CLINICAL STUDY PROTOCOL

	Document Number:	**c02362157-07**
EudraCT No.:	n/a	
BI Study No.:	352.2069	
BI Investigational Product(s):	n/a	
Title:	Observational study in healthy subjects and patients with COPD to assess the relationship between clinical, imaging and biomarker measurements, and progression of emphysema over three years [FOOTPRINTS®].	
Brief Title:	Emphysema Progression Biomarker Study	
Clinical Phase:	n/a	
Trial Clinical Monitor:	[redacted] Phone: +[redacted] Fax: +[redacted]	
Project Advisor:	[redacted]	
Status:	Final Protocol (Revised Protocol (based on Global Amendment 5))	
Version and Date:	**Version: 6.0**	**Date: 24 Feb 2020**

CLINICAL STUDY PROTOCOL SYNOPSIS

Name of company:		**Boehringer Ingelheim**	
Name of finished product: n/a			
Name of active ingredient: n/a			
Protocol date: 02 Sep 2015	**Study number:** 352.2069		**Revision date:** 24 Feb 2020

Title of study:	Observational study in healthy subjects and patients with COPD to assess the relationship between clinical, imaging and biomarker measurements, and progression of emphysema over three years [FOOTPRINTS®].
Coordinating Investigator:	n/a
Study site(s):	Multi-center, multi-national study, ~ 12 participating countries, ~ 50 sites.
Clinical phase:	n/a
Objective(s):	The overall objective of this study is to explore, if any of the biomarkers (soluble, functional imaging and physiological) assessed within healthy subjects, patients with COPD and patients with COPD and A1ATdeficiency are correlated to COPD disease progression, particularly emphysema progression over 156 weeks.
Methodology:	Prospective, longitudinal study.
No. of subjects:	
total entered:	Up to 455 subjects entered including: • 60 Healthy subjects without airflow limitation • 125 patients with COPD GOLD 1 • 125 patients with COPD GOLD 2 • 125 patients with COPD GOLD 3 • Up to 20 patients with COPD and A1AT deficiency (ZZ genotype)
Diagnosis:	• Healthy Subjects • COPD GOLD grade 1, 2, 3 • COPD and A1AT deficiency (ZZ genotype)

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Main criteria for inclusion:	• COPD and healthy subjects of both sex aged ≥ 40 and ≤ 70 years • COPD with A1ATD of both sex aged ≥ 30 and ≤ 70 years • COPD and healthy ex-smokers with a smoking history ≥ 20 pack years • COPD with A1ATD ex-smokers with a smoking history ≥ 10 pack years • Body mass index (BMI) of ≥ 18 and ≤ 35 kg/m^2 (≤ 30 kg/m^2 in the MRI substudy)
Duration of observation:	156 weeks (~ 3 years)
Assessments:	**Clinical assessments:** • Spirometry • Body plethysmography • Pulse oximetry • Diffusing capacity of the lung for carbon monoxide • Questionnaires**:** mMRC, CAT, SGRQ • BODE index • 6 minute walk test (6 MWT) • Medical Events of Special Interest (MESI) • Adverse Events **Biofluids:** • Blood • Induced Sputum (at selected sites) **Imaging assessments:** • Chest CT (inspiratory/expiratory) • Magnetic Resonance Imaging (MRI) (in a subset of healthy subjects and patients with COPD without A1ATD)
Biobanking:	Unspecified biomarker testing in blood in all subjects and sputum in a subset of subjects
Safety criteria:	Vital signs, physical examination, safety laboratory, urine pregnancy testing, 12-lead electrocardiogram (ECG) and adverse event reporting
Statistical methods:	Descriptive statistics, Pearson and rank-based correlation, multivariate statistical prediction model

FLOWCHART

Study Periods		**Screening Period**	**Observational Period**								
Visit		**1**	**2**	**3**	**4**	☎	**5**	☎	☎	☎	**6**
Weeks				**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**
Days	**Prior to any study related procedure**	**-28 to -1**	**1**	**84**	**182**	**273**	**364**	**455**	**546**	**637**	**728**
Time window for visits			see[17]	± 7d	± 14d	± 14d	± 14d	± 14d	± 14d	± 14d	± 14d
Informed consent[1]	X										
Demographics		X									
Medical history		X									
Physical examination, BMI[10]		X					X				X
Vital signs		X					X				X
Review of in-/exclusion criteria		X	X[12]								
MESI Check		X	X	X	X	X	X	X	X	X	X
Smoking Status/Cotinine Test[18]		X	X	X	X		X				X
Restrictions Check[8]		X	X		X		X				X
Urine pregnancy test[2]		X	X		X		X				X
Safety laboratory[3,5]		X	X	X	X		X				X
A1ATD testing[14]		X									
12 lead-ECG		X					X				X
BODE index[15]			X								X
mMRC[4]		X	X				X				X
CAT[4]			X				X				X
SGRQ[4]			X				X				X
Pulse oximetry		X	X		X		X				X
Spirometry (PFT)[19]		X	X	see[21]	X		X				X
Lung diffusion capacity[20]		X	X		X		X				X
Body plethysmography[20]			X		X		X				X
Chest CT			X				X				X
MRI (in a substudy only)[7]			X		X		X				X
Induced sputum[16]			X	X	X		X				X
6 minute walk test (6 MWT)		X[11]	X								X
BM blood collection[5]			X	X	X		X				X
DNA banking (optional)[9]			X								
Re-/Dispense and review subject reminder diary[13]		X	X	X	X	X[22]	X	X[22]	X[22]	X[22]	X
Adverse events		X	X	X	X	X	X	X	X	X	X
Concomitant therapy		X	X	X	X	X	X	X	X	X	X
IRT subject visit registration		X	X	X	X	X	X	X	X	X	X
Completion of subject participation											
Vital status and COPD exacerbation status collection[6]							X				X

FLOWCHART (continued)

Study Periods	Observational Period			
Visit	☎	☎	☎	**7**
Weeks	**117**	**130**	**143**	**156**
Days	**819**	**910**	**1001**	**1092**
Time window for visits	± 14d	± 14d	± 14d	± 14d
Informed consent[1]				
Demographics				
Medical history				
Physical examination, BMI[10]				X
Vital signs				X
Review of in-/exclusion criteria				
MESI Check	X	X	X	X
Smoking Status/Cotinine Test[18]				X
Restrictions Check[8]				X
Urine pregnancy test[2]				X
Safety laboratory[3,5]				X
A1ATD testing[14]				
12 lead-ECG				X
BODE index[15]				X
mMRC[4]				X
CAT[4]				X
SGRQ[4]				X
Pulse oximetry				X
Spirometry (PFT)[19]				X
Lung diffusion capacity[20]				X
Body plethysmography[20]				X
Chest CT				X
MRI (in a substudy only)[7]				X
Induced sputum[16]				X
6 minute walk test (6 MWT)				X
BM blood collection[5]				X
DNA banking (optional)[9]				
Re-/Dispense and review subject reminder diary[13]	X[22]	X[22]	X[22]	X
Adverse events	X	X	X	X
Concomitant therapy	X	X	X	X
IRT subject visit registration	X	X	X	X
Completion of subject participation				X
Vital status and COPD exacerbation status collection[6]				X

1 All subjects must sign an informed consent consistent with ICH-GCP guidelines prior to participation in the study, which includes the application of medication short-term restrictions prior to lung function testing. Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions

2 Urine pregnancy testing in women of childbearing potential only (to be assessed prior to blood collection and imaging assessments)

3 A full panel of hematology, blood chemistry, and coagulation parameters will be done at visits 1, 2, 5, 6 and 7. The reduced panel comprises hematology, [redacted], and creatinine at visits 3 and 4. Refer to Section 5.9.3

4 mMRC, followed by CAT and SGRQ in patients with COPD/COPD and A1AT deficiency only will be self-administered at the beginning of the visit and should precede any discussion with a health professional

