maternity leave/ 7 Run own business 8 Temporary contract 9 Working on probation/ training 10 Farmer 11 Other, specify: _____ 12 Prefer not to say
Q4 -> ASK THOSE ONLY WHO SELECTED CODE 1 OR 2 ABOVE (WORKING FULL-TIME OR PART-TIME)	

Table 12. Classification for the Socio-Economic Status Questionnaire in Poland

Question	Answer
Question 4. Could you please specify your occupation?	1 White-collar worker 2 Blue-collar worker (driver, shop assistant etc.) 3 Independent specialist 4 Manager/ director 5 Company's owner 6 Freelancer 7 Education/ health sector 8 Other, specify: _____ 9 Prefer not to say
Question 5. Including yourself, how many people live in your house?	1 1 2 2 3 3 4 4 5 5 6 6 7 7 8 8 9 9 10 10+ 11 Prefer not to say l
Question 6. Could you please tell me how big is your family net monthly income? (please include the income generated by all family members living with you after tax deduction)	1 Below PLN 1 000 2 PLN 1 000 – 1 500 3 PLN 1 501 – 2 000 4 PLN 2 001 – 2 500 5 PLN 2 501 – 3 000 6 PLN 3 001 – 3 500 7 PLN 3 501 – 4 000 8 PLN 4 001 – 5 000 9 Above PLN 5 000 10 Don't know 11 Prefer not to say

SES QUESTIONNAIRE IN GERMANY

The questionnaire in Table 13 below will be administered in the subjects in Germany.

Table 13. Classification for the Socio-Economic Status Questionnaire in Germany

Question	Answer
Question 1. In total, including yourself, how many people live in your household?	
Question 2. Register Town size	1 Up to 1.999 Inhabitants 2 2.000 to 4.999 Inhabitants 3 5.000 to 19.999 Inhabitants 4 20.000 to 49.999 Inhabitants 5 50.000 to 99.999 Inhabitants 6 100.000 to 499.999 Inhabitants 7 500.000 Inhabitants and more 8 Prefer not to say
Question 3. What is your marital status?	1 Married, living with spouse 2 Married, not living with spouse 3 Single 4 Divorced 5 Widowed 6 Prefer not to say
Question 4. Are you living together with a partner?	1 Yes 2 No 3 Prefer not to say
Question 5. Are you doing the housework?	1 Mainly by myself 2 Together with other person(s) 3 No 4 Prefer not to say
Question 6. Are you the head of household?	1 Yes 2 No 3 Prefer not to say
Question 7. Which type of school are you attending / was the last one that you attended?	1 Primary school / Lower Secondary Education 2 Junior high school / Professional school / Commercial school 3 Senior high school 4 University / College / University of applied sciences degree 5 Prefer not to say

Table 13. Classification for the Socio-Economic Status Questionnaire in Germany

Question	Answer
Question 8. Which educational level or professional level did you reach?	1 Still in training/ apprenticeship 2 Apprenticeship, not (yet) completed 3 Apprenticeship, completed 4 Professional school/ Vocational school / Technical school completed / Master Certificate 5 High School Certificate / general qualification for university 6 University degree / University of applied sciences degree 7 Different form of education 8 None of these 9 Prefer not to say
Question 9. What is your working status?	1 Full-time working 2 Part-time working 3 (Currently) Unemployed 4 Retired/ Pensioner (formerly working) 5 Retired/ Pensioner (formerly not working) 6 In education (Trainee) 7 In education (Pupil) 8 In education (Student at University / University of applied sciences) 9 Not working (was working before) 10 Not working (never worked) 11 Prefer not to say

Table 13. Classification for the Socio-Economic Status Questionnaire in Germany

Question	Answer
Question 10. What is your current occupation?	1 Self-employed (greater business) 2 Self-employed (middle business) 3 Self-employed (smaller business) 4 Freelance, freelance as an academic 5 Farmer 6 White collar (office worker) – higher leading position 7 White collar (office worker) – middle leading position 8 White collar (office worker) – qualified 9 White collar (office worker) – normal 10 Civil Servant – senior official 11 Civil Servant – higher service 12 Civil Servant – middle 13 Civil Servant – normal 14 Skilled worker 15 Semi-skilled worker 16 Unskilled worker 17 Have never worked 18 Prefer not to say
Question 11. How many persons in your household have an own income? That means how many persons earn money themselves or have got an income from their pensions, rents, interests and from of that kind?	
Question 12. Once you have summed up: what is then the approximate monthly net household income you have got after tax and social insurance? Into which net household income group would your household be categorized?	1 Up to 500 Euro 2 to 1000 Euro 3 to 1500 Euro 4 to 2000 Euro 5 to 2500 Euro 6 to 3000 Euro 7 to 3500 Euro 8 to 4000 Euro 9 to 5000 Euro 10 to 6000 Euro 11 Above 6000 Euro 12 Prefer not to say

7.2.6 Lifestyle Assessment

Subjects will be asked questions to capture diet, alcohol intake, sleep deficit, exercise and exposure to passive smoking at V1, V2, V8, V11 and V17. These variables (values at Baseline) will be used as Baseline covariates in the analysis (see Section 12.1.4.2 "Covariates for Endpoint Analysis Model").

The lifestyle questions are shown in Table 14.

Table 14. Lifestyle Questionnaire

	Question	Answer
1	How many times per week do you eat fast food (e.g. hamburger, hot dog, pizza, French fries)?	Numeric response
2	How many alcoholic drinks do you have a day?	Numeric response
3	How many times a week do you exercise?	Numeric response
4	What is the average duration of each exercise session? (record in minutes)	Numeric response, in minutes
5	How many nights per week do you sleep less than 6 hours?	Numeric response
6	Do you live in a household with one or more smokers, other than yourself?	1 Yes 2 No

The total weekly time exercise (minutes/week) will be in general derived as [item 3]x[item 4] of the Lifestyle assessment questions. Subsequent to data review findings, the following derivation rules will also be applied:

- If the result is greater than 3360 min (corresponding to an average of a daily exercise of 8 hours) then the total weekly time exercise is set to 3360.

- If the reply to item 3 is missing the total weekly time exercise is missing, apart from when item 4 is zero which results into a total weekly time exercise equal to zero. Similarly, if the reply to item 4 is missing the total weekly time exercise is missing, apart from when item 3 is zero which results into a total weekly time exercise equal to zero.

8 SAMPLE SIZE JUSTIFICATION

Smokers willing to quit smoking within the next 30 days at screening will be enrolled in this study.

Enrollment is planned for 950 adults with at least 2 weeks of abstinence after the AQD. Unsuccessful quitters will be discontinued from the study. Subjects who discontinued the study after V5 will not be replaced.

Since no formal hypotheses have been formulated for the objectives, sample size calculations are based on precision of effect estimates for FEV_1. Other endpoints are assumed to exhibit a larger effect size than FEV_1 and thus would result in smaller sample size estimates. The sample size of this study is based on our current understanding of the effect and variability of SC from the results of the Lung Health Study [16] in the subject intending to quit smoking at Baseline, since no data on the attrition rate at 12 months after 2 weeks of smoking cessation are available. In particular, approximately 190 subjects are needed to estimate the mean increase from Baseline of 1.98 [% pred.] [16] in FEV_1 at V17, with a 90% probability of obtaining a margin of error (95% CI) of at most ±1 [% pred.]. The anticipated SD of the change from Baseline of 6.4 [% pred.] was estimated using the results of the Lung Health Study [16] and includes an inflation of 10% in order to account for additional sources of variability, including the multi-national nature of the study. As the analysis will only be conducted in successful quitters, this sample size was increased to 950, to account for a predicted continuous abstinence rate of 20% expected at week 52 for continuous quitters after 2 weeks from AQD. This is based on an assumed increase of 5% from the 15% abstinence rate at week 52 expected for subjects at enrollment [17]. Sample size calculations are conducted using SAS® version 9.2 for the 95% CI of the mean differences between paired observations (proc power onesamplemeans) [18]. The SAS® implementation of the method published by Beal [19] is adopted to estimate the probability of obtaining at most the target 95% CI of ± 1 [% pred.].

The overall enrollment and attrition rate will be monitored during the recruitment phase of the study and sample size may be adapted to ensure at least 190 successful quitters complete V17.

9 CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSIS

The definition of Full Safety Population and Quitters Population was updated to clarify that only subjects with data contributing to the planned analysis will be included.

Subjects from Site 515 in Japan will be excluded from tables and figures, data will be kept in the listings. Safety data of the full safety population including subjects from Site 515 will be summarized as described in section 12.5.4 “Safety Monitoring”. Findings have been identified during monitoring visits and confirmed in the for-cause audit, they raise concerns

on respecting the rights of the study subjects and the validity, reliability and integrity of data reported by the site, leading to the closure of this site.

Residual Volume parameter will be derived and summarized for the interpretation of lung volume data. FEV_1 Reversibility will be derived and summarized for the interpretation of Spirometry data. The Apo B/Apo A1 ratio will be analyzed and results will be used for the interpretation of Apolipoprotein data.

In addition to compliance criteria defined in protocol and leading to study discontinuation, for analysis purposes subjects will not be considered compliant to continuous abstinence in case of Free cotinine concentration ≥ 50 ng/mL in 24-hour-urine at V17 or in case of Total NNAL concentration ≥ 75.9 pg/mL in 24-hour-urine at V11 or V17 (see Section 12.4 "Measurements of Compliance").

All received Stethographics data will be listed, but the analysis of both Stethographics and Stethos data will be described in a separate SAP. COPD scores both raw and weighted will be listed.

10 ANALYSIS POPULATIONS

Screened Population
All subjects who provide informed consent will comprise the Screened population. Listings will be produced for the Screened population.

Full Safety Population
All subjects in the Screened population who have been enrolled per "Enrolled / Screen Failure" eCRF page and having at least one valid value for safety assessment at Enrollment or later will comprise the Full Safety population.

Enrolled Population
The Enrolled population is composed by all subjects in the full safety population excluding those from Site 515 in Japan. This site was closed because findings have been identified during monitoring visits and confirmed in the for-cause audit concerning the validity, reliability and integrity of data reported by the site.

Quitters Population
All enrolled subjects with at least one valid clinical risk endpoint, biomarker of exposure, or questionnaire assessment after AQD contributing to analysis at 3 months, or 6 months or 1 year, with no major protocol deviations impacting the overall subject evaluability (see Section 11.1.1 "Major Protocol Deviations") will comprise the Quitters population. Data collected after the evidence of non-compliance to continuous abstinence (see Section 12.4 "Measurements of Compliance") will not be considered for the analysis. For subjects who are lost to follow-up, or who drop out of the study, the analyses will include all data up to the point of their last data collection.

Depending on the period during which subjects in the Quitters population continuously abstained from smoking (and with no major protocol deviations which impact data evaluability [see Section 11.1.1 "Major Protocol Deviations"]), quitters may be included in one or more Abstinence sets described in Table 15. These are the main populations of interest for analysis. Subjects will be excluded from analysis subsets Abstinence3m in case of non-compliance to continuous abstinence in the period [AQD , V8]. The same approach will be used for Abstinence6m and Abstinence12m sets in case of non-compliance to continuous abstinence in the period [AQD , V11] and [AQD , V17], respectively. Subjects who discontinued without evidence of non-compliance and subjects lost to follow-up will be included in Abstinence3m only if they were considered compliant at V8. In the same way, subjects who discontinued without evidence of non-compliance and subjects lost to follow-up will be included in the Abstinence6m and Abstinence12m only if they were considered compliant at V11 and V17, respectively.

Table 15. Quitters Population Analysis Subsets

Subset Name	Compliance Period
Abstinence3m	From AQD to V8 or later
Abstinence6m	From AQD to V11 or later
Abstinence12m	From AQD to V17

11 PROTOCOL DEVIATIONS

Protocol deviations (PDs) are defined as deviations from the study procedures as defined in this document, including but not limited to any violation of inclusion/exclusion criteria, assessments not performed or performed outside the scheduled time windows, or use of drugs that are known to affect study endpoints.

Information following site monitoring and other reviews will be documented in the site visit reports, follow-up letters, audit documentation, or other manual review and subsequently recorded in an electronic data capture (EDC) system. Additional protocol deviations may be identified in the data review, these will also be recorded in the EDC system.

All deviations will be reviewed to determine their impact when subjects are assigned to analysis populations. All deviations will be reviewed before being definitively classified as major or minor; all major deviations will be further reviewed to determine whether or not the deviation impacts the evaluability of the results and therefore should result in the subject being excluded from the Quitters population or from any analysis subset.