5 Fasted safety and biomarker blood sampling. Dedicated serum and plasma samples for biobanking will be collected in additional tubes

6 Phone Call: for all subjects who prematurely discontinue during observational phase. Please refer to Section 6.2.2

7 Prior to each MRI assessment, subject must meet criteria described in Section 5.3

8 Restrictions must be checked at first at the clinic visit. Please refer to Section 4.2.2 and 6.1.1.1

9 Blood draw can be done at Visit 2 or any later visit. Refer to Section 5.8.4

10 BMI will be calculated automatically on the eCRF. Refer to Appendix 10.4.3

11 The 6 MWT at Visit 1 will be performed to train the subjects for the procedure

12 Criteria, which apply at visit 2 only, not subsequent visits

13 Refer to Section 3.1.1

14 Genetic test on A1AT deficiency performed on all subjects

15 Done in patient with COPD/COPD and A1ATD only

16 Induced Sputum will be collected in all subjects at selected sites only

17 Refer to Section 6.1

18 A positive cotinine test is not exclusionary during screening and observational phase but should be explained and documented by the investigator

19 Spirometry will be done pre and post Salbutamol (Albuterol) administration at visits indicated in the flowchart

20 Lung diffusion capacity and bodyplethysmography will be done post Salbutamol (Albuterol) administration only at visits indicated in the flowchart

21 FEV_1 measurement to assess safety criteria for the sputum induction procedure can be done on the centrally provided spirometer or on a local device

22 At the phone call visits subject reminder diary is reviewed

TABLE OF CONTENTS

ABBREVIATIONS

A1AT	Alpha-1 Antitrypsin
A1PI	Alpha-1 Proteinase Inhibitor
AE	Adverse Event
ANOVA	Analysis of Variance
AP/ALP	Alkaline Phosphatase
aPTT	Activated Partial Thromboplastin Time
ATS	American Thoracic Society
AUC	Area under the curve
BI	Boehringer Ingelheim
b.i.d.	bis in die (twice daily dosing)
BM	Biomarker
BMI	Body Mass Index
BP	Blood Pressure
CAT	COPD Assessment Test Questionnaire
[redacted]	[redacted]
CART	Classification and Regression Tree
CI	Confidence Interval
CK	Creatine Kinase
CML	Local Clinical Monitor
COPD	Chronic Obstructive Pulmonary Disease
CRA	Clinical Research Associate
CT	Computed Tomography
CSP	Clinical Study Protocol
CSR	Clinical Study Report
[redacted]	[redacted]
DNA	Deoxyribonucleic Acid
eCRF	Electronic Case Report Form
ECG	Electrocardiography/Electrocardiogram
ERS	European Respiratory Society
ERV	Expiratory Reserve Volume
EudraCT	European Clinical Trials Database
FEV_1	Forced Expiratory Volume in 1st second
FRC	Functional Residual Capacity
GCP	Good Clinical Practice
GGT/γ-GT	Gamma-Glutamyl Transferase
GLI	Global Lung Function Initiative
GOLD	Global Initiative for Chronic Obstructive Lung Disease
Hb	Hemoglobin
Hct	Hematocrit
[redacted]	[redacted]
IC	Inspiratory Capacity
ICH	International Conference on Harmonisation
[redacted]	[redacted]
IEC	Independent Ethics Committee

[redacted]	[redacted]
i.m.	intramuscular
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
i.v.	intravenous
IVC	Inspiratory Vital Capacity
JRS	Japanese Respiratory Society
LDH	Lactic Dehydrogenase
MCV	Mean Corpuscular Volume
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Cellular Hemoglobin Concentration
MedDRA	Medical Dictionary for Drug Regulatory Activities
MESI	Medical Events of Special Interest
mL	Milliliter
MMPs	Matrixmetalloproteinases
mMRC	Modified Medical research Council Dyspnea Scale
MRI	Magnet Resonance Imaging
mSv	milliSievert
µM	Micrometer
NE	Neutrophil Elastase
NSP	Neutrophil-derived Serine Protease
OPU	Operative Unit
PDE-4	Phosphodiesterase 4
PFT	Pulmonary Function Test
p.o.	per os (oral)
PR	Pulse Rate
PRO	Patient Reported Outcome
[redacted]	[redacted]
q.d.	quaque die (once a day)
RNA	Ribonucleic acid
ROC	Receiver Operating Characteristics
RV	Residual Volume
SAE	Serious Adverse Event
SC	Steering Committee
s.c.	subcutaneous
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamate-pyruvate transaminase
SGRQ	St George's Respiratory Questionnaire
SOP	Standard Operating Procedure
[redacted]	[redacted]
Sv	Sievert
TCM	Trial Clinical Monitor
t.i.d.	ter in die (3 times a day)
TMF	Trial Master File
TLC	Total Lung Capacity

TSAP	Trial Statistical Analysis Plan
[redacted]	[redacted]
6 MWT	6 Minute Walk Test

1. INTRODUCTION

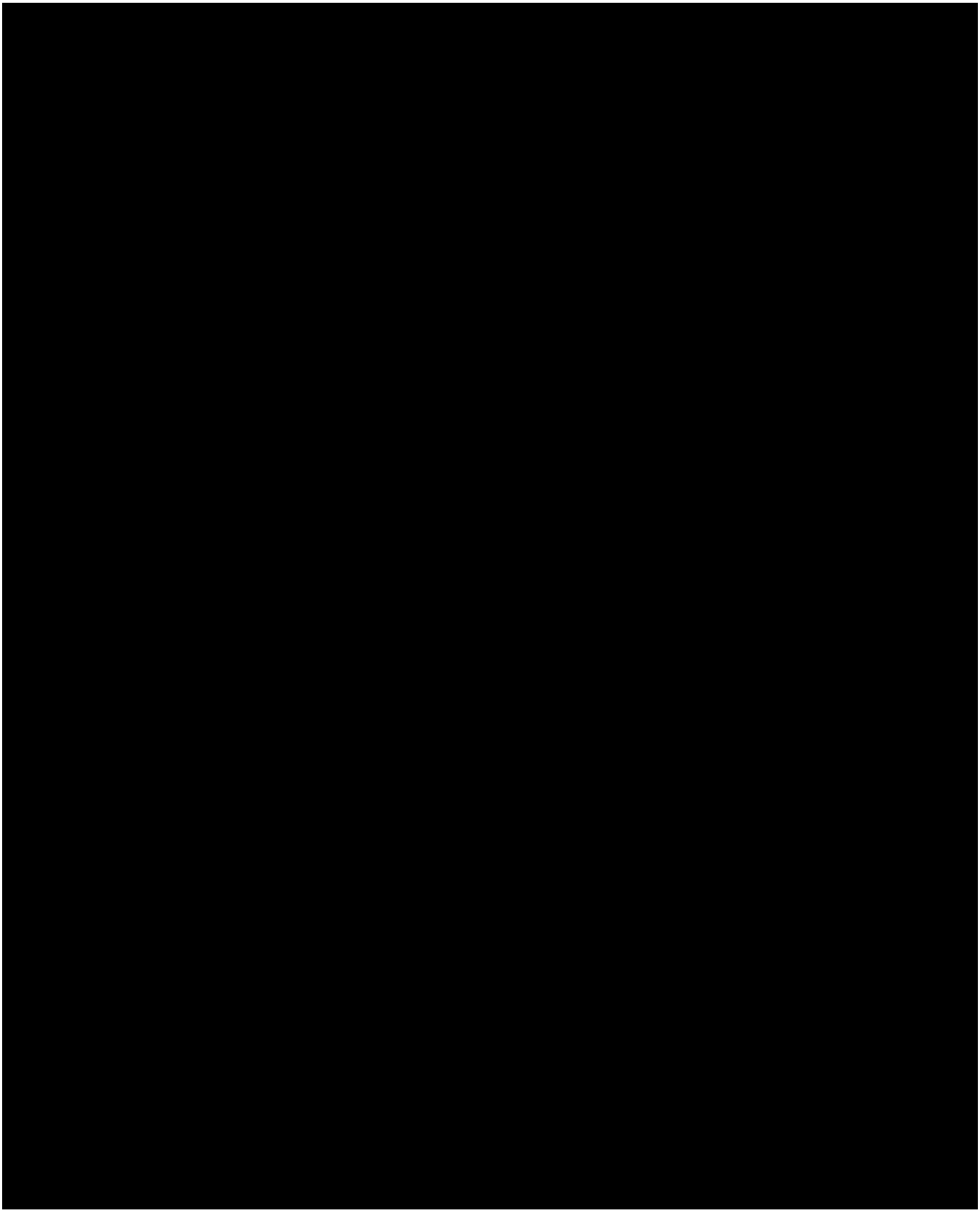
1.1 MEDICAL BACKGROUND

The chronic airflow limitation characteristic of COPD is caused by a mixture of small airways disease (obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which vary from patient to patient [P15-01740]. Estimates for emphysema in patients with COPD vary up to 60%.