11.1.1 Major Protocol Deviations

Major protocol deviations are protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.

Subjects with major PDs below will be identified to determine whether they will be excluded from any of the analysis populations.

The categories for the major deviations will include, but are not limited to the deviations presented in Table 16. The major PDs will be classified as having an impact on endpoints evaluability, or not having an impact on endpoints evaluability.

Table 16. Definition of Major Protocol Deviations

Category	Description
Entry Violation	Violation of inclusion/exclusion criteria.
Duration of 24 hour collection	Total urine collection covering a period of less than 20 hours or more than 28 hours for assessments
Visit window deviation	Visit conducted out of window for more than 30 days. See Details in Table 18.

Among the above criterion, violations of inclusion criteria 1 or 2, or of the exclusion criteria 2, 15, 16, 18, or 19 will be considered as impacting evaluability. The other violation of inclusion criteria will be assessed for their impact on the Quitters population (or analysis subsets) and evaluated during the pre-analysis data review.

All major protocol deviations impacting evaluablity will impact the overall subject evaluability leading to the exclusion from the Quitters.

In case of 24 hour urine collection covering a period of less than 20 hours or more than 28 hours, the results of the markers in 24 hour urine for that time point will be considered not reliable and flagged to be excluded from the analysis (see Section 12.1.6 "Handling of 24 Hour Urine Collection").

In case of scheduled assessments conducted out of window for more than 30 days since the nominal visit study day, the analysis time point of the assessment will be programmatically remapped (see Section 12.1.8 "Handling of Scheduled Assessments Conducted out of Window for More Than 30 Days").

11.1.2 Minor Protocol Deviations

The categories for the minor deviations may include, but are not limited to the deviations presented in Table 17. The assessment windows specified in the clinical study protocol are shown in Table 18.

Table 17. Definition of Minor Protocol Deviation Categories

Category	Description
Procedural violation	Violation of any study procedures not affecting safety or data evaluability.
Concomitant Medication	Use of any medications interfering with the study endpoints (See Appendix 2 in the study protocol) Or use of NRT more than 3 months (+2 weeks) after the start date

Table 17. Definition of Minor Protocol Deviation Categories

Category	Description
	of NRT
Duration of 24 hour collection	Total urine collection covering a period of 20- 23 hours or 25-28 hours for assessments
Visit window deviation	Visit conducted out of window for not more than 30 days. See Details in Table 18.
Date/Time missing	Assessment date or time missing
Assessment missing	Assessment not performed
Visit missing	Scheduled visit not done

Table 18. Assessment Windows

Assessment	Nominal Time point(s)	Window
Ambulatory Visit	From V1 to V2	Not more than 42 days
	From V2 to TQD	Not more than 14 days
	From TQD to V3	Not more than 2 days
	From TQD to AQD	Not more than 14 days
	From AQD to V4	1 week +/- 3 days
	From AQD to V5	2 weeks +/- 3 days
	From AQD to subsequent monthly visits	Planned date +/- 8 days
Phone Contact	From V17 to V18	4 weeks +/- 3 days

Note: phone contact is planned only for subjects who complete V17

12 PLANNED STATISTICAL METHODS

12.1 General Considerations

Data analysis will be performed using SAS®, version 9.2 or higher.

Listings will be provided for all data collected in the Screened population. All data listings will be ordered by region, study center, subject, and study visit unless otherwise specified. All unscheduled assessments will be included in the listings. Baseline values will be flagged in listings.

12.1.1 Stratified Presentation

Stratified presentations will be conducted for all the Abstinence sets for the descriptive summaries of Clinical risk endpoints using stratification criteria based on the following Baseline subject characteristics:

1. Sex (male; female)
2. Region (US, EU, JP). Centers from UK, Poland and Germany will be pooled to region EU.

Stratified presentations will also be conducted for:

- Demographics by sex and by region for the Enrolled population and for all the Abstinence sets.
- Quitting rates (*i.e.*, rate of subjects continuously smoking abstinent) over study visits by region, and by country within Europe for the Enrolled and Quitters populations.
- Adverse event tables by region.

12.1.2 Subgroup Analyses

No subgroup analyses will be performed.

12.1.3 Descriptive Statistics

Descriptive statistics will be presented overall and at each time point, where applicable.

For continuous data, summary statistics will include the number of subjects (n), the number and percent of subjects with missing data, the arithmetic mean, arithmetic standard deviation (SD), median, first and third quartiles, minimum, maximum; for data analyzed in the log scale the geometric mean and geometric coefficient of variation (CV) will also be presented. Summary statistics (geometric and arithmetic mean, SD, median, first and third quartiles, minimum and maximum) will be reported with 3 significant digits when below 1000; and they will be reported with all significant digits apart from the decimal digits when above or equal 1000. Summary statistics below 0.0001 will be displayed as 0. The geometric coefficient of variation (CV) and relative change (RC) from baseline will be reported as % with two decimal places.

For categorical data, frequency counts and percentages will be presented, missing values will be regarded as an own category if any missing value exists. Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Categorical variables will be presented as defined in Section 12.1.4.1.

12.1.4 Definitions for Statistical Analysis

12.1.4.1 Categorical Variables

Categorical variables used in this study are shown in Table 19 below.

Table 19. Categorical Variables Definitions

Variable	Categories	
BMI (kg/m^2)	Underweight:	<18.5
	Normal weight:	≥ 18.5 and < 25.0
	Overweight:	≥ 25.0 and < 30.0
	Obese:	≥ 30.0
COPD staging [20] (Subjects in GOLD1-4 with FEV_1 [L] / FVC [L] < 0.7; FEV_1 post-bronchodilator)	Normal:	FEV_1 [L] / FVC [L] ≥ 0.7
	GOLD1: Mild	FEV_1 ≥ 80 %pred
	GOLD2: Moderate	50 ≤ FEV_1 < 80 %pred
	GOLD3: Severe	30 ≤ FEV_1 < 50 %pred
	GOLD4: Very Severe	FEV_1 < 30 %pred
Visit labels	V1	Screening
	V2	Baseline Visit
	V3	After TQD
	V4	Week 1
	V5	Week 2
	V6	Month 1
	V7	Month 2
	V8	Month 3
	V9	Month 4
	V10	Month 5
	V11	Month 6
	V12	Month 7
	V13	Month 8
	V14	Month 9
	V15	Month 10
	V16	Month 11
	V17	Month 12
	V18	Month 13
COHb level	≤ 2%	
	> 2%	

Table 19. Categorical Variables Definitions

Variable	Categories
Race	White
	Black or African American
	American Indian or Alaska Native
	Asian
	Native Hawaiian or Other Pacific Islander
	Any combination from eCRF e.g. White and Black
Ethnicity	Hispanic or Latino
	Not Hispanic or Latino
	Japanese
Race/Ethnicity	White Hispanic
	White not Hispanic
	Black or African American
	Asian
	Other
Caucasian origin	Caucasian: White, and not Hispanic or Latino, and not Japanese
	Non-caucasian: Not white or, Hispanic or Latino, or Japanese
FTND total score	Mild: 0 – 3
	Moderate: 4 – 6
	Severe: 7 – 10
CO breath test level (ppm)	≤ 10
	> 10
SES (Educational attainment) in US	Low
	Moderate
	High
SES (Annual household income) in US	Low
	Moderate
	High
SES (Composite)	Low
	Moderate
	High
Adverse event severity	Mild
	Moderate
	Severe
Adverse event relationship to study procedure	Related
	Not related

12.1.4.2 Covariates for Endpoint Analysis Model

The variables listed as "defined covariates" in Table 20 will be included in the analysis model. The "evaluated covariates" specified in Table 20 will be considered for their inclusion in the analysis model, as described in Section 12.5.1. The purpose of the model is to evaluate the effect of these Baseline covariates on the change from Baseline in endpoints over time.

Table 20. Baseline Covariates for Analysis

Endpoint	Defined Covariates[1]	Evaluated Covariates[1]
WBC	Age, Smoking Intensity	Smoking duration, Smoking rate, Smoking history intensity, Race/Ethnicity, Sleep Deficit, Caucasian origin
HbA1c	Smoking Intensity	Age, Smoking duration, Smoking rate, Smoking history intensity, Caucasian origin
COHb	Age, Smoking Intensity	Other exposure, Caucasian origin
LDL-C, HDL-C	Age, Smoking Intensity	Smoking duration, Smoking rate, Smoking history intensity, Diet, Alcohol intake, Exercise, BMI, Caucasian origin
sICAM-1	Age, Smoking Intensity	Smoking duration, Smoking rate, Smoking history Intensity, Caucasian origin
Apo A1, Apo B, Apo B/Apo A1 ratio	Age, Smoking Intensity	Same as HDL-C
Fibrinogen	Age, Smoking Intensity	Smoking duration, Smoking rate, Smoking history intensity, Caucasian origin
11-DTXB_2	Age, Smoking Intensity	Smoking duration, Smoking rate, Smoking history intensity, Caucasian origin
8-epi-PGF2α	Age, Smoking Intensity	Smoking duration, Smoking rate, Smoking history intensity, BMI, Weight, Caucasian origin
FEV_1[3]	Smoking Intensity	Smoking duration, Smoking rate, Smoking history intensity, Age^2, Race/Ethnicity[2], $Height^2$, Diet, Exercise, BMI, Weight, Caucasian origin
CYP2A6	Smoking Intensity	Age, Smoking duration, Smoking rate, Smoking history intensity, Caucasian origin

Table 20. Baseline Covariates for Analysis

Endpoint	Defined Covariates[1]	Evaluated Covariates[1]
Cough	Smoking Intensity	Age, Smoking duration, Smoking rate, Smoking history intensity, Caucasian origin
Total NNAL (if at least 30% of the values above lower limit of quantification [LLOQ])	Age, Smoking Intensity	Other exposure, Caucasian origin

1 Listed covariates are defined as follows:
- Smoking Intensity: average daily CC consumption at Baseline during last year
- Smoking duration and smoking rate are defined respectively from the questions on "Questions on Smoking History/Habits" at Baseline item 2 and item 4 as defined in Section 7.2.1 "Questions on Smoking History/Habits". Smoking history intensity (pack-years) is defined as smoking duration x smoking rate / 20.
- Sex: (male/female)
- Age, Weight, Height, BMI: continuous variable (Height and Weight are included only if BMI is excluded from the model)
- Race/Ethnicity: (White Hispanic, White not Hispanic, Black or African American, Asian, Other). White Hispanic and White not Hispanic will be derived as a combination of race and ethnicity.
- Diet:, Alcohol Intake, Exercise (total weekly time), Sleep deficit, and Other exposure as collected in the Lifestyle questions

2 These variables are already accounted for in the %predicted assessment.

3 Both pre and post bronchodilator % predicted FEV_1 will be analysed using the same covariates.

12.1.5 Handling of Dropouts or Missing Data (Including Outside the Limits of Quantification)

In case of imputation, both the raw value and the imputed values will be reported in listings.

For laboratory parameters outside the limit of quantification, the following imputation will be performed:

- Values below the LLOQ will be imputed as 0.5 x LLOQ.
- Values above the upper limit of quantification (ULOQ) will be imputed as the ULOQ.

If either of the cotinine or trans-3'hydroxycotinine concentration is below LLOQ then the ratio to measure the CYP2A6 activity will not be calculated (see Section 7.1.3 "CYP2A6").

The number of values below LLOQ or above ULOQ will be presented in each summary table, as well as the statistics on the other quantitative values.

However, if 50% or more data are below LLOQ or above ULOQ, only the number (%) of values below LLOQ or above ULOQ will be reported in the summaries, together with minimum (if no value below LLOQ is present) and maximum (if no value above ULOQ are present) of the observed values, and no other statistics will be reported.

For questionnaires, no imputation will be performed (see Section 7.2).

For compliance assessment:

- In case of missing data for one or more measurements used for compliance assessment (see Section 12.4), only the available information will be used.
- In case of missing data for all measurements of compliance at one visit (or subject missed one visit), the subject will be considered compliant, unless they discontinued early or were lost to follow-up without evidence of non-compliance (see next bullet).
- Subjects discontinued or lost to follow-up without evidence of non-compliance will be considered compliant until the date of last contact where the subject demonstrated compliance.
- If data are missing over two consecutive visits (or subject missed two consecutive scheduled visits) for reported product use and/or CO breath test, when also no urine cotinine test and free cotinine data are available, the subject is considered non-compliant since the first of the two consecutive visits.