There is no treatment for disease progression in COPD, and current treatment options, apart from smoking cessation do not prevent decline of FEV_1 (forced expiratory volume in 1 second) over time, nor inhibit the lung structural damages. COPD is a heterogeneous disease with at least 2 clinical well recognized phenotypes (bronchitic and emphysematous). Both can be present alone or in combination, with varying degrees of severity.

The bronchitis phenotype is defined according to historic clinical criteria, i.e. the presence of cough and sputum on most days over 3 months in 2 consecutive years. Emphysema definition is based on pathological changes identified by radiological/functional outcomes, or ultimately on pathology. Clinical data suggests that the rate of decline of FEV_1 varies across individual patients with COPD regardless of their initial GOLD (Global Initiative for Chronic Obstructive Lung Disease) FEV_1 grade category, with a faster rate of decline observed in the emphysematous phenotype, but also in current smokers, and following COPD exacerbations. The only COPD genotype identified so far is alpha1-antitrypsin deficiency. Severe deficiency of alpha1-antitrypsin is associated with a strong tendency for development of emphysema, often, but not always, panlobular in character and basal in distribution. This emphysema is thought to be the result of inadequate neutralisation of naturally occurring proteases, such as neutrophil elastase, by alpha1 proteinase inhibitor (A1PI), which normally serves as a protease inhibitor [R15-4639]. It is synthesized predominantly in the liver and functions as a serine proteinase inhibitor or serpin and provides essential protection to lung tissue against the actions of proteolytic enzymes such as neutrophil elastase (NE) and proteinase 3 (PR3). The most common deficient phenotype is PiZ, which encompasses both PiZZ and PiZ null genotypes. The majority of individuals with ‘severe pathophysiological deficiency’, classified by a serum A1AT level below the putative protective threshold (11 µM), have the PiZZ genotype [R15-4638].

[redacted]



[redacted]

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE STUDY

Pharmacological treatment of COPD is currently based on bronchodilators and anti-inflammatory drugs. Approved medicines may relieve symptoms, reduce exacerbations and/or improve health status and exercise tolerance, but there is no treatment for disease progression in COPD, and systematic treatment options, apart from smoking cessation, do not prevent rate of decline of FEV_1 over time, nor inhibit the lung structural damages.

More in depth understanding of COPD patient phenotypes and the course and drivers of COPD disease progression is required to address this unmet medical need and enable drug development aiming at a reduction of COPD disease progression.
Biomarkers may assist, beside clinical parameters, in characterizing patients and potentially in predicting and monitoring their disease course.

[redacted] increase the understanding of the underlying pathophysiology of emphysema progression.

BI plans to conduct this longitudinal emphysema progression biomarker study to identify biomarkers (soluble, functional imaging and physiological) that may be useful in differentiating a patient population with ongoing emphysematous destruction of lung parenchyma, which may enable development of drugs aiming at the reduction of COPD progression.

Rationale for the study extension to 3 years

It has become known from consortia data ( ) that lung density decline, as assessed by CT and lung function decline, do not correlate across GOLD stages [R18-1744]. Therefore, besides characterizing emphysema progression in patients it will be important to also assess lung function decline by spirometry since this describes an additional high risk COPD patient subgroup with a large unmet medical need. Since detection of lung function decline is expected to take longer (3 years) than detection of lung density decline, the study is being extended to a 3 year observation time.

This study will include 60 healthy subjects (ex-smokers without airflow limitation), 125 COPD GOLD 1, 125 COPD GOLD 2, 125 COPD GOLD 3, and up to 20 patients with COPD and A1AT deficiency (ZZ genotype). Soluble and imaging biomarkers will be investigated addressing different aspects of disease pathways postulated to be relevant for COPD

2.2

2.3 BENEFIT - RISK ASSESSMENT

This study is an observational study with no alteration in patient's usual medication treatment. There will be no direct benefit for the participating subjects except the benefit which derives from the periodic monitoring of their health or disease status by the investigator and site staff. All subjects are allowed to continue their usual care.
The subject`s participation in the study requires standard medical procedures known to patients with respiratory diseases. The examinations include common procedures like

physical examination, cotinine test to determine smoking status, 12-lead ECG, spirometry, body plethysmography, and D_{LCO}. Induction of sputum could result in bronchoconstriction and is performed after bronchodilation, but is usually quickly reversible with short acting ß-2-agonist treatment [R12-5301].

Other procedures include common medical practices such as disease-specific questionnaires, routine blood sampling for safety assessment, and biomarker collection. All these procedures are known to have an acceptable safety risk and may also be performed in healthy volunteers. A total blood volume of approximately 500 mL will be drawn over a period of about 3 years. Approximately 12 ml will be drawn at the screening visit and approximately 80 to 90 mL per biomarker sampling time point (Visit 2 – 7). This is much less than the volume of a normal blood donation (400 mL). No safety-related risk to the patients is expected from this blood withdrawal.

Monitoring for pregnancy will occur at the screening visit and prior to imaging procedures (CT and MRI) at Visits 2, 4, 5, 6, and 7 in order to avoid further risk. Pregnant women will be discontinued from further study participation, but should be followed up for vital status and COPD exacerbation status collection.

Imaging examinations are important components of this study. Chest CT plays a pivotal role to analyze pathologies of pulmonary emphysema not only in its morphological aspect but also in the assessment of severity. CT will also contribute to the phenotyping of COPD, such as primarily parenchymal disease or primarily airway disease [R15-4823].
[redacted] The annual exposure from natural background radiation is 2 – 3 mSv. The radiation dose applied per chest CT scan is approximately 5 times lower than the maximum effective annual dose limit of 20 mSv for people occupationally exposed (radiation workers) in Germany and about 12 times lower than the annual dose limit of 50 mSv for radiation workers in the US. The level of exposure of the chest CT scans is associated with a low additional lifetime risk of cancer (0.02 %), based on the assumption of the International Commission on Radiological Protection (ICRP) of 2007 [R15-3219] estimating an excess life-time cancer mortality risk of about 5% per Sv. Subjects with an increased risk of lung cancer (e.g. ex-smokers and smokers) may benefit from the CT assessment [R12-3778], considering the sensitivity of chest CT for lung cancer, critical for treatment success.
Chest CT scans will be performed in 40 to 70 years old subjects (30 to 70 years in patients with COPD and A1ATD) to accurately assess lung disease including emphysema, air trapping, small airway disease, and airway wall thickness.
Magnet Resonance Imaging (MRI) will be conducted in a subset of subjects (substudy). MRI uses strong magnetic fields and radio waves to generate cross-sectional images of the body. In this study, MRI will be used to acquire morphological and functional information of the lungs and the heart. In contrast to CT, MRI does not use ionizing radiation (X-rays) and there are no known harmful effects associated with temporary exposure to the strong magnetic field of MRI scanners in patients without foreign bodies. Potential safety concerns are related to implanted medical devices, which can malfunction or heat up during the exams. Dyes from tattoos and tattooed eyeliners can cause skin or eye irritation, and medication patches can cause skin burn due to heating effects. Some subjects might suffer from claustrophobia

during the examination. Subjects in the MRI scanner will be exposed to some noise, which will be minimized by ear protection but can still cause some discomfort. The use of contrast agent during the examinations is accompanied with a slight risk of an allergic reaction. However, the risk of a significant allergic reaction is 1:150,000 examinations. Additionally, MRI contrast agents can cause problems in patients with significant kidney disease. To minimize the risk, kidney function will be measured before the MRI scans. Only male and non-pregnant female subjects (without implanted devices susceptible to magnetic influence) who present with stable clinical conditions and tolerate repeated MRI scanning will be considered for inclusion into the study.