For Missing or Partial Dates:

- Missing dates for Visits after AQD will be imputed for the calculation of compliance by adding nominal days to the AQD. If the imputed date falls after EOS date (*e.g.* for early terminated subjects), then the end of study date will be used.
- Partial dates will not be imputed for Adverse Events (AEs), for medical history, and for concomitant medications, but assumptions will be made as follows to assign them to specific analysis categories:

Date information	AE data	Medical History/Concomitant Disease data	Prior and Concomitant Medication data
Missing or Partial date (*e.g.*, --May2012, or ----2011). If month/year is the same as, or later than the month and/or year of Screening.	Included in summaries	Concomitant disease	Concomitant medication
Partial date, (*e.g.*, --May2012, or ----2011). If month and/or year is earlier than the month and/or year of Screening.	Listings only	Medical history	Prior medication

12.1.5.1 Insufficient Data for Analysis/Presentation

If there are no values or events at the general value then the break out should not be presented. For example if the number of AEs related to study procedure is zero then the presentation by severity of related events will not be produced.

Some of the TFLs will not have sufficient numbers of subjects or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the center of the table, such as, “No applicable data is available for this summary.”. The « empty table » message will be adapted to its content.

Stratified summaries will not be presented if less than 4 subjects are available in any one strata.

12.1.6 Handling of 24 Hour Urine Collection

The 24 hour urine collection samples should be collected over 24 hours i.e. from 23 up to 25 hours. Samples collection covering a period of 20- 23 hours or 25-28 hours are considered as a minor deviation and no impacting the analysis.

In case of 24 hour urine collection covering a period of less than 20 hours or more than 28 hours, the results of the markers in 24 hour urine for that time point will be considered not reliable and flagged to be excluded from the analysis (assessments with missing start or end time will be flagged to be excluded from the analysis).

12.1.7 Handling of Assessments Prior TQD or AQD

Both planned and unplanned assessments prior TQD or AQD will be re-mapped as below.

- If visit date < enrollment date then analysis timepoint = Screening
- If visit ≥ enrollment date and < min(TQD, AQD) date then analysis timepoint = Baseline visit
- If visit date ≥ enrollment date and both no TQD and no AQD dates then analysis timepoint = Baseline visit
- If visit date ≥ enrollment date and ≥ TQD and < AQD date then analysis timepoint = After TQD
- If visit date ≥ enrollment date and ≥ TQD and no AQD date then analysis timepoint = After TQD

Baseline value will be the last available value prior to Target quit date (TQD) or AQD, whichever comes first. This value will come from either the Screening or the Baseline visit analysis timepoints.

12.1.8 Handling of Scheduled Assessments Conducted out of Window for More Than 30 Days

In case of scheduled assessments conducted out of window for more than 30 days since the nominal visit study day, the analysis time point of the assessment will be programmatically remapped to the analysis time point using the time windows described in Table 21.

Re-mapping post-AQD will not be performed for subjects with no AQD date.

Table 21. Visit Mapping

Visits / Timepoint (Week)	Nominal Day	Time Window (in Days) for Assessments
AQD	1	1
V4 / Week 1	8	]1; 11]
V5 / Week 2	15	]11 ; 22]
V6 / Month 1 (Week 4)	29	]22 ; 46]
V7 / Month 2 (Week 9)	64	]46 ; 78]
V8 / Month 3 (Week 13)	92	]78 ; 106]
V9 / Month 4 (Week 17)	120	]106 ; 137]
V10 / Month 5 (Week 22)	155	]137 ; 169]
V11 / Month 6 (Week 26)	183	]169 ; 197]
V12 / Month 7 (Week 30)	211	]197 ; 228]
V13 / Month 8 (Week 35)	246	]228 ; 260]
V14 / Month 9 (Week 39)	274	]260 ; 288]
V15 / Month 10 (Week 43)	302	]288 ; 319]
V16 / Month 11 (Week 48)	337	]319 ; 351]
V17 / Month 12 (Week 52)	365	]351 ; 379]
V18 / Month 13 (Week 56)	393	>379

12.1.9 Handling of Unplanned and Early Termination Assessment Data

Unplanned assessments will be in general excluded from the analysis and summary statistics. However certain assessments planned for scheduled visits are reported within unscheduled visit forms in the eCRF (e.g. repeated/delayed assessments). Given that it is not practical to

re-assign them to the pertaining scheduled visits in the eCRF, these data will be accounted for in the analysis and summaries by applying the following re-mapping algorithm to each unscheduled visit:

- For subjects with an AQD, if Unscheduled visit date ≥ AQD then:

    1. Determine the unscheduled visit study day.

    2. Determine the reference scheduled visit as the latest previous (≤) scheduled visit recorded and determine the nominal study day from Table 21.

    3. If unscheduled visit study day ≤ nominal study day of the reference scheduled visit + 30 days then unscheduled visit assessments will be assigned to the analysis time point of the reference scheduled visit (see Table 19); otherwise data will be remapped to the analysis time point using the time windows described in Table 21.

For example, a subject with V11 and V12 conducted at day 183 and 215, respectively, and with missing lab assessments at V11 but recorded on an unscheduled visit at day 214, will not have the unscheduled lab assessments mapped to Month 6 (because performed 31 later than nominal V11 study day) but mapped to Month 7 (because the unscheduled study day is in the)197; 228) time window of Month 7).

Unscheduled assessments will be labelled as unscheduled and presented together with the re-mapped analysis time point in the listings.

Early Termination Assessments data will be re-mapped using the same algorithm and will be presented in listings labelled as early termination visit together with the re-mapped analysis time point.

Data from Unscheduled and Early Termination assessments will be combined with data from scheduled visits in the analysis and summary statistics only if there are not scheduled visit data for the same parameters at that re-mapped analysis time point, and only if the data are scheduled to be collected at that analysis time point. In case of both Unscheduled and Early Termination assessments re-mapped to the same analysis time point, the Early Termination will be analysed.

12.1.10 Multi-center Studies

For the purpose of the listings, the term ‘Center’ will be used to define each investigator site. The homogeneity across centers will not be investigated. The analysis will be stratified by region only.

12.1.11 Significance Level for Inferential Analysis

This study has no formal pre-specified hypotheses associated with the study objectives. Unless stated otherwise, all quoted confidence intervals are two-sided 95% confidence intervals.

12.1.12 Multiple Comparisons / Multiplicity

No adjustments for multiplicity will be made.

12.2 Disposition of Subjects

Subject disposition including informed consent and visits performed will be listed (Listing 15.3.1.1.1-3). Unmet inclusion and met exclusion criteria will also be listed for each subject (Listing 15.3.1.2).

The number and percent of the following categories of subjects will be summarized from the Screened population: screened, screening failures, enrolled, having completed V8, V11, V17, and discontinued, as well as reasons for screening failures (Table 15.2.1.1).

All subjects who discontinued the study will be categorized by their primary reason for discontinuation and summarized for the Enrolled and Quitters populations (Table 15.2.1.2). Discontinued subjects will include enrolled subjects who withdraw from the study (subject's decision), and subjects who are removed from the study (*e.g.,* subjects who are not continuously abstinent from smoking after AQD).

The number and percent of subjects with protocol deviations, and the number of protocol deviations, will be summarized overall and by region for the Enrolled population (Table 15.2.1.3.1). Summaries will be broken down by main deviation category (major/minor), sub-categories (*i.e.*, PD category) and evaluability (*i.e.*, with or without evaluability impact). Subjects will be counted once per deviation category, and can be counted for more than one deviation category.

Analysis sets and reasons for exclusions from analyses will be summarized overall, by country and by region with the percentage of Quitters and of each subpopulation based on the total number of Enrolled subjects (Table 15.2.1.3.2). The protocol deviations will be listed (Listing 15.3.1.3), as well as the assignment to analysis sets and reason for exclusion (Listing 15.3.1.4).

12.3 Demographics and Other Baseline Characteristics

All demographic and Baseline subject characteristics data will be listed (Listing 15.3.1.5), and will be summarized for the Enrolled population, and all the Abstinence sets (Table 15.2.1.4.1.1).

The sex, age, ethnicity, race, body weight, height, BMI and waist circumference will be summarized overall, by region (Table 15.2.1.4.1.2-4), by sex (Table 15.2.1.4.2).

COPD staging at Baseline will be derived as defined in in Table 19, and will also be summarized.

12.3.1 Subject Reported Outcomes Collected at Baseline

Other Baseline characteristics for diet, alcohol intake, sleep deficit, exercise and exposure to passive smoking (as defined in Section 7.2.6 "Lifestyle Assessment" and summarized as in Section 12.5.5.1 "Lifestyle Assessment") will also be included in Demographics and Baseline Characteristics (Tables 15.2.1.4.1.1 to 15.2.1.4.2.4).

12.3.1.1 Questions on Smoking History/Habits

Smoking history as collected from the Questions on Smoking History/Habits (Section 7.2.1 "Questions on Smoking History/Habits") at V1 and V2 will be listed (Listing 15.3.1.6). The answers to questions will be summarized separately (Table 15.2.1.5). The Baseline average daily number of cigarettes smoked over the past year will be summarized both as numeric and by category ("10-19 cig/day" vs. ">19 cig/day") in general tables above about Demographics and Baseline Characteristics (Tables 15.2.1.4.1.1 to 15.2.1.4.2.4). The smoking duration (in years) and smoking history intensity (in pack-years) will also be summarized in these general tables.

12.3.1.2 Prochaska 'Stage of Change' Questionnaire: Intention to Quit Smoking

Subject answers to items from the Prochaska questionnaire and derived smokers' stage category for the intention to quit (see Section 7.2.2 "Prochaska 'Stage of Change' Questionnaire: Intention to Quit Smoking") will be provided in listings (Listing 15.3.1.7). The questions will be summarized separately (Table 15.2.1.6). The smokers' stage for the intention to quit will be summarized in the Demographics and Baseline Characteristics (Tables 15.2.1.4.1.1 to 15.2.1.4.2.4).

12.3.1.3 FTND Questionnaire

Subject answers to items from the FTND questionnaire (see Section 7.2.3 "Fagerström Test for Nicotine Dependence (FTND)") will be provided in listings only (Listing 15.3.1.8). The total score will be summarized as continuous and categorical in the Demographics and Baseline Characteristics (Tables 15.2.1.4.1.1 to 15.2.1.4.2.4).

12.3.1.4 Socio-Economic Status Questionnaire

Subject answers, individual educational attainment, annual household income and composite classifications from the SES questionnaire (see Section 7.2.5 "Socio-Economic Status Questionnaires") will be listed by country (Listing 15.3.1.9.1-5). The answers to questions will be summarized descriptively by country (Table 15.2.1.7.1-5). The number and percentage of subjects in each of the socio-economic status gradings will also be summarized for US (as low, moderate or high) and UK (based on external vendor input).

12.3.2 Additional Endpoints at Screening and Baseline

The following data collected at V1 and V2 will be provided in listings only (Listing 15.3.1.10):

- Urine drug screen.
- Cotinine urine test.
- Alcohol urine or breath test.
- Urine pregnancy test.
- Serology.

12.3.3 Medical History and Concomitant Disease

Medical history is defined as any condition that started and ended prior to V1. Concomitant disease is defined as any condition that is ongoing at V1. In case of missing or partial dates, classification into prior or concomitant disease will be handled as described in Section 12.1.5 "Handling of Dropouts or Missing Data (Including Outside the Limits of Quantification)".

Medical history and concomitant disease will be coded using version 18.0 of the Medical Dictionary for Regulatory Activities (MedDRA) or a later version. They will be listed separately by region (country), center and subject number, System Organ Class (SOC) and Preferred Term (PT) within SOC (Listing 15.3.1.11).

Number and percent of subjects with Medical History and Concomitant diseases will be summarized by SOC and PT for the Enrolled population (Tables 15.2.1.8 and 15.2.1.9).

12.4 Measurements of Compliance

Continuous abstinence from smoking is defined by meeting all the following criteria:

- No self-reporting by the subject of use of any of the following product from AQD onwards:
    - Tobacco product, such as CC, snus, cigars.
    - Nicotine-containing products, other than NRT.
    - NRT continued after the allowed timeframe, i.e. TQD + 3 months (90 days) (+2 weeks [14 days]).
    - Electronic cigarettes (with or without nicotine).
- CO breath test ≤ 10 ppm, as verified at each visit from V4 onwards [21].
- Urine cotinine test < 100 ng/mL in spot urine at site, as verified at each visit from V10 onwards [21].
- Free cotinine concentration < 50 ng/mL in 24-hour-urine collected at V11 [21].