3. DESCRIPTION OF DESIGN AND STUDY POPULATION

3.1 OVERALL STUDY DESIGN AND PLAN

This is a prospective longitudinal biomarker study in healthy subjects, patients with COPD and patients with COPD and A1ATD to phenotype COPD patients; the study investigates biomarkers potentially associated with emphysema. The study does not include administration of any investigational medicinal product.

This is a multi-national, multi-center study and involves approximately 12 participating countries with approximately 50 sites. It consists of 2 consecutive periods including a screening and an observational period.

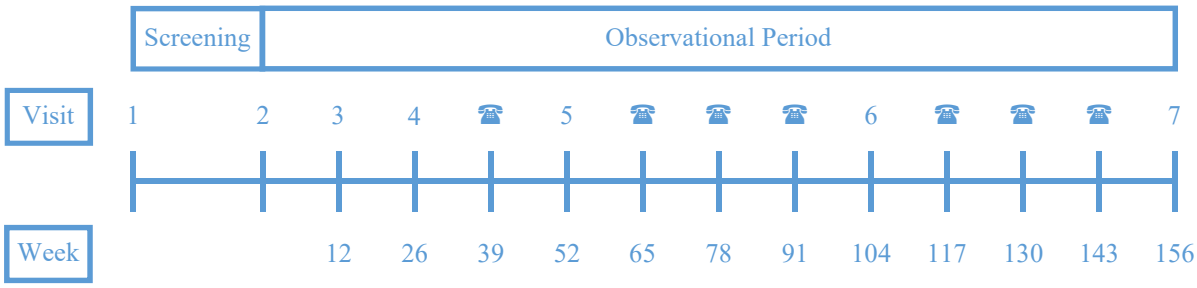


Figure 3.1: 1 Overview of Study Design

After informed consent all subjects will enter the screening period (Visit 1) to confirm eligibility. All subjects who meet all inclusion criteria and do not present any of the exclusion criteria will enter the observational period of the study at Visit 2. Based on inclusion and exclusion criteria, subjects will be assigned to the following groups:

- Healthy subjects
- Patients with COPD grade 1
- Patients with COPD grade 2
- Patients with COPD grade 3
- Patients with COPD and A1AT deficiency

The observational period lasts 3 years and includes 7 site visits and additional phone contacts to assess subjects' status, ask for potential Medical Events of Special Interest (MESI) (including COPD exacerbations) and Adverse Events, and for changes in concomitant medication.

The observational period will be completed at Visit 7 or at the discontinuation visit, which is regarded as study completion.

All subjects who prematurely discontinue during the observational phase will be followed for vital status and COPD exacerbation status (the second for patients with COPD and patients with COPD and A1AT deficiency only) via phone calls until their hypothetical Visit 7 date (i.e. 156 weeks after Visit 2). Please refer to Section 3.3.5.1 and Section 6.2.2.

MRI will be performed in a subset of healthy subjects and patients with COPD (excluding patients with COPD and A1AT deficiency) only (substudy).

Sputum induction and processing will be performed in all subjects at selected sites only.

For a description of reporting of adverse events, see Section 5.9.6.2.

All study relevant documentation will be stored by Boehringer Ingelheim in the trial master file (TMF). Study relevant documentation for the study site(s) will be filed in the Investigator Site File (ISF) at the investigational site(s).

3.1.1 Administrative structure of the study

The sponsor of this study is Boehringer Ingelheim. The study will be conducted at clinical research center(s) specialized for pulmonary diseases, and experienced in the management of patients with COPD, A1ATD as well as in the recruitment of healthy volunteers.

A central laboratory facility will handle all standard safety blood laboratory analyses of the study.

Spirometric lung function assessment will be performed by an external vendor's equipment in order to allow centralized reading.

ECG, imaging assessments, body plethysmography, pulse oximetry, 6 MWT, D_{LCO} and induction of sputum (at selected sites only) will be performed with the site´s own equipment according to international accepted guidelines (where applicable). Please refer to Section 5.2 et seqq. and the ISF.

All samples collected for pre-specified biomarker assessments and biobanking will be prepared by the site according to instructions given in the ISF and frozen until shipment to the central CRO as indicated in the ISF. The biomarkers will be analyzed by the sponsor or contractors of the sponsor. Details are given in Section 5.8.

Recruitment: screening of subjects for this study is competitive, i.e. screening for the study will stop at all sites, when it is anticipated that a sufficient number of subjects have been screened to meet the planned number of study participants of up to 455 subjects. Investigators will be notified when the appropriate number of subjects has been screened and screening is complete, and will not be allowed to recruit additional subjects for this study.
Regarding the planned number of subjects per group (health volunteers, COPD grade 1, 2, 3, patients with COPD and A1ATD) the same strategy will be applied to ensure a balanced and sufficient number of subjects per stratum. In other words, once a group of subjects is complete, the investigators will be notified in a timely manner to stop recruiting new subjects

to this specific cohort. Overall recruitment might be terminated independently of the number of enrolled A1ATD patients.

IRT: an Interactive Response Technology (IRT) system will be used in this study to keep track of subject enrollment. Sites are requested to register subject visits (clinic visits and phone calls) via IRT.

Subject reminder diary: all subjects will be provided with a paper diary to serve as a reminder to support the collection of Medical Events of Special Interest (MESI), adverse events and concomitant therapy at clinic and telephone visits. The subject reminder diary will be used to note new medical events, changes in symptoms, and medication usage between visits and serves as a reminder for the subjects. The subject reminder diaries will not be collected by the site and remains the exclusive property of the subject.

In case of discontinuation from the observational phase, subjects are encouraged to continue utilization of their reminder diaries in order to be able to answer questions on their COPD exacerbation status (only patients with COPD and patients with COPD and A1AT deficiency).

Boehringer Ingelheim has appointed a Trial Clinical Monitor, responsible for coordinating all required activities, in order to

- manage the study in accordance with applicable regulations and internal SOPs
- direct the clinical study team in the preparation, conduct, and reporting of the study
- order the materials as needed for the study
- ensure appropriate training and information of local clinical monitors (CML), Clinical Research Associates (CRAs), and Investigators of participating countries

Data Management and Statistical Evaluation will be conducted by BI or contractors of the sponsor.

A joint Steering Committee (SC) consisting of experts independent of the Sponsor and internal BI experts will be established. The composition of the SC will be documented in the Trial Master File (TMF). The tasks and responsibilities will be agreed in contracts between the SC members and the Sponsor and also summarized in an SC-charter filed in the TMF.

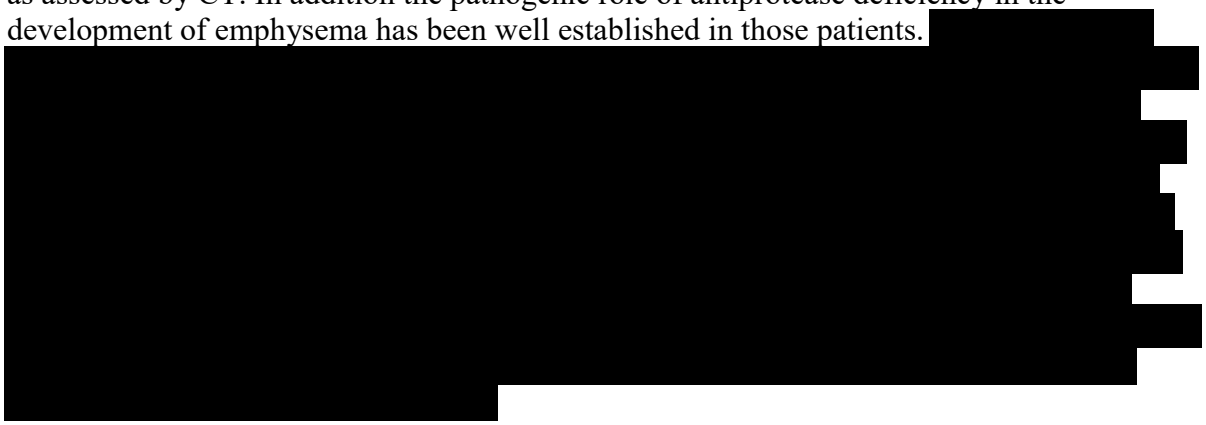
3.2 DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

This biomarker study is planned to longitudinally assess biomarkers in different biofluids (whole blood, serum, plasma, induced sputum) and clinical parameters over a 3 year time period in 60 healthy subjects, 375 patients with COPD and up to 20 patients with A1ATD associated COPD in order to establish surrogate markers for emphysema progression.

[redacted]

The observational period of 156 weeks has been chosen to allow longitudinal assessment of emphysema progression by CT density over time. Inclusion of healthy subjects is needed to

provide a comparison for these biomarkers with subjects without airflow limitation. Patients with COPD and A1AT deficiency have been chosen, since they present with an earlier onset of emphysema and a faster decline in lung function as well as a faster change in lung density as assessed by CT. In addition the pathogenic role of antiprotease deficiency in the development of emphysema has been well established in those patients.



3.3 SELECTION OF STUDY POPULATION

It is planned to enroll 60 healthy subjects, 125 patients with COPD of mild, 125 patients of moderate, 125 patients of severe disease stage and up to 20 patients with COPD and A1AT deficiency in approximately 50 sites.

A log of all subjects enrolled into the study (i.e. who have signed informed consent) will be maintained in the ISF at the investigational site irrespective of whether they have entered the observational period or not.

3.3.1 Main diagnosis for study entry

Population of healthy subjects, patients with COPD (GOLD grade 1 to 3) and patients with A1ATD according to the respective inclusion and exclusion criteria will be included into the study.

3.3.2 Healthy subjects

3.3.2.1 Inclusion criteria

1. All subjects must sign an informed consent consistent with ICH-GCP guidelines prior to participation in the study, which also includes the application of study restrictions.
2. Males and females must be healthy at the discretion of the investigator according to the following criteria: Based upon a complete medical history, including the physical examination, vital signs (BP, PR), 12-lead ECG, clinical laboratory tests.
3. Subjects must be ex-smokers for at least 9 months with a smoking history of ≥ 20 pack years (see appendix 10.4, calculation of number of pack years).
4. Subjects must be between the ages of ≥ 40 and ≤ 70 years.
5. Subject must have a body mass index (BMI) of ≥ 18 and ≤ 35 kg/m^2 (≤ 30 kg/m^2 in the MRI subset).

6. Subjects must have normal lung function values at Visit 1 with a documented post-bronchodilator $FEV_1 \geq 80\%$ of predicted normal (GLI 2012 [R15-0845] and JRS 2014 [R15-2073]; and a post-bronchodilator $FEV_1/FVC \geq$ lower limit of normal (GLI 2012 [R15-0845] and JRS 2014 [R15-2073] documentation).
7. Subjects must have a mean post D_{LCO} over all acceptable measurements at Visit 1 of ≥ 70 % of predicted normal (see Section 5.6).
8. Subjects must be able to perform all study related procedures including technically acceptable pulmonary function tests, body plethysmography, D_{LCO}, sputum induction (if applicable), chest CT, and MRI (if applicable).
9. Subjects must be on stable therapy (not limited to respiratory medication) for the last 4 weeks prior to Visit 1.

3.3.2.2 Exclusion criteria

1. Previous participation in this study or participation in another trial with an investigational drug within 6 weeks prior to Visit 1 or during the study.
2. Respiratory tract infection in the 4 weeks prior to Visit 1 or during the screening period prior to Visit 2, if rescheduling rules of Section 6.1.1.4 cannot be met.
3. Significant pulmonary disease or other significant medical conditions* (as determined by medical history, examination and clinical investigations at screening) that may, in the opinion of the investigator result in any of the following:
    a. Put the subject at risk because of participation in the study
    b. Cause concern regarding the subject's ability to participate in the study

    * e. g. rheumatoid arthritis, inflammatory bowel disease, severe liver disease, psoriasis, hematological, infectious and psychiatric diseases.
4. Documented history of asthma. For subjects with allergic rhinitis or atopy, source documentation is required to verify that the subject does not have asthma.
5. Planned surgery during the study expected to interfere with study procedures and outcome.
6. Blood withdrawal of more than 100 mL within the past six weeks prior to Visit 1 and between Visit 1 and 2.
7. Significant alcohol or drug abuse in the opinion of the investigator within past 2 years prior to Visit 1.
8. Women who are pregnant, nursing, or who plan to become pregnant while in the study.
9. Place of permanent residence of less than 3 month prior to Visit 1.
10. For the MRI subset: subjects who do not meet the following criteria for the MRI assessment at Visit 2: systolic blood pressure between 90 and 180 mmHg (SBP), diastolic blood pressure between 50 and 110 mmHg (DBP), pulse rate between 40 and

110 bpm, ear temperature between 35 - 37.5°C, and a glomerular filtration rate (GFR) ≥ 30 mL/min (GFR must not be older than 14 days from the MRI assessment).

11. Subjects who are heterozygous or homozygous for the A1AT Z or S allele.
12. Subjects presenting with an immunocompromising condition (e. g. patient is positive for Human Immunodeficiency Virus (HIV) or has a history of Hepatitis B or C).

3.3.3 Patients with COPD

3.3.3.1 Inclusion criteria

1. All patients must sign an informed consent consistent with ICH-GCP guidelines prior to participation in the study, which also includes the application of study restrictions.
2. Patients must be male or female outpatient.
3. Patients must be between the ages of ≥ 40 and ≤ 70 years.
4. Patients must have a body mass index (BMI) of ≥ 18 and ≤ 35 kg/m^2 (≤ 30 kg/m^2 in the MRI subset).
5. Patients must have a current diagnosis of COPD made by a physician prior to or during Visit 1 and an mMRC [R00-0206] score of 1 or more. The diagnosis of COPD must be in accordance with the GOLD Guidelines [P15-01740] and must be documented by the following criteria:

   Known relatively stable airway obstruction with a post-bronchodilator FEV_1/FVC < 70 %.
6. The current COPD must be mild, moderate or severe based on lung function and symptoms and the clinical situation must have been stabilized for at least 4 weeks prior to Visit 1. The following definitions adapted from the GOLD Guidelines [P15-01740] apply:
   a. Mild: post-bronchodilator FEV_1 ≥ 80% of predicted normal (GLI 2012 [R15-0845] and JRS 2014 [R15-2073] at Visit 1.
   b. Moderate: 50% ≤ post-bronchodilator FEV_1 < 80% of predicted normal (GLI 2012 [R15-0845] and JRS 2014 [R15-2073] without chronic respiratory failure at Visit 1.
   c. Severe: 30% ≤ post-bronchodilator FEV_1 < 50% of predicted normal (GLI 2012 [R15-0845] and JRS 2014 [R15-2073] without chronic respiratory failure at Visit 1.
7. Patients must be ex-smokers for at least 9 months with a smoking history of ≥ 20 pack years (see appendix 10.4, calculation of number of pack years).
8. Patients must be able to perform all study related procedures including technically acceptable pulmonary function tests, body plethysmography, D_{LCO}, sputum induction (if applicable), chest CT, and MRI (if applicable).
9. Patients must be on stable therapy (not limited to respiratory medication) for the last 4 weeks prior to Visit 1.