If any of these four criteria is not met, the subject must be discontinued.

In case of missing data until V17, compliance will be evaluated as described in Section 12.1.5 "Handling of Dropouts or Missing Data (Including Outside the Limits of Quantification)". At V18, compliance will be only evaluated by self-reporting by the subject. Continuous smoking abstinence will be summarized in Section 12.5.3 "Continuous Smoking Abstinence", and will be listed (Listing 15.3.2.1). Smoking cessation information/advice and support provided to the subject to prevent him/her from smoking during the study will also be listed (Listing 15.3.2.2).

Data collected at or after evidence of non-compliance to continuous abstinence will not be considered for the analysis. In addition, for analysis purposes subjects will not be considered compliant to continuous abstinence if:

- Subject discontinued with main reason of non-compliance with smoking abstinence, irrespective of available compliance tool data.

- Free cotinine concentration ≥ 50 ng/mL or Total NNAL concentration ≥ 75.9 pg/mL in 24-hour-urine collected at V17 [4, 21] and all data collected at V17 will be excluded from the analysis.

- Total NNAL concentration ≥ 75.9 pg/mL in 24-hour-urine collected at V11, and all data collected at V11 or later will be excluded from the analysis [4].

The table reporting the schedule of continuous smoking abstinence tools is in Appendix 16.6.

12.5 Planned Statistical Analyses

12.5.1 Clinical, Biological and Functional Changes

The list of the clinical risk endpoints is provided in Appendix 16.2, the list of parameters measured by the computerized multichannel lung sound analysis (Stethographics and Stethos) in Appendix 16.3, and the DLCO and KCO parameters about lung diffusion are listed in Appendix 16.4.

Clinical risk endpoints associated with cardiovascular and respiratory diseases and xenobiotics and genotoxicity data will be summarized at Baseline, V8, V11 and V17. Gas transfer data will also be summarized at V5, V6, and V7. Spirometry data will be collected prior and post-bronchodilator. Spirometry predicted values will be standardized as detailed in the Vitalograph Customer requirements specification for Spirometry assessment [3]. Predicted values for Lung function parameters will be derived by a central provider.

The level of biological and functional markers associated with:

1. CVD (WBC total count, HbA1c, COHb, HDL-C and LDL-C, MPO, sICAM-1, Apo A1 and Apo B, apoB/apoA1 ratio, hs-CRP, fibrinogen, homocysteine, albumin, 11-DTXB2, 8-epi-PGF2α),
2. respiratory disease (pre- and post-bronchodilatator FEV_1, FVC, FEV_1/FVC ratio and FEF 25-75, reversibility in FEV_1, VC, TLC, FRC, IC, RV, cough symptoms, amount of sputum and bothersomeness of cough symptom detailed in Section 12.5.5.2 "Cough-VAS Questionnaire"),
3. respiratory disease and assessed/collected at the Heart Lung Centre at the [redacted] only (Stethographics and Stethos parameters measured by the computerized multichannel lung sound analysis as listed in Appendix 16.3, DLCO and KCO parameters about lung diffusion as listed in Appendix 16.4)
4. xenobiotic metabolism (CYP2A6)
5. and genotoxicity (Total NNAL)

and their change from Baseline will be summarized as reported in Section 12.1.3 "Descriptive Statistics" for the Abstinence sets (Tables 15.2.2.1.1.1, 15.2.2.2.1.1, 15.2.2.3.1 and 15.2.2.4.1.1), by region (Tables 15.2.2.1.1.2-4, 15.2.2.2.1.2-4 and 15.2.2.4.1.2-4), and by sex (Tables 15.2.2.1.2, 15.2.2.2.2, 15.2.2.3.2 and 15.2.2.4.2). Supporting listings will be provided for all the data collected including the change from Baseline (Listings 15.3.3.1 to 15.3.3.7).

Apart from WBC total count, HbA1c, HDL-C, LDL-C, Apo A1, Apo B, Apo B/Apo A1, spirometry, lung volume, cough-VAS and gas transfer endpoints, the biological and functional endpoints values will be log-transformed ($base_e$) prior to the analysis. These endpoint parameters will be analyzed in the logarithmic scale and summary estimates will be back-transformed to provide results in the original scale. Summaries will only be presented on the original scale. The geometric mean and CV will be presented in addition to the (arithmetic) mean and SD.

Summary statistics of endpoints will also include the mean change from Baseline, together with 95% confidence interval (CI). Absolute and percent change from Baseline will also be summarized for endpoints analyzed in the real and logarithmic scale, respectively.

The listing and summary of the COHb data will include the concentration, the percent change from Baseline within levels, and a flag whether a subject's COHb was <2%.

Urinary markers (albumin, 11-DTXB2 and 8-epi-PGF2α) will be summarized adjusted for creatinine, as defined in Section 7.1.1 "Clinical Risk Endpoints and Biomarkers of Exposure in Urine". The percent of change from Baseline in the concentration adjusted for creatinine, and the quantity excreted will also be summarized. The listing will include the quantity excreted, the concentration adjusted for creatinine and the percent change from Baseline in the concentration adjusted for creatinine at each visit.

Line graphs of biological and functional markers mean (or geometrical mean for log transformed parameters) levels and 95% CI over time will be produced (Figures 15.1.2.1.*, 15.1.2.2.*, 15.1.2.3.* and 15.1.2.4.*).

Graphs will be produced for the Abstinence12m and summaries will be produced for the Abstinence sets.

All received Stethographics data will be listed, but the analysis of Stethographics and Stethos data will be described in a separate SAP.

Nasal and buccal epithelium scrapes, as well as transcriptomics and lipidomics, will be analyzed separately. The analysis methods and results presentation details will be defined in a separate SAP. The reasons from eCRF when the assessments were not collected will be listed (Listings 15.3.3.8 and 15.3.3.9).

12.5.1.1 Endpoint Analysis Model

For the subset of clinical risk endpoints listed in Table 20 (see Section 12.1.4.2 "Covariates for Endpoint Analysis Model"), the change over time will be modeled using random measurement effects models in the Abstinence3m set. Changes to the specific statistical model due to convergence issues will be documented.

The SAS procedure PROC GLIMMIX will be used with the restricted maximum likelihood method for estimation of the parameters. The mixed model will have the change from baseline as dependent variable and the following covariates will be included in the model: Sex, region, Baseline endpoint value, Visit. Visit will be treated as a categorical variable (number of weeks from the baseline) in the model i.e. 13, 26 and 52 weeks. A RANDOM statement will be used to model within-subject variation over visits.

A fully general mean and covariance structure will be used, so an unstructured covariance matrix (type=un) will be used to represent the correlation of the repeated measures within each subject. In case of non-convergence of the preferred model, an alternative covariance

structure will be used in such order: a heterogeneous compound symmetry covariance structure (type=csh), and a Toeplitz covariance structure (type=toeph), heterogeneous autoregressive (1) (type=arh(1)), and variance components (type=vc).

The denominator degrees of freedom will be determined using the method of Kenward and Roger (1997). In case of non-convergence of the preferred model or memory space issues, the Kenward-Roger method will be replaced by Satterthwaite approximation.

Model will also include terms from the "Defined Covariates", and consider for the inclusion the "Evaluated Covariates" selected by a backward elimination process using the p-values. At each step, the "Evaluated Covariate" with the highest p-value will be excluded from the model. Final model will retain the subset of "Evaluated Covariates" resulting in all p-values below 0.157 [22]. No interaction between covariates will be included in the model. During the modelling process, if correlated covariates such as race/ethnicity and Caucasian origin do not provide parameter estimates or causes convergence issues then one of them may be dropped.

Goodness of fit will be evaluated by the analysis of residuals (model diagnostics) and by comparing the values predicted versus the observed parameter changes (calibration) (Supportive SAS outputs as Statistical Appendices 15.4.*). Least square (LS) estimates of the effect of variables included in the model will be reported together with the 95% CI.

The SAS code for the mixed model to be used is shown below:

```
Proc glimmix data=_data_ method=rspl;
Class subject region sex visit;
Model endpoint = sex region baseline visit <covariates> /s
                          ddfm=kr dist=normal link=identity cl;
Random visit / subject=subject type=un residual;
Lsmeans sex          / alpha=0.05 cl;
Lsmeans region       / alpha=0.05 cl;
Lsmeans visit        / alpha=0.05 cl;
Lsmeans <covariate1> / alpha=0.05 cl;
Lsmeans <covariate2> / alpha=0.05 cl;
Run;
```

The LS means and estimate of the difference along with its 95% CI will be presented in tables for FEV_1, WBC total count, HbA1c, LDL-C, HDL-C, Apo A1, Apo B, and Apo B/Apo A1. For other clinical risk endpoints analyzed after log transformation, results will be presented back transformed in the original scale. The endpoint analysis will be summarized (Tables 15.2.2.1.3, 15.2.2.2.3 and 15.2.2.4.3).

For cough (*i.e.*, cough experienced in the last 24 hours) Yes/No binary variable, the SAS code to be used for this model is shown below.

```
Proc glimmix data=_data method=rspl;
Class subject region sex visit;
```

```
Model endpoint (event='1') = sex region baseline visit
                             <covariates> / dist=binary
                                            link= identity;
Random visit / subject=subject type=un residual;
Lsmeans sex          / alpha=0.05 cl;
Lsmeans region       / alpha=0.05 cl;
Lsmeans visit        / alpha=0.05 cl;
Lsmeans <covariate1> / alpha=0.05 cl;
Lsmeans <covariate2> / alpha=0.05 cl;
Run;
```

In the case of non-convergence for binary endpoint, a logit instead of identity link may be used to fit the model and odds ratios presented.

The model for Total NNAL will be added only if there will be at least 30% of the values above LLOQ.

In case of computational issues for a clinical risk endpoint e.g. due to lack of valid data, this endpoint may not be analyzed.

12.5.2 Biomarkers of Exposure to HPHCs

The list of biomarkers of exposure to HPHCs is provided in Appendix 16.5.

The level of BoExp parameters (CO, Neq, MHBMA, 3-HPMA, CEMA, B[a]P, Total 1-OHP, 3-HMPMA, Total NNN, 4-ABP, S-PMA, 1-NA, 2-NA, o-tol, HEMA, S-BMA) and their change from Baseline will be summarized at Baseline, V8, V11 and V17 as reported in Section 12.1.3 "Descriptive Statistics" for the Abstinence sets (Table 15.2.3.1). Supporting listings will be provided for all the data collected including the change from Baseline (Listings 15.3.3.1 to 15.3.3.2).

CO will be described within the compliance summaries (see Section 12.4 "Measurements of Compliance").

All other BoExp values at Baseline, V8, V11 and V17 will be log-transformed ($base_e$) prior to the analysis. Summaries will be presented on the original scale.

Concentration of BoExp in urine will be summarized adjusted for creatinine, as defined in Section 7.1.1 "Clinical Risk Endpoints and Biomarkers of Exposure in Urine". The percent of change from Baseline in the concentration adjusted for creatinine, and the quantity excreted will also be summarized. The listing will include the quantity excreted, the concentration adjusted for creatinine and the percent change from Baseline in the concentration adjusted for creatinine at each visit.

Descriptive statistics will be provided for endpoint parameters and Baseline characteristics of the population retained in the study at each assessment time point. Summary statistics of

endpoints will also include the percent change from Baseline, together with 95% CI for BoExp having at least 50% of the measured values above the limit of quantification (LOQ).

Line graphs of biological and functional markers mean (or geometrical mean for log transformed parameters) levels and 95% CI over time will be produced (Figures 15.1.3.1.*).

Graphs will be produced for the Abstinence12m and summaries will be performed for all the Abstinence sets.

12.5.2.1 Nicotine Exposure

The level of Neq in 24 hour urine both adjusted for creatinine and the quantity excreted, nicotine and cotinine in plasma will be listed (Listings 15.3.3.1 and 15.3.3.2) and summarized over time (Table 15.2.3.2).

Line graphs of Neq in 24 hour urine adjusted for creatinine, Nicotine and Cotinine in plasma levels showing geometrical mean and 95% CI over time will also be presented (Figures 15.1.3.2.*).

Summaries and graphs will be produced for all the Abstinence sets.

12.5.3 Continuous Smoking Abstinence

Continuous smoking abstinence as defined in Section 12.4 "Measurements of Compliance" will be summarized at V4 to V17, as well as the quitting status reported at V18, for the Quitters population and Abstinence Sets (Table 15.2.4.1).

Time-to-event analysis using Kaplan-Meier (KM) methodology will be adopted to describe the estimated rate of subjects who are continuously smoking abstinent from AQD to V17. Time from AQD nominal visit time will be used to calculate the time to event or censoring. Relapse events are defined as non-compliance to continuous abstinence (Section 12.4 "Measurements of Compliance"). Subjects without an event at the time of analysis will be censored at the last visit where compliance was demonstrated.

The number of subjects at risk of relapse event, number of events and estimated continuous abstinence rates and 95% CI (using the log-log transformation) will be presented from AQD to V17. Summaries and graphs will be produced overall and by region for the Quitters population at each visit following the AQD of smoking cessation (Table 15.2.4.2, Figures 15.1.4.2.* and Statistical Appendices 15.4.*), and also summarized by country within Europe.

The SAS procedure PROC LIFETEST will be used with the Kaplan-Meier method. The SAS code to be used for this time-to-event analysis is shown below:

```
Proc lifetest data=_data method=km
              atrisk alpha=0.05 conftype= loglog;
        /* 1 flags the censored event */
         Time time_to_event*censored(1);
         <by region;>
Run;
```

12.5.4 Safety Monitoring

Safety variables monitored in this study include: AEs; vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate); ECG data; concomitant medication, clinical chemistry, hematology, urine analysis safety panel, physical examination.

Adverse event data will serve as the primary assessment of safety.

12.5.4.1 Safety Reporting

All safety data collected during the study will be provided in listings for the Screened population.

Summaries will be produced overall and by region, from V2 to V18, for the Enrolled population. They will be repeated for Abstinence12m, except otherwise stated.

AE summaries will be repeated for Abstinence6m, and with a cut-off at 6 months.

The full safety population will be used for the production of specific safety summaries. Additional post-hoc analysis may be conducted if deemed necessary for interpretation purposes.

Safety data collected before Baseline will be provided in listings only.

12.5.4.2 Adverse Events

Any new, clinically relevant, abnormal finding or worsening of a pre-existing condition/concomitant disease detected during the study (including the safety follow-up period) will be documented as an AE and/or SAE as described in the Safety Management Plan.

All AEs occurring from the signing of informed consent will be recorded electronically.

ALL ADVERSE EVENTS

General AE summary table (Tables 15.2.5.1.*) will include the number of events and the number and percentage of subjects reporting at least one event for the following categories:

- Any AE.

- AE broken down by severity including each subject only once with his worst severity.
- AE related to study procedure.
- SAE overall and by seriousness criteria (fatal, life-threatening, requires hospitalization, results in disability/incapacity, congenital anomaly/birth defect).
- AE leading to death.
- AE leading to any action taken overall and broken down by action (study discontinuation, other action taken).

The summary table of AEs (Tables 15.2.5.2.*) will be presented with a breakdown of the number of events, as well as the number and percentage of subjects reporting each AE, categorized by SOC and PT coded according to MedDRA (version 18.0 or a later version).

The summary table of AEs categorized by SOC and PT will also be produced on the full safety population, in case there is at least one AE in subjects excluded from the safety population (e.g. Site 515).

A summary table by SOC and PT for all AEs with an incidence >5% will be produced (Tables 15.2.5.3.*).

A summary table by SOC and PT and severity will be produced (Table 15.2.5.4), as well as a summary table by SOC and PT and relationship to study procedure (Table 15.2.5.5). If a subject has more than one occurrence of the same AE, the subject will be counted only once within a PT with the worst occurrence based on the presentation (*e.g.*, for presentation by severity = most severe, for presentation by relationship to study procedures = related). AEs with missing intensity or relationship will be counted and presented as "missing" in the summary outputs.

AEs will be listed by region, center, subject number, AE start date, SOC and PT (Listing 15.3.4.1).

SERIOUS ADVERSE EVENTS (INCLUDING DEATHS)

Summary table of SAEs (Table 15.2.5.6) will be presented using the same approach as for AEs (see Section "All Adverse Events"), and including the number of events and the number and percentage of subjects reporting at least one SAE broken down by seriousness criteria (fatal, life-threatening, requires hospitalization, results in disability/incapacity, congenital anomaly/birth defect, important medical events).

SAEs will also be listed in separate listings by region, center, subject number, SOC and PT (Listing 15.3.4.2).

A listing of deaths will also be produced in case at least one death occurs during study.

ADVERSE EVENTS LEADING TO DISCONTINUATION

Summary table of AEs leading to withdrawal (Table 15.2.5.7) will be presented using the same approach as for AEs (see Section "All Adverse Events").

AEs leading to withdrawal will also be listed in separate listings ordered by region, center, subject number, SOC and PT (Listing 15.3.4.3).

LABORATORY ABNORMALITIES

The shift in toxicity grades from Baseline to worst grade recorded during the abstinence period will be presented in tables for the clinical chemistry, hematology and urinalysis parameters. Details related to the laboratory abnormalities summaries are in Section 12.5.4.3 "Clinical Laboratory Evaluation".

12.5.4.3 Clinical Laboratory Evaluation

Hematology, clinical chemistry and urine analysis parameters assessed at V1, V2, V8, V11, and V17 are listed in Table 22.

Table 22. List of Laboratory Safety Parameters

Hematology	Clinical Chemistry	Urine analysis
Hematocrit	Albumin	pH
Hemoglobin	Total protein	Bilirubin
Mean corpuscular hemoglobin	Alkaline phosphatase	Glucose
Mean corpuscular hemoglobin concentration	Alanine aminotransferase	Nitrite
Mean corpuscular volume	Aspartate aminotransferase	Red blood cell traces
Platelet count	Blood urea nitrogen	Protein
Red blood cell count	Creatinine	Specific gravity
WBC count	Gamma-glutamyl transferase	
Differential WBC count:	Fasting Glucose	
Neutrophils	Lactate dehydrogenase	
Basophils	Potassium	
Eosinophils	Sodium	
Lymphocytes	Total bilirubin	
Monocytes	Direct bilirubin	
	Total cholesterol	
	Triglycerides	

Any clinical safety laboratory test result that is outside of the normal reference range will be reviewed by the investigator or designee and assessed for clinical relevance. If an abnormal laboratory result is detected after Screening and considered clinically relevant, this will be recorded as an AE.

The grading scheme used in the Common Terminology Criteria for Adverse Events and Common Toxicity Criteria [CTCAE] version 4.03) will be used by the PI or designee to assess abnormal laboratory values, following the process detailed in Safety Management Plans developed for each country. These CTCAE grades will be derived by programs in the creation of the datasets.

Listings for the clinical laboratory will be provided by region, center, subject number and visit (Listings 15.1.4.4 to 15.1.4.6). Data will include the following information: normal/ high/low, abnormal clinically significant, PI's or designee's comments, change from Baseline, and CTCAE grade. Only CTCAE grades greater than zero will be reported.

Laboratory data will be summarized overall and by region. For each laboratory parameter, values at Baseline and at post-Baseline visits will be summarized together with changes from Baseline (Tables 15.2.5.8.*, 15.2.5.9.* and 15.2.5.10.*). The number and percentage of subjects with normal results, high/low results (with respect to the reference range) and abnormal clinically significant results (as defined by PI's or designee's comments) will also be tabulated for each laboratory parameter and timepoint.

12.5.4.4 Vital Signs, Physical Findings and Other Observations Related to Safety

BODY WEIGHT

Body weight at V1, V2, V8, V11 and V17 Visits; and body height recorded at V1 will also be listed together with BMI. Listings will also include waist circumference assessments at V2, V8, V11 and V17 (Listing 15.3.4.7).

Descriptive statistics of body weight, waist circumference, body height and BMI (BMI will also be categorized as shown in Section 12.1.4.1 "Categorical Variables") and their change from Baseline will be summarized at Baseline, V8, V11 and V17 (Table 15.2.5.11).

VITAL SIGNS

Systolic and diastolic blood pressure, pulse rate and respiratory rate measured during the study (V1, V2, and V4 to V17) will be listed and summarized (Listing 15.3.4.8 and Table 15.2.5.12). Vital signs assessments after Baseline will be listed and summarized together with change from Baseline.

SPIROMETRY

Spirometry parameters (FEV_1, FVC, FEV_1/FVC, and FEF 25-75) assessed at Screening Visit (V1), V2, V8, V11 and V17 (with and without bronchodilatator assessments) will be clinically interpreted (categories: normal, abnormal, abnormal clinically significant) and COPD staging will be evaluated [20]. COPD staging will be derived as defined in Table 19.

The number and percentage of subjects with normal/abnormal/abnormal clinically significant results will be summarized together with changes in COPD categories (Table 15.2.5.13).

Spirometry parameters and COPD staging will be listed (Listing 15.3.3.4).

ELECTROCARDIOGRAM

The ECG data will be obtained directly from the 12-lead ECG traces (*i.e.*, not centrally read). These data include the PR, QT, and QTcB intervals; QRS duration; and heart rate; and normality evaluation (normal, abnormal, clinically relevant). In addition the QTcF value will be presented. QTcB and QTcF will be calculated as detailed in Section 7 "DERIVED AND COMPUTED VARIABLES".

ECG data values and normality evaluations will be listed at V1, V11 and V17, together with changes from Baseline and shift in normality (Listing 15.3.4.9). ECG data from subjects which had significant clinical findings will be flagged in listings.

Descriptive statistics will be presented for ECG Baseline data at V1. ECG data will be summarized at V11 and V17 together with changes from Baseline, and the number and percentage of subjects with normal/abnormal/abnormal clinically significant results (Table 15.2.5.14). The table will not be repeated for Abstinence12m.

PHYSICAL EXAMINATION

Physical examination data recorded at V1, V2, V8, V11 and V17 will be listed by region, center and subject number (Listing 15.3.4.10). Subject's data with abnormal and abnormal clinically significant physical examination findings will be flagged. The number of subjects (%) with normal, abnormal and abnormal clinically significant results will be tabulated by body systems at Baseline, V8, V11 and V17 (Table 15.2.5.15). The table will not be repeated for Abstinence12m.

PRIOR AND CONCOMITANT MEDICATION

Prior medication is defined as any medication that started and ended prior to V1. Concomitant medication is defined as any medication starting on or after V1 or starting prior to V1 and ongoing at Screening. Medications starting after the completion/withdrawal date will be listed but will not be classified or summarized.

In case of missing or partial dates, classification into prior or concomitant medication will be handled as described in Section 12.1.5 "Handling of Dropouts or Missing Data (Including Outside the Limits of Quantification)".

All medication will be coded using PT and Anatomical Therapeutic and Chemical (ATC) codes (World Health Organization-Drug Dictionary Enhanced [WHO-DDE] dictionary using version of March 2015 or a later version). A flag will be presented on the listing indicating whether the medication is prior or concomitant.

Concomitant medication will be summarized for the Enrolled population showing the number (%) of subjects who used the medication at least once (according to ATC 1st and 2nd levels and preferred drug name). They will be summarized by ATC 1st and 2nd levels (Table 15.2.5.16.1), and by preferred drug name (Table 15.2.5.16.2). The table by preferred drug name will not be repeated for Abstinence12m.

Prior and concomitant medication will be listed by region, center, subject number and ATC codes (Listing 15.3.4.11).

12.5.5 Subject Reported Outcomes

12.5.5.1 Lifestyle Assessment

The lifestyle will be assessed by means of the lifestyle questionnaire, as described in Section 7.2.6 "Lifestyle Assessment".

The change from Baseline will be calculated for the numeric items at V8, V11 and V17. The responses to the individual items, and change from Baseline will be listed (Listing 15.3.5.1) and summarized for the Abstinence sets (Table 15.2.5.17). The number and percentage of subjects reporting living in a household with one or more smokers will also be summarized, as well as the shift from Baseline.

12.5.5.2 Cough-VAS Questionnaire

Cough symptoms will be assessed by means of the cough-VAS questionnaire, as described in Section 7.2.4 "Cough-VAS Questionnaire".

The change from Baseline will be calculated for the VAS score evaluating the level of cough bother at V8, V11 and V17. For the calculation of the change from Baseline, missing VAS values will be imputed with zero when no cough was reported.