3.3.3.2 Exclusion criteria

1. Significant pulmonary disease other than COPD or other significant medical conditions* (as determined by medical history, examination and clinical investigations at screening) that may, in the opinion of the investigator result in any of the following:
    a. Put the patient at risk because of participation in the study
    b. Cause concern regarding the patient's ability to participate in the study

    * e. g. rheumatoid arthritis, inflammatory bowel disease, severe liver disease, psoriasis, hematological, infectious and psychiatric diseases.
2. Any respiratory tract infection or COPD exacerbation in the 4 weeks prior to Visit 1 or during the screening period prior to Visit 2, if rescheduling rules of Section 6.1.1.4 cannot be met.
3. A malignancy for which the patient has undergone resection, radiation or chemotherapy within past 5 years. Patients with treated basal cell carcinoma or fully cured squamous cell carcinoma are allowed.
4. Documented history of asthma. For patients with allergic rhinitis or atopy, source documentation is required to verify that the subject does not have asthma.
5. Hospitalization for respiratory failure during the year prior to Visit 1.
6. A history of cystic fibrosis.
7. Clinical diagnosis of bronchiectasis requiring specific treatment.
8. A clinically relevant abnormal baseline hematology, blood chemistry in the opinion of the investigator.
9. Planned surgery during the study expected to interfere with study procedures and outcome.
10. Blood withdrawal of more than 100 mL within the past six weeks prior to Visit 1 and between Visit 1 and 2.
11. Known active tuberculosis.
12. Previous participation in this study or participation in another trial with an investigational drug within 6 weeks prior to Visit 1 or during the study.
13. Significant alcohol or drug abuse in the opinion of the investigator within past 2 years prior to Visit 1.
14. Inability to comply with restrictions regarding medication, diet and life style (see Section 4.2.2).
15. Newly added anti-inflammatory treatment within 4 weeks prior to Visit 1.
16. Patients with change in any therapy within 4 weeks prior to Visit 1.
17. Patients on treatment with PDE-4 inhibitors (e.g. Roflumilast) and maintenance treatment with Methylxanthines (e.g. Theophylline). Refer to Table 4.2.2: 1

18. Women who are pregnant, nursing, or who plan to become pregnant while in the study.
19. Place of permanent residence of less than 3 month prior to Visit 1.
20. For the MRI subset: patients who do not meet the following criteria for the MRI assessment at Visit 2: systolic blood pressure between 90 and 180 mmHg (SBP), diastolic blood pressure between 50 and 110 mmHg (DBP), pulse rate between 40 and 110 bpm, ear temperature between 35 - 37.5°C, and a glomerular filtration rate (GFR) ≥ 30 mL/min (GFR must not be older than 14 days from the MRI assessment).
21. Patients who are heterozygous or homozygous for the A1AT Z or S allele
22. Patients presenting with an immunocompromising condition (e. g. patient is positive for Human Immunodeficiency Virus (HIV) or has a history of Hepatitis B or C).

3.3.4 Patients with COPD and A1AT deficiency

3.3.4.1 Inclusion criteria

1. All patients must sign an informed consent consistent with ICH-GCP guidelines prior to participation in the study, which also includes the application of study restrictions.
2. Patients must have a documented (prior to Visit 2) A1AT deficiency of ZZ genotype (see appendix 10.4.4).
3. Patients must be male or female outpatient.
4. Patients must be ex-smokers for at least 9 months with a smoking history of ≥ 10 pack years (see appendix 10.4, calculation of number of pack years).
5. Patients must have a current diagnosis of mild, moderate or severe COPD made by a physician prior to or during Visit 1 and an mMRC score of 1 or more. The diagnosis of COPD must be in accordance with the GOLD Guidelines [P15-01740] and must be documented by the following criteria:

   Known relatively stable airway obstruction with a post-bronchodilator FEV_1 of ≥ 30% of predicted normal and a post-bronchodilator $FEV_1/FVC < 70$ %.
6. Patients must be between the ages of ≥ 30 and ≤ 70 years.
7. Patients must have a body mass index (BMI) of ≥ 18 and ≤ 35 kg/m^2.
8. Patients must be able to perform all study related procedures including technically acceptable pulmonary function tests, body plethysmography, D_{LCO}, sputum induction (if applicable), and chest CT.
9. Patients must be on stable therapy (not limited to respiratory medication) for the last 4 weeks prior to Visit 1.

3.3.4.2 Exclusion criteria

1. Significant pulmonary disease other than COPD or other significant medical conditions* (as determined by medical history, examination and clinical investigations at screening) that may, in the opinion of the investigator result in any of the following:
   a. Put the patient at risk because of participation in the study
   b. Cause concern regarding the patient's ability to participate in the study.

   * e. g. rheumatoid arthritis, inflammatory bowel disease, severe liver disease, psoriasis, hematological, infectious and psychiatric diseases.
2. Any respiratory tract infection or COPD exacerbation in the 4 weeks prior to Visit 1 or during the screening period prior to Visit 2, if rescheduling rules of Section 6.1.1.4 cannot be met.
3. Documented history of asthma. For subjects with allergic rhinitis or atopy, source documentation is required to verify that the subject does not have asthma.
4. Current and planned A1AT augmentation therapy.
5. Newly added anti-inflammatory treatment within 4 weeks prior to Visit 1.
6. Patients on treatment with PDE-4 inhibitors (e.g. Roflumilast) and maintenance treatment with Methylxanthines (e.g. Theophylline). Refer to Table 4.2.2: 1
7. A malignancy for which the patient has undergone resection, radiation or chemotherapy within past 5 years. Patients with treated basal cell carcinoma or fully cured squamous cell carcinoma are allowed.
8. Hospitalization for respiratory failure during the year prior to Visit 1.
9. A history of cystic fibrosis.
10. Clinical diagnosis of bronchiectasis requiring specific treatment.
11. Clinically relevant abnormal baseline hematology, blood chemistry in the opinion of the investigator.
12. Planned surgery during the study expected to interfere with study procedures and outcome.
13. Blood withdrawal of more than 100 mL within the past six weeks prior to Visit 1 and between Visit 1 and 2.
14. Known active tuberculosis.
15. Previous participation in this study or participation in another trial with an investigational drug within 6 weeks prior to Visit 1 or during the study.
16. Significant alcohol or drug abuse in the opinion of the investigator within past 2 years prior to Visit 1.
17. Inability to comply with restrictions regarding medication, diet and life style (see Section 4.2.2).
18. Patients with change in any therapy within 4 weeks prior to Visit 1.

19. Women who are pregnant, nursing, or who plan to become pregnant while in the study.
20. Place of permanent residence of less than 3 month prior to Visit 1.
21. Patients presenting with an immunocompromising condition (e. g. patient is positive for Human Immunodeficiency Virus (HIV) or has a history of Hepatitis B or C).

3.3.5 Removal of subjects from the study

3.3.5.1 Removal of individual subjects

In general, no subject should be removed from the study for a protocol violation before discussion with the clinical monitor.

An individual subject is to be withdrawn from study if any of the following criteria apply:

- The subject withdraws consent for study participation, without the need to justify the decision.
- The subject is no longer able to participate for medical reasons (such as surgery, adverse events, and other diseases).
- The subject re-starts smoking at any time during the study (based on the investigators discretion). Refer to Section 4.2.2.2
- The subject becomes pregnant. Refer to Section 5.9.5
- A confirmed malignancy for which the patient is likely to undergo resection, radiation or chemotherapy.