The VAS score and change from Baseline and 3 Likert scales measuring the intensity, the frequency of cough and the amount of sputum production will be listed (Listing 15.3.5.2) and summarized for all subjects who filled in the questionnaire from the Abstinence sets (Table 15.2.5.18). The number and percentage of subjects reporting a cough will also be summarized, as well as the shift from Baseline.

The answers to the open question related to any other important observation will be listed.

13 ANALYSES AND REPORTING

No confirmatory analysis is foreseen in this study although data will be used to evaluate the effect of SC for benchmarking purposes in the context of Philip Morris International (PMI) products assessment programs. The details of the methods used to evaluate the reference effect of SC for specific endpoints and population characteristics will be provided in separate analysis plans, and results will be reported separately.

13.1 Interim Analyses and Data Monitoring

No formal interim analysis of the data is foreseen. However, interim raw SAS data sets will be extracted for the purpose of providing data for the design and interpretation of assessment studies of PMI candidate modified risk tobacco products (MRTPs). For this purpose, the analysis methods for the combined analysis will be detailed in a separate SAP.

The interim cut-off will be at V11 and data will be flagged for the inclusion in the interim analysis excluding subjects discontinued at V8 or earlier. Only clean data will be part of the interim SAS data sets as defined in the Data Review Plan.

The interim TFLs produced for this study to participate in the combined analysis mentioned above are listed in Appendix 16.7.

A Clinical Research Associate ("Monitor") from [redacted] will be responsible for the monitoring of the study. Monitoring will be performed according to [redacted] standard operating procedures (SOPs) and as per the agreed monitoring plan with PMI.

The PI, or a designated member of the PI's staff, must be available during the monitoring visit to review the data and resolve any queries, and to allow direct access to the subject's records for source data verification.

All changes to the source data will have to be approved by the PI.

Upon finalization of this document, it will be specified which TFLs will be produced for Safety reporting, Topline results, Final Analysis, and Clinicaltrials.gov reporting purposes.

13.2 Safety Reporting

Statistical summaries required for safety reporting will be made available to PMI medical safety officer following database lock. The TFLs are listed in Appendix 16.7.

13.3 Topline Results

Topline results, composed of key statistics and study results listings, will be made available to PMI management following database lock and prior to completion of the complete set of TFLs. The topline TFLs are listed in Appendix 16.7.

13.4 Final Analysis

The final analysis will be performed will be performed only after database lock. A pre-analysis data review meeting will be held prior to database lock and completion of the final analyses. In addition, no database may be locked, or analyses completed until the final version of this SAP has been approved.

Any post-hoc, additional exploratory analyses completed to support planned study analyses, which were not identified in this SAP, will be documented and reported as applicable. Any results from these unplanned analyses will also be clearly identified in the text of the CSR.

The list of all tables, figures and listings to be presented are included in the relevant sections of the SAP and in Appendix 16.7.

13.5 Clinical Trials.gov

Statistical summaries which will be evaluated for publishing on the Clinical trials.gov website are listed in the table of contents in Appendix 16.7.

14 DATA PRESENTATION

A separate TFL style guide document will be provided by PMI.

15 REFERENCES

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16 APPENDICES

16.1 Study Assessments

Visits Assessments (± Time Window in Days)	Screening	Baseline		AQD	Smoking Abstinence Period [m]															Safety Follow-Up Period [n]
	V1	V2	V3		V4 (±3)	V5 (±3)	V6 (±8)	V7 (±8)	V8 (±8)	V9 (±8)	V10 (±8)	V11 (±8)	V12 (±8)	V13 (±8)	V14 (±8)	V15 (±8)	V16 (±8)	V17 (±8)	ET	V18 (±3)
					W1	W2	W4	W9	W13	W17	W22	W26	W30	W35	W39	W43	W48	W52		W56
ICF main study and additional ICFs	•																			
Information on the risk of smoking / smoking cessation advice [a]	•	•																		
Inclusion/exclusion criteria	•	•																		
Enrolment		•																		
Individual TQD [b]		•																		
Individual AQD [c]				•																
Smoking cessation support [d]		•	•		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
Self-reporting by the subject on continuous smoking abstinence					•	•	•	•	•	•	•	•	•	•	•	•	•	•		•[n]
Demographics	•																			
Medical history	•																			

Visits Assessments (± Time Window in Days)	Scree-ning	Base-line		AQD	Smoking Abstinence Period [m]															Safety Follow-Up Period [n]
	V1	V2	V3		V4 (±3)	V5 (±3)	V6 (±8)	V7 (±8)	V8 (±8)	V9 (±8)	V10 (±8)	V11 (±8)	V12 (±8)	V13 (±8)	V14 (±8)	V15 (±8)	V16 (±8)	V17 (±8)	ET	V18 (±3)
					W1	W2	W4	W9	W13	W17	W22	W26	W30	W35	W39	W43	W48	W52		W56
Concomitant diseases	•																			
Prior/concomitant medication	•	•	•		•	•	•	•	•	•	•	•	•	•	•	•	•	•		
B: HIV, hepatitis B and C	•																			
U : Drug screen	•																			
U: Cotinine test (cut-off ≥ 200 ng/mL)	•	•																		
U: Cotinine test (cut-off < 100 ng/mL)											•	•	•	•	•	•	•	•		
Alcohol U or breath test	•																			
U: Pregnancy test (all females)	•	•			•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
B/U: Clinical chemistry, hematology, urine analysis [e]	•	•							•			•						•	•	
ECG	•											•						•	•	
Vital signs [f]	•	•			•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
Weight	•	•							•			•						•		

Visits Assessments (± Time Window in Days)	Screening	Baseline		AQD	Smoking Abstinence Period [m]														Safety Follow-Up Period [n]
	V1	V2	V3		V4 (±3)	V5 (±3)	V6 (±8)	V7 (±8)	V8 (±8)	V9 (±8)	V10 (±8)	V11 (±8)	V12 (±8)	V13 (±8)	V14 (±8)	V15 (±8)	V16 (±8)	V17 (±8)	ET	V18 (±3)
					W1	W2	W4	W9	W13	W17	W22	W26	W30	W35	W39	W43	W48	W52		W56
Height	•																			
Waist circumference		•							•			•						•		
Physical examination	•	•							•			•						•	•	
CO breath test [g]		•			•	•	•	•	•	•	•	•	•	•	•	•	•	•		
Spirometry pre- and post-bronchodilator [h]	•	•							•			•						•	•	
Lung volumes (at selected sites) [h]		•							•			•						•	•	
Computerized multichannel lung sounds analysis (Stethographics and Stethos, at the QASMC)		•							•			•						•		
Gas transfer [h] (at the QASMC)		•				•	•	•	•			•						•		
B: COHb		•				•[h*]	•[h*]	•[h*]	•			•						•		
U: Full list of BoExp [i]		•							•											
U: Reduced list of BoExp [i]												•						•		
B: CYP2A6		•							•			•						•		

Visits Assessments (± Time Window in Days)	Scree-ning	Base-line		AQD	Smoking Abstinence Period [m]															Safety Follow-Up Period [n]
	V1	V2	V3		V4 (±3)	V5 (±3)	V6 (±8)	V7 (±8)	V8 (±8)	V9 (±8)	V10 (±8)	V11 (±8)	V12 (±8)	V13 (±8)	V14 (±8)	V15 (±8)	V16 (±8)	V17 (±8)	ET	V18 (±3)
					W1	W2	W4	W9	W13	W17	W22	W26	W30	W35	W39	W43	W48	W52		W56
B : Nicotine / cotinine		•							•			•						•		
B: CVD clinical risk endpoints [j]		•							•			•						•		
U: CVD clinical risk endpoints [j]		•							•			•						•		
FTND Questionnaire		•																		
Cough VAS Questionnaire		•							•			•						•		
Prochaska's Questionnaire	•																			
Questions about smoking history/habits	•	•																		
SES questionnaire [k]		•																		
Lifestyle questions	•	•							•			•						•		
AE/SAE recording	•	•	•		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Nasal/buccal scrapes (at the QASMC)		•							•			•						•		
B: bio-banking for transcriptomics / lipidomics [l]		•							•			•						•		

Visits Assessments (± Time Window in Days)	Screening	Baseline		AQD	Smoking Abstinence Period [m]															Safety Follow-Up Period [n]
	V1	V2	V3		V4 (±3)	V5 (±3)	V6 (±8)	V7 (±8)	V8 (±8)	V9 (±8)	V10 (±8)	V11 (±8)	V12 (±8)	V13 (±8)	V14 (±8)	V15 (±8)	V16 (±8)	V17 (±8)	ET	V18 (±3)
					W1	W2	W4	W9	W13	W17	W22	W26	W30	W35	W39	W43	W48	W52		W56
B: bio-banking for clinical risk endpoints and BoExp [l]		•							•			•						•		
U: bio-banking for Clinical risk endpoints and BoExp [l]		•							•			•						•		

Abbreviations: AE = Adverse event; AQD = Actual quit date; B = Blood sample required; BoExp = Biomarkers of exposure; CO = Carbon monoxide; COHb = Carboxyhemoglobin; CVD = Cardiovascular disease; CYP = Cytochrome P450; ECG = Electrocardiogram; ET = Early Termination; FTND = Fagerström Test for Nicotine Dependence; HIV = Human immunodeficiency virus; ICF = Informed consent form; SAE = Serious adverse event; SES = Socio-Economic Situation; TQD = Target quit date; U = Urine sample required; V = Visit; VAS = Visual Analog Scale; W = Week.

a. At V2, advices on the risk of smoking and smoking cessation advice should be the last assessment of the day.

b. At V2, subjects will be asked to define their TQD. This TQD has to be within 14 days after the check-out of V2 and V3 has to be within 24 to 48 hours after TQD.

c. Subjects will record their AQD which has to be within 14 days after the TQD. Of note, the AQD is not a visit.

d. Smoking cessation support including smoking cessation counseling and behavioral support throughout the study according to the smoking cessation support plan. Additional SC support will be offered at any time when requested by the subject.

e. The list of clinical chemistry, hematology and urine analysis parameters is detailed in Table 22.

f. Systolic and diastolic blood pressure, pulse and respiratory rate.

g. CO breath test will be done with a smokerlyser or similar.

h. The lung function tests must be performed in the following sequence when appropriate:

- Spirometry without salbutamol
- Lung volume (VC, TLC, and IC)*

- Gas transfer*
- Spirometry with salbutamol

* Lung volumes and gas transfer will be assessed at the [redacted] Blood sample for COHb measurement has to be collected just prior to the gas transfer measurement.

i. Full and reduced lists of urinary BoExp are provided in Appendix 16.5. Free cotinine concentration (part of the nicotine equivalents) will be determined in 24-hour urine collected at Visit 11 (cut-off ≥ 50 ng/mL) as a criterion for discontinuation at the time the results are made available.

j. List of clinical risk endpoints assessed in the different matrices is provided in Appendix 16.2

k. A country specific Socio-Economic Situation questionnaire will be completed in the following countries: US, UK, Poland, Germany and Japan

l. Only in subjects who signed an additional ICF.

m. For the visits, a time window of ± 8 days is allowed from the AQD, with the exception of V4 and V5 (± 3 days)

n. Self-reporting by the subject on continuous smoking abstinence at Visit 18 (Week 56) is performed via phone contact if the subject has previously completed V17.