Removal from the screening phase:

As long as a subject has not finished Visit 2, the subject is not considered to belong to the observational phase. Prior to Visit 2, reasons for withdrawal can be related to the criteria described above or to eligibility criteria (please refer to Section 3.3.2, 3.3.3, and 3.3.4). The data of subjects who withdraw prior to Visit 2 will be entered into the eCRF.

Removal from the observational phase:

Given the subject's agreement, the subject should come to the site for a discontinuation visit at the time of the next scheduled visit. The subject will undergo the procedures of this particular visit as outlined in the flowchart and Section 6.2.2. If not possible, the subject should be encouraged to at least undergo the procedures for safety assessments. Women who become pregnant should undergo the procedures for safety assessments only (safety assessments comprise procedures outlined in Section 5.9).
The withdrawn subject should be followed-up for vital status and COPD exacerbation status. Please refer to Section 6.2.2.

For all subjects the reason for withdrawal (e.g. adverse events) must be recorded in the eCRF. These data will be included in the study database and reported.

3.3.5.2 Discontinuation of the study by the sponsor

Boehringer Ingelheim reserves the right to discontinue the study overall or at a particular study site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular study site
2. Emergence of any safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the study
3. Violation of GCP, the CSP, or the contract disturbing the appropriate conduct of the study

The Investigator / the study site will be reimbursed for reasonable expenses incurred in case of study termination (except in case of the third reason).

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

No study medication is administered in the study. All subjects are allowed to continue and change (e.g. in case disease progression occurs) their standard of care medications during the observational phase of the study. In case a patient is placed on alpha1-antitrypsin augmentation therapy during the observational period of the study, the patient can continue the study.

4.2 CONCOMITANT MEDICATION, RESTRICTIONS, AND RESCUE MEDICATION

4.2.1 Rescue medication, emergency procedures, and additional medication(s)

Rescue medication

Administration of rescue medication can occur at any point during the study as deemed necessary by the subject or the investigator. If the subject requires rescue medication during the pulmonary function tests (PFT) and/or sputum induction (if applicable), visits will be continued if possible. The visit should not be re-scheduled.
All test-day rescue medication administered before the conclusion of all study-related procedures of this visit will be recorded in the source data and captured in the eCRF.
Rescue medication will not be provided by BI and should be made available by the investigational site.

Emergency procedure

In the case of adverse events on a visit day, the subjects will be treated and kept under supervision at the study site as necessary or transferred to hospital until such time that all the results of the evaluations have returned to a medically acceptable level.
There are no special emergency procedures to be followed.

Additional medications

Subjects will be requested to inhale salbutamol (albuterol) as part of their spirometry, sputum induction (if applicable) and imaging assessments at visits indicated in the flowchart.
If subjects participate in the MRI substudy, they will be requested to receive an injection of a Gadolinium-based contrast agent at visits indicated in the flowchart.

4.2.2 Restrictions

There is no medication restricted from being used during the observational phase of the study, except for those listed in table 4.2.2: 1. Patients who are on alpha1-antitrypsin augmentation therapy must not be enrolled into the study.
There are short-term restrictions prior to Visit 1 and 2 (see table 4.2.2: 1), which are needed for the stability of lung function values and other assessments. It is recommended to avoid, if possible, short acting bronchodilators in the 8 hours prior to the clinic visits. Administration of marketed salbutamol (albuterol) which is needed for study procedures (e.g. PFTs, sputum induction) should not exceed the total daily dose.
Treatment of adverse events is not restricted and within the responsibility of the investigator.

Table 4.2.2: 1 Overview of permitted, restricted, medications and therapies

Drug Class	Prior to Visit 1	Between Visits 1 and 2	Observational period
Corticosteroid - nasal/ocular	Permitted	Permitted	Permitted
Corticosteroid – oral, inhaled[1]	Permitted[3]	Permitted (stable dose)[5]	Permitted
Corticosteroid – i.v., i.m.	Permitted[3]	Not permitted[5]	Permitted
Short-acting β2-adrenergic agonist – Inhaled[2] (SABA)	Permitted[3]	Permitted (stable dose)[5]	Permitted
Long-acting β2-adrenergic agonist – Inhaled[2] (LABA)	Permitted[3]	Permitted (stable dose)[5]	Permitted
Short-acting anticholinergic – Inhaled (SAMA)	Permitted[3]	Permitted (stable dose)[5]	Permitted
Long-acting anticholinergic – Inhaled[2] (LAMA)	Permitted[3]	Permitted (stable dose)[5]	Permitted
Leukotriene modifier	Permitted[3]	Permitted (stable dose)[5]	Permitted
Cromolyn sodium / nedocromil sodium	Permitted[3]	Permitted (stable dose)[5]	Permitted
Methylxanthines	Not Permitted[4]	Not Permitted	Permitted
PDE-4 inhibitors	Not Permitted[4]	Not Permitted	Permitted
Immunomodulators (e.g. methotrexate)	Not Permitted[4]	Not permitted	Permitted
Immunotherapy (e.g. sub cutaneous or sublingual)	Permitted[3]	Permitted	Permitted
Biologic antagonists (e.g. Omalizumab)	Not permitted[4]	Not permitted	Not permitted
A1AT augmentation therapy	Not permitted	Not permitted	Permitted
Other investigational drugs	Not permitted	Not permitted	Not permitted

Footnotes:

1. For patients taking stable maintenance OCS with a total daily dose of ≤ 20 mg prednisone or equivalent
2. Includes fixed dose combination therapy
3. Allowed as stable dose for at least 4 weeks before Visit 1
4. Allowed before Visit 1 with a washout period of 3 months or 6 half-lives whichever is greater
5. If unstable (e.g. in case of exacerbations), extend screening period (see Section 6.1.1.4)

4.2.2.1 Restrictions regarding concomitant medication

Medications allowed to control acute COPD exacerbations or respiratory tract infection (RTI) as medically necessary during the study:

- Increases in the dose or addition of oral steroids are allowed. Pulmonary function testing visits should not occur within 14 days of the last administered dose of an increase or addition of oral steroids. Regular pulmonary function testing visits

may be postponed to meet this restriction. Subsequent visits will not be adjusted, but will be scheduled as originally planned.

- Additions of theophylline preparations are allowed during the observational portion of the study. Pulmonary function testing visits should not occur within 14 days of the last dose. Regular pulmonary function testing visits may be postponed to accommodate this restriction. Subsequent visits will not be adjusted, but will be scheduled as originally planned.

- The use of antibiotics is not restricted and may be prescribed as medically necessary for COPD exacerbations and / or infections. If antibiotics are prescribed for a respiratory infection prior to pulmonary function testing visits, the visit will be postponed for 14 days after intake of the last dose. Regular pulmonary function testing visits may be postponed to accommodate this restriction. Subsequent visits will not be adjusted, but will be scheduled as originally planned.

4.2.2.2 Restrictions on diet and life style

- Blood donations after Visit 2 until the end of study should be discouraged.
- Restart of smoking until the end of study should be discouraged. Refer to Section 3.3.5.1.

Restrictions prior to and during PFT visits:

- Prior to pulmonary function testing and throughout the testing period, the subject must remain in the building where the pulmonary function testing is performed.
- On pulmonary function test days (including the screening visit), subjects must refrain from strenuous activity for at least 12 hours prior to pulmonary function testing and throughout the testing period. Subjects should also avoid cold temperatures, environmental smoke, dust or areas with strong odors (e.g. perfumes).

5. VARIABLES AND THEIR ASSESSMENT

5.1 SUMMARY OF STUDY OUTCOMES AND ASSESSMENTS

5.1.1 Main outcome measures

- Change of lung density assessed by CT over the course of the study
- Lung function decline over the course of the study
- Number, duration and severity of exacerbations during the course of the study

5.1.2 Assessments

- CT scanning
- MRI
- Spirometry: FEV_1 and FVC
- Diffusing capacity of the lungs for carbon monoxide: D_{LCO}, D_{LCO}/VA
- Body plethysmography: TLC, IC, RV, ERV, IVC
- Medical Events of Special Interest (including COPD exacerbations)
- Biomarker
  - Blood (plasma, serum, whole blood)
  - Induced sputum (cells, supernatant) (at selected sites only)
- Safety Assessments (including Adverse Events, refer to Section 5.9)
- Pulse oximetry: SpO_2
- BODE index
- Symptom Questionnaires:
  - Modified British Medical Research Council questionnaire (mMRC)
  - COPD Assessment test questionnaire (CAT)
  - St George's Respiratory Questionnaire (SGRQ)
- 6 minute walk test (6 MWT)

5.2 COMPUTED TOMOGRAPHY (CT)

A chest CT scan will be performed as indicated in the flowchart according to specifications detailed in the Central Imaging Vendor manual. A low dose inspiratory chest CT scan [redacted] to assess airway wall thickness and emphysema and an expiratory scan [redacted] to assess air trapping will be performed. To achieve optimal image quality, the chest CT will be done with subjects being in a state of bronchodilation, e.g. after administration of salbutamol (albuterol). Before beginning the chest CT scan, the inspiration/expiration maneuvers should be explained carefully to the subject. All scans on each subject will be completed on the same scanner used for the baseline CT and accredited for use by the Central Imaging Vendor. Chest CT scan will be performed at timepoints given in the flowchart. If a chest CT scan cannot be scheduled during the regular study visit, it has to be performed within 14 days after the visit. In this case, administration of salbutamol (albuterol) should be performed prior to the imaging assessment in patients with COPD as well as in healthy subjects (see Section 6.1.1.3).
All scans will be digitally transferred for central review within a pre-specified time period. Phantom scans using the COPDGene Phantom have to be carried out regularly for quality

assurance purposes according to the Central Imaging Vendor manual. Further information on chest CT is provided in a separate manual filed in the ISF.

5.3 MAGNETIC RESONANCE IMAGING (MRI)

Magnetic resonance imaging (MRI) at 1.5 Tesla will be performed in a subset of healthy subjects and patients with COPD (not in patients with COPD and A1ATD) at selected sites to assess functional parameters using a cardio-pulmonary acquisition protocol according to specifications detailed in the Central Imaging Vendor manual. Overall 110 subjects, approximately 20 healthy subjects and 30 in each stratum of patients with COPD (GOLD grade 1, 2, 3) will be enrolled.
Morphological imaging of the lungs will be performed using an ultra-short-TE pulse sequence as well as fast T1- and T2-weighted pulse sequences. Cardiac cine images will be acquired in two and four chamber view as well as in short-axis view. Flow measurements using phase-contrast acquisitions will be performed in the pulmonary artery and the aorta. Contrast-enhanced time-resolved 3D MRA of the whole lung will be used to assess perfusion after the intravenous bolus injection of a marketed standard MRI gadolinium contrast agent. To achieve optimal image quality, MRI will be done with subjects being in a state of bronchodilation, e.g. after administration of salbutamol (albuterol). Before beginning the MRI acquisitions, the breath hold maneuvers should be explained carefully to the subject. All subjects undergoing MRI must be checked for the following criteria: 90-180 mmHg (SBP), 50-110 mmHg (DBP), 40-110 bpm (pulse rate), an ear temperature within 35-37.5°C, and a GFR ≥ 30 mL/min at each visit involving the MRI procedure (see flowchart). Subjects who do not meet all of these criteria are not eligible for the MRI procedure. GFR values must not be older than 14 days from the MRI assessment and can be assessed locally, if necessary. Please refer to Appendix 10.7.
All scans on each subject will be completed on the same MR scanner used for the baseline MRI and accredited for use by the Central Imaging Vendor. MRI scan will be performed at visits given in the flowchart. If an MRI examination cannot be scheduled during the regular study visit, it has to be performed within 14 days after the visit. In this case, administration of salbutamol (albuterol) should be performed prior to the imaging assessment in patients with COPD as well as in healthy subjects (see Section 6.1.1.3).
All scans will be digitally transferred for central review within a pre-specified time period. Further information is provided in a separate manual filed in the ISF.

With implementation of CSP Version 6.0, the MRI sub-study will be stopped for all subjects who agreed to participate in this part of the study. No future MRI assessments should be conducted on these subjects (please also see section 7.4).

5.4 SPIROMETRY (PFT)

The spirometer and its use, including calibration (refer to procedural manual for timepoints), must meet ATS/ERS criteria [P05-12782]. The spirometry equipment will be provided by BI via a CRO for all participating sites. Spirometry will be conducted with the subject in a seated position. It is preferable that the same trained individual performs the PFTs for a given subject. The best of three efforts will be defined as the highest FEV_1 and the highest FVC each obtained on any of three blows meeting the ATS criteria (with a maximum of eight

attempts). The highest FEV_1 and FVC will be selected regardless of whether they come from different spirometric maneuvers or from the same maneuver. The 24-hour clock time of the first maneuver will be recorded.

At Visit 1, the PFT should be started between 7:00 a.m. and 10:00 a.m. At each following site visit, PFT will always start at approximately the same time of the day, i.e. with ± 60 minutes maximum difference between start of the tests at Visit 1 and the tests conducted on subsequent visits up to Visit 7.
At Visit 3, sites can use the spirometer provided by BI or a local device to assess the safety criteria (FEV_1) for the sputum induction procedure.

Post-bronchodilator (salbutamol (albuterol)) testing:
Following the completion of three acceptable pre-bronchodilator forced expiratory manoeuvers, salbutamol (albuterol) will be administered to each subject. After a gentle and incomplete expiration, a dose of approximately 100 µg of salbutamol (albuterol) is inhaled in one breath to total lung capacity. The breath is inhaled for 5 – 10 sec before the subject exhales. Four separate doses (total dose approximately 400 µg) are delivered at approximately 30 sec intervals (this dose ensures that the response is high on the salbutamol (albuterol) dose - response curve). Three additional, acceptable post-bronchodilator force expiratory manoeuver tests are recorded 15 – 30 minutes after the last dose of salbutamol (albuterol) is inhaled ([P05-12782], modified in regard to timing of post-bronchodilator maneuvers).

During the study, a central quality control center will receive the data of spirometry measurements electronically to ensure that the sites maintain the same standard throughout the study. The central quality center will review the spirometry measurement data and report to the sponsor on data quality and, if required, actions to be taken.

5.5 DIFFUSING CAPACITY OF THE LUNGS FOR CARBON MONOXIDE (D_{LCO})

Diffusing capacity of the lung for carbon monoxide (D_{LCO}) measurement will be performed according to American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines [R06-2002], after salbutamol (albuterol). The site will use its own D_{LCO} equipment and conduct all measurements with the same D_{LCO} equipment (e.g. if several devices would be available at the site). Before beginning the test, the maneuvers should be demonstrated and the subject carefully instructed. The subject should have rested 10 minutes before the test starts. D_{LCO} will be measured by single breath, breath-holding technique: The subjects inhale a volume of defined gas during an inspiration to total lung capacity, hold their breath for 10 seconds, and then perform an expiration smooth, unforced, without hesitation or interruption, and total exhalation time should not exceed 4 seconds. All measurements are to be made with the subjects seated upright and their nose clipped. Between the D_{LCO} maneuvers a minimum waiting time of 4 minutes is required.

D_{LCO} will be measured at timepoints given in the flowchart.
The following parameters will be reported:

- D_{LCO}: Diffusing capacity for the lungs measured using carbon monoxide

- D_{LCO}/VA: Diffusing capacity for carbon monoxide per unit of alveolar volume

For predicted normal values, different sites may use different prediction formulas, based on the method used to measure D_{LCO}. In any case, the calculation method used must be in compliance with the ATS/ERS guideline on D_{LCO} measurements [R06-2002], and the prediction formula appropriate for that method. Raw data (gas mixture, equation used for prediction of normal