16.2 Summary of Clinical Risk Endpoints

Clinical Risk Endpoints	Measure-ment of	Biofluid / Function	Log-trans-formed	Effect Measure
Respiratory				
Forced expiratory volume in 1 second (FEV_1)	Spirometry		No	Absolute increase
Forced vital capacity (FVC)	Spirometry		No	Absolute increase
Forced expiratory flow 25-75 (FEF 25-75)	Spirometry		No	Absolute increase
FEV_1/FVC	Spirometry		No	Absolute increase
Reversibility in FEV_1	Spirometry		No	Absolute increase
Total lung volumes, inspiratory capacity and functional residual capacity(**)	Lung volume	Lung	No	Absolute increase
Diffusing capacity for lung carbon monoxide (DLCO) (***)	Gas transfer		No	Absolute increase
Computerized multichannel lung sounds analysis (Stethographics and Stethos) (***)	Wheezing and Crackling rate		Yes	Absolute decrease
Frequency / intensity of cough symptoms	Lung response (respiratory symptoms)		No	Absolute decrease
Cardiovascular				
High density lipoprotein cholesterol (HDL-C)	Lipid metabolism	Serum	No	Absolute increase
Low density lipoprotein cholesterol (LDL-C)	Lipid metabolism	Serum	No	Absolute decrease
White blood cell (WBC) total count (*)	Inflammation	Blood	No	Absolute decrease
High sensitivity C-reactive protein (hs-CRP)	Inflammation	Serum	Yes	Percent reduction
Platelet count*	Inflammation	Blood	Yes	Percent reduction
Fibrinogen	Inflammation	Plasma	Yes	Percent reduction
Soluble intercellular adhesion	Endothelial	Serum	Yes	Percent

Clinical Risk Endpoints	Measure-ment of	Biofluid / Function	Log-trans-formed	Effect Measure
molecule-1 (sICAM-1)	dysfunction			reduction
11-dehydrothromboxane B2 (11-DTX-B2)	Platelet activation	Urine	Yes	Percent reduction
Albumin	Endothelial dysfunction	Urine	Yes	Percent reduction
Homocysteine	Endothelial dysfunction	Plasma	Yes	Percent reduction
8-epi-prostaglandin F2α (8-epi-$PGF_{2\alpha}$)	Oxidative stress	Urine	Yes	Percent reduction
Myeloperoxidase (MPO)	Oxidative stress	Serum	Yes	Percent reduction
Apolipoprotein A1 (Apo A1)	Lipid metabolism	Serum	No	Absolute increase
Apolipoprotein B (Apo B)	Lipid metabolism	Serum	No	Absolute decrease
Apolipoprotein B/A1 (Apo B/Apo A1)	Lipid metabolism	Derived	No	Absolute decrease
Carboxyhemoglobin (COHb)	Transport of oxygen by hemoglobin	Blood	Yes	Percent reduction
Glycosylated hemoglobin (HbA1c)	Insulin resistance	Blood	No	Percent reduction
Xenobiotics				
Cytochrome 2A6 (CYP2A6) activity	Nicotine metabolism	Plasma	Yes	Percent increase
Genotoxicity				
Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (Total NNAL)	Exposure to carcinogenic HPHC (NNK)	Urine	Yes	Percent reduction

* Measured as part of the safety laboratory parameters.

** Measured in selected centers.

*** Measured/assessed at the [redacted] only.

16.3 Parameters Measured by the Computerized Multichannel Lung Sound Analysis (Stethographics and Stethos)

The following parameters are derived from the Stethographics software after input of recorded lung sounds captured by the Stethographics device and the Stethos device.

	Parameter	Log-transformed	Effect Measure
1	Expiratory Crackle Rate (per minute)	Yes	Percent Decrease
2	Expiratory Wheeze Rate (per minute)	Yes	Percent Decrease
3	Inspiratory Crackle Rate (per minute)	Yes	Percent Decrease
4	Inspiratory Wheeze Rate (per minute)	Yes	Percent Decrease
5	Dynamic Range Score	Yes	Percent Decrease
6	Inspiratory Chest RMS Score	Yes	Percent Decrease
7	Channel Asynchrony	Yes	Percent Decrease
8	Lag Score	Yes	Percent Decrease
9	Lag Time-Integrated Amplitude	Yes	Percent Decrease
10	Lead STDEV (average lead and lag of chest channels compared to the tracheal channel) Score	Yes	Percent Decrease
11	Lead Score	Yes	Percent Decrease
12	Lead Time-Integrated Amplitude	Yes	Percent Decrease
13	Low Frequency / High Frequency Sound ratio	Yes	Percent Decrease
14	Inspiration duration / Expiration duration	Yes	Percent Decrease
15	Peak Inspiratory Amplitude / Peak Expiratory Amplitude	Yes	Percent Decrease
16	Slope of Chest vs. Trachea During Inspiration	Yes	Percent Decrease
17	COPD score not weighted	Yes	Absolute decrease

	Parameter	Log-transformed	Effect Measure
18	COPD score weighted	Yes	Absolute decrease

16.4 Summary of Lung Diffusion

The lung diffusion parameters are as below:

	Parameter	Log-transformed	Effect Measure
1	Diffusing capacity for lung carbon monoxide (DLCO)	No	Absolute increase
2	Alveolar Volume (VA)	No	Absolute increase
3	Transfer Coefficient (KCO or DLCO/VA)	No	Absolute increase
4	Inspired Volume (VI)	No	Absolute increase

16.5 Summary of Biomarkers of Exposure to HPHC

Biomarkers of Exposure to HPHC will be log-transformed, except CO.

HPHC [smoke phase]	HPHC list	Biomarker	Matrix	$t_{1/2\beta}$	Reduced List of BoExp
1,3-Butadiene [gas]	FDA-18, FDA-93, HC PMI-58, WHO-18	Monohydroxybutenylmercapturic acid (MHBMA)	Urine	4 to 16 h	•
1-Aminonaphthalene [particulate]	FDA-18, FDA-93, HC PMI-58	1-Aminonaphthalene (1-NA)	Urine	Not described	
2-Aminonaphthalene [particulate]	FDA-18, FDA-93, HC PMI-58, WHO-18	2-Aminonaphthalene (2-NA)	Urine	9 h	
4-Aminobiphenyl [particulate]	FDA-18, FDA-93, HC PMI-58, WHO-18	4-Aminobiphenyl (4-ABP)	Urine	26 h	
Acrolein [gas]	FDA-18, FDA-93, HC PMI-58, WHO-18	3-Hydroxypropyl-mercapturic acid (3-HPMA)	Urine	10 h	•
Acrylonitrile [gas]	FDA-18, FDA-93, HC PMI-58, WHO-18	2-Cyanoethylmercapturic acid (CEMA)	Urine	17 h	•
Benzene [gas]	FDA-18, FDA-93, HC PMI-58, WHO-18	S-Phenyl-mercapturic acid (S-PMA)	Urine	9 to 15 h	
Benzo[a]pyrene [particulate]	FDA-18, FDA-93, HC PMI-58, WHO-18	3-Hydroxybenzo[a]pyrene B[a]P	Urine	3 to 4 h	•

HPHC [smoke phase]	HPHC list	Biomarker	Matrix	$t_{1/2\beta}$	Reduced List of BoExp
Carbon monoxide [gas]	FDA-18 FDA-93 HC PMI-58 WHO-18	CO	Breath	/	●
Pyrene	FDA-18 FDA-93 HC PMI-58 WHO-18	Total 1-hydroxypyene (total 1-OHP)	Urine	6 to 35 h	●
Crotonaldehyde [gas]	FDA-18, FDA-93, HC PMI-58, WHO-18	3-Hydroxy-1-methylpropyl-mercapturic acid (3-HMPMA)	Urine	2 days	●
Ethylene oxide [gas]	FDA-93, PMI-58	2-Hydroxyethyl-mercapturic acid (HEMA)	Urine	5 h	
NNN [particulate]	FDA-18, FDA-93, HC PMI-58, WHO-18	Total N-nitrosonornicotine (Total NNN)	Urine	15 h	●
o-Toluidine [gas]	FDA-93, PMI-58	o-Toluidine (o-TOL)	Urine	10 to 16 h	
Toluene [gas]	FDA-18, FDA-93, HC PMI-58, WHO-18	S-benzyl-mercapturic acid (S-BMA)	Urine	9 h	
Nicotine [particulate]	FDA-18, FDA-93, HC PMI-58	Nicotine (NIC-P)	Plasma	1 to 2 h	●
		Cotinine (COT-P) 3-OH Cotinine (3-OHCOTP)	Plasma	16 to 18 h -	●
		Nicotine equivalents (Neq)	Urine	16 h (estimated)	●

16.6 Schedule of Continuous Smoking Abstinence Assessment Tools by Protocol Version

The following table summarizes the tools used for compliance assessment and for the exclusion of data from analysis as detailed in Section 12.4 "Measurements of Compliance"

	Visit								Protocol Version		
Assessments	**V4-V7**	**V8**	**V9**	**V10**	**V11**	**V12-V16**	**V17**	**V18**			
Self-reporting	X	X	X	X	X	X	X	X	v5.0 [redacted] v4.0)	v6.0 (only Poland)	v7.0 ([redacted] v5.0)
CO breath test (≤ 10 ppm)	X	X	X	X	X	X	X				
Urine cotinine test (< 100 ng/mL)				X	X	X	X				
Free cotinine (< 50 ng/mL)					X		X(*)				
Total NNAL (< 75 ng/mL)					X(*)		X(*)				

(*) Free cotinine test at V17 and Total NNAL at V11 and V17 were not used as criterion for compliance leading to subject discontinuation in the study protocol v7.0 ([redacted] v5.0)

16.7 Tables, Listings, and Figures

The tables below reports all the TFLs and flags those required for interim analysis, safety reporting, topline results, final analysis and clinicaltrial.gov reporting.

Tables

Table No.	Title	Interim Analysis (Y/N)	Safety (Y/N)	Topline (Y/N)	Final Analysis (Y/N)	Clinical Trial.gov (Y/N)
15.2.1.1	Summary of Subject Disposition – Screened Population	Y		Y	Y	Y
15.2.1.2	Summary of Reasons for Premature Discontinuation – Enrolled and Quitters Population				Y	
15.2.1.3.1	Summary of Protocol Deviations by Region – Enrolled Population				Y	
15.2.1.3.2	Analysis Sets and Reasons for Exclusions from Analyses by Region and Country – All Subjects				Y	
15.2.1.4.1.1	Summary of Demographics and Other Baseline Characteristics (All Regions) – Abstinence sets and Enrolled Population	Y		Y	Y	Y
15.2.1.4.1.2	Summary of Demographics and Other Baseline Characteristics (US) – Abstinence sets and Enrolled Population	Y		Y	Y	
15.2.1.4.1.3	Summary of Demographics and Other Baseline Characteristics (Europe) – Abstinence sets and Enrolled Population				Y	

Table No.	Title	Interim Analysis (Y/N)	Safety (Y/N)	Topline (Y/N)	Final Analysis (Y/N)	Clinical Trial.gov (Y/N)
15.2.1.4.1.4	Summary of Demographics and Other Baseline Characteristics (Japan) – Abstinence sets and Enrolled Population				Y	
15.2.1.4.2	Summary of Demographics and Other Baseline Characteristics by Sex (All Regions) – Enrolled Population				Y	
15.2.1.5	Summary of Questions on Smoking History/Habits – Abstinence sets and Enrolled Population				Y	
15.2.1.6	Summary of Prochaska 'Stage of Change' Questionnaire – Abstinence sets and Enrolled Population				Y	
15.2.1.7.1	Summary of Socio-Economic Status Questionnaire (US) – Abstinence sets and Enrolled Population				Y	
15.2.1.7.2	Summary of Socio-Economic Status Questionnaire (Japan) – Abstinence sets and Enrolled Population				Y	
15.2.1.7.3	Summary of Socio-Economic Status Questionnaire (UK) – Abstinence sets and Enrolled Population				Y	
15.2.1.7.4	Summary of Socio-Economic Status Questionnaire (Poland) – Abstinence sets and Enrolled Population				Y	
15.2.1.7.5	Summary of Socio-Economic Status Questionnaire (Germany) – Abstinence sets and Enrolled Population				Y	
15.2.1.8	Summary of Medical History – Abstinence Sets and Enrolled Population		Y		Y	

Table No.	Title	Interim Analysis (Y/N)	Safety (Y/N)	Topline (Y/N)	Final Analysis (Y/N)	Clinical Trial.gov (Y/N)
15.2.1.9	Summary of Concomitant Diseases – Abstinence Sets and Enrolled Population		Y		Y	
15.2.2.1.1.1	Descriptive Statistics of Clinical Risk Endpoints Associated with Cardiovascular Disease (All Regions) – Abstinence Sets	Y		Y	Y	Y
15.2.2.1.1.2	Descriptive Statistics of Clinical Risk Endpoints Associated with Cardiovascular Disease (US) – Abstinence Sets	Y		Y	Y	
15.2.2.1.1.3	Descriptive Statistics of Clinical Risk Endpoints Associated with Cardiovascular Disease (Europe) – Abstinence Sets				Y	
15.2.2.1.1.4	Descriptive Statistics of Clinical Risk Endpoints Associated with Cardiovascular Disease (Japan) – Abstinence Sets				Y	
15.2.2.1.2	Descriptive Statistics of Clinical Risk Endpoints Associated with Cardiovascular Disease by Sex – Abstinence Sets				Y	
15.2.2.1.3	Analysis of the Covariates Associated with Cardiovascular Disease Clinical Risk Endpoints – Abstinence Sets				Y	
15.2.2.2.1.1	Descriptive Statistics of Clinical Risk Endpoints Associated with Respiratory Disease (All Regions) – Abstinence Sets	Y		Y	Y	
15.2.2.2.1.2	Descriptive Statistics of Clinical Risk Endpoints Associated with Respiratory Disease (US) – Abstinence Sets	Y		Y	Y	
15.2.2.2.1.3	Descriptive Statistics of Clinical Risk Endpoints Associated with Respiratory Disease (Europe) – Abstinence Sets				Y	

Table No.	Title	Interim Analysis (Y/N)	Safety (Y/N)	Topline (Y/N)	Final Analysis (Y/N)	Clinical Trial.gov (Y/N)
15.2.2.2.1.4	Descriptive Statistics of Clinical Risk Endpoints Associated with Respiratory Disease (Japan) – Abstinence Sets				Y	
15.2.2.2.2	Descriptive Statistics of Clinical Risk Endpoints Associated with Respiratory Disease by Sex – Abstinence Sets				Y	
15.2.2.2.3	Analysis of the Covariates Associated with Respiratory Disease Clinical Risk Endpoints – Abstinence Sets				Y	
15.2.2.3.1	Descriptive Statistics of Clinical Risk Endpoints Associated with Respiratory Disease assessed at the [redacted] – Abstinence Sets				Y	
15.2.2.3.2	Descriptive Statistics of Clinical Risk Endpoints Associated with Respiratory Disease assessed at the [redacted] by Sex – Abstinence Sets				Y	
15.2.2.4.1.1	Descriptive Statistics of Clinical Risk Endpoints Associated with Xenobiotics and Genotoxicity (All Regions) – Abstinence Sets	Y		Y	Y	Y
15.2.2.4.1.2	Descriptive Statistics of Clinical Risk Endpoints Associated with Xenobiotics and Genotoxicity (US) – Abstinence Sets	Y		Y	Y	
15.2.2.4.1.3	Descriptive Statistics of Clinical Risk Endpoints Associated with Xenobiotics and Genotoxicity (Europe) – Abstinence Sets				Y	
15.2.2.4.1.4	Descriptive Statistics of Clinical Risk Endpoints Associated with Xenobiotics and Genotoxicity (Japan) – Abstinence Sets				Y	

Table No.	Title	Interim Analysis (Y/N)	Safety (Y/N)	Topline (Y/N)	Final Analysis (Y/N)	Clinical Trial.gov (Y/N)
15.2.2.4.2	Descriptive Statistics of Clinical Risk Endpoints Associated with Xenobiotics and Genotoxicity by Sex – Abstinence Sets				Y	
15.2.2.4.3	Analysis of the Covariates Associated with Clinical Risk Endpoints Associated with Xenobiotics and Genotoxicity – Abstinence Sets				Y	
15.2.3.1	Descriptive Statistics of Biomarkers of Exposure to HPHC (All Regions) – Abstinence Sets	Y		Y	Y	
15.2.3.2	Descriptive Statistics of Nicotine Exposure (All Regions) – Abstinence Sets				Y	
15.2.4.1	Summary of Compliance to Continuous Abstinence and Reported Abstinence at Month 13 – Enrolled and Quitters Population				Y	
15.2.4.2	Summary of Rate of Continuous Smoking Abstinence over Time by Region, by EU Country, and Overall – Quitters Population	Y		Y	Y	
15.2.5.1.1	Summary of Adverse Events – Enrolled Population		Y	Y	Y	
15.2.5.1.2	Summary of Adverse Events in 6 Months – Enrolled Population	Y	Y		Y	
15.2.5.2.1	Summary of Adverse Events by System Organ Class and Preferred Term – Enrolled Population		Y	Y	Y	
15.2.5.2.2	Summary of Adverse Events by System Organ Class and Preferred Term in 6 Months – Enrolled Population	Y	Y		Y	

Table No.	Title	Interim Analysis (Y/N)	Safety (Y/N)	Topline (Y/N)	Final Analysis (Y/N)	Clinical Trial.gov (Y/N)
15.2.5.2.3	Summary of Adverse Events by System Organ Class and Preferred Term – Full Safety Population		Y	Y	Y	
15.2.5.3.1	Summary of Adverse Events (Incidence >5% in any Column) by System Organ Class and Preferred Term – Enrolled Population		Y		Y	Y
15.2.5.3.2	Summary of Adverse Events (Incidence >5% in any Column) by System Organ Class and Preferred Term in 6 Months – Enrolled Population		Y		Y	Y
15.2.5.4	Summary of Adverse Events by System Organ Class and Preferred Term and Severity – Enrolled Population		Y		Y	
15.2.5.5	Summary of Adverse Events by System Organ Class and Preferred Term and Relationship to Study Procedure – Enrolled Population		Y		Y	
15.2.5.6	Summary of Serious Adverse Events by System Organ Class and Preferred Term and Seriousness Criteria – Enrolled Population		Y		Y	
15.2.5.7	Summary of Adverse Events Leading to Discontinuation by System Organ Class and Preferred Term – Enrolled Population		Y		Y	
15.2.5.8.1	Summary of Clinical Chemistry Parameters – Enrolled Population		Y		Y	
15.2.5.8.2	Summary of Clinical Chemistry Parameters – Abstinence12m Set		Y		Y	

Table No.	Title	Interim Analysis (Y/N)	Safety (Y/N)	Topline (Y/N)	Final Analysis (Y/N)	Clinical Trial.gov (Y/N)
15.2.5.9.1	Summary of Hematology Parameters – Enrolled Population		Y		Y	
15.2.5.9.2	Summary of Hematology Parameters – Abstinence12m Set		Y		Y	
15.2.5.10.1	Summary of Urinalysis Parameters – Enrolled Population		Y		Y	
15.2.5.10.2	Summary of Urinalysis Parameters – Abstinence12m Set		Y		Y	
15.2.5.11	Summary of Weight, BMI and Waist Circumference Results (Note: title per PMI example, this also includes Height at Screening) – Enrolled Population		Y		Y	
15.2.5.12	Summary of Vital Signs – Enrolled Population		Y		Y	
15.2.5.13	Summary of Spirometry Results – Enrolled Population		Y		Y	
15.2.5.14	Summary of ECG Results - Enrolled Population		Y		Y	
15.2.5.15	Summary of Physical Examination of Body Systems – Enrolled Population		Y		Y	
15.2.5.16.1	Summary of Concomitant Medication by Anatomical Therapeutic Classes (ATC) 1 and 2 - Enrolled Population		Y		Y	
15.2.5.16.2	Summary of Concomitant Medication by Preferred Drug Name – Enrolled Population		Y		Y	
15.2.5.17	Summary of Lifestyle Assessment – Abstinence Sets				Y	

Table No.	Title	Interim Analysis (Y/N)	Safety (Y/N)	Topline (Y/N)	Final Analysis (Y/N)	Clinical Trial.gov (Y/N)
15.2.5.18	Summary of Cough-VAS Questionnaire – Abstinence Sets				Y	

Listings

Listing No.	Title	Interim Analysis (Y/N)	Safety (Y/N)	Topline (Y/N)	Final Analysis (Y/N)	Clinical Trial.gov (Y/N)
15.3.1.1.1	Listing of Informed Consent				Y	
15.3.1.1.2	Listing of Subject Disposition				Y	
15.3.1.1.3	Listing of Visits				Y	
15.3.1.2	Listing of Unmet Inclusion / Exclusion Criteria				Y	
15.3.1.3	Listing of Protocol Deviations				Y	
15.3.1.4	Listing of Assignment to Analysis Sets and Reasons for Exclusions				Y	
15.3.1.5	Listing of Demographics				Y	
15.3.1.6	Listing of Smoking History/Habits				Y	
15.3.1.7	Listing of the Prochaska ‘Stage of Change’ Questionnaire				Y	
15.3.1.8	Listing of the Fagerstrom Test for Nicotine Dependence Results				Y	
15.3.1.9.1	Listing of Socio-Economic Questionnaire Results – US				Y	
15.3.1.9.2	Listing of Socio-Economic Questionnaire Results – Japan				Y	
15.3.1.9.3	Listing of Socio-Economic Questionnaire Results – UK				Y	

Listing No.	Title	Interim Analysis (Y/N)	Safety (Y/N)	Topline (Y/N)	Final Analysis (Y/N)	Clinical Trial.gov (Y/N)
15.3.1.9.4	Listing of Socio-Economic Questionnaire Results – Poland				Y	
15.3.1.9.5	Listing of Socio-Economic Questionnaire Results – Germany				Y	
15.3.1.10	Listing of the Urine Tests, Serology and Alcohol Breath Test				Y	
15.3.1.11	Listing of Medical History and Concomitant Diseases		Y		Y	
15.3.2.1	Listing of Smoking Abstinence Status and Compliance				Y	
15.3.2.2	Listing of Smoking Cessation Information/Advice and Support				Y	
15.3.3.1	Listing of Urinary Biomarkers				Y	
15.3.3.2	Listing of Blood, Plasma, Serum, and Exhaled Air Biomarkers				Y	
15.3.3.3	Listing of CYP2A6 Activity and Changes from Baseline				Y	
15.3.3.4	Listing of Spirometry Data and COPD Staging				Y	
15.3.3.5	Listing of Lung Volume Data				Y	
15.3.3.6	Listing of Computerized multichannel lung sounds analysis (Stethographics)				Y	
15.3.3.7	Listing of Lung Diffusion Data				Y	
15.3.3.8	Listing of Nasal and Buccal Epithelium Samples Not Collected				Y	

Listing No.	Title	Interim Analysis (Y/N)	Safety (Y/N)	Topline (Y/N)	Final Analysis (Y/N)	Clinical Trial.gov (Y/N)
15.3.3.9	Listing of Transcriptomics and Lipidomics Samples Not Collected				Y	
15.3.4.1	Listing of Adverse Events		Y		Y	
15.3.4.2	Listing of Serious Adverse Events		Y		Y	
15.3.4.3	Listing of Adverse Events Leading to Discontinuation		Y		Y	
15.3.4.4	Listing of Clinical Chemistry Data, Shift, Changes from Baseline and CTCAE grades		Y		Y	
15.3.4.5	Listing of Hematology Data, Shift, Changes from Baseline and CTCAE grades		Y		Y	
15.3.4.6	Listing of Urinalysis Data, Shift, Changes from Baseline and CTCAE grades		Y		Y	
15.3.4.7	Listing of Height at Baseline, Weight, Waist Circumference, BMI		Y		Y	
15.3.4.8	Listing of Vital Signs Data and Changes from Baseline		Y		Y	
15.3.4.9	Listing of ECG Data and Changes from Baseline		Y		Y	
15.3.4.10	Listing of Physical Examination Findings, Shift and Changes from Baseline		Y		Y	
15.3.4.11	Listing of Prior and Concomitant medication		Y		Y	

Listing No.	Title	Interim Analysis (Y/N)	Safety (Y/N)	Topline (Y/N)	Final Analysis (Y/N)	Clinical Trial.gov (Y/N)
15.3.5.1	Listing of Lifestyle Assessment				Y	
15.3.5.2	Listing of Cough-VAS questionnaire				Y	

Figures

Figure No.	Title	Interim Analysis (Y/N)	Safety (Y/N)	Topline (Y/N)	Final Analysis (Y/N)	Clinical Trial.gov (Y/N)
15.1.2.1.*	Clinical Risk Endpoints Associated with Cardiovascular Disease Mean and 95% CI – Abstinence12m Set			Y	Y	Y
15.1.2.2.*	Clinical Risk Endpoints Associated with Respiratory Disease Mean and 95% CI – Abstinence12m Set			Y	Y	Y
15.1.2.3.*	Clinical Risk Endpoints Associated with Respiratory Disease assessed at the [redacted] Mean and 95% CI – Abstinence12m Set				Y	
15.1.2.4.*	Clinical Risk Endpoints Associated with Xenobiotics and Genotoxicity Mean and 95% CI – Abstinence12m			Y	Y	Y
15.1.3.1.*	Biomarkers of Exposure to HPHC Mean and 95% CI – Abstinence12m Set				Y	
15.1.3.2.*	Nicotine Exposure Mean and 95% CI – Abstinence12m Set				Y	
15.1.4.2.1	Rate of Continuous Smoking Abstinence over Time – Quitters Population				Y	
15.1.4.2.2	Rate of Continuous Smoking Abstinence over Time by Region and Overall – Quitters Population				Y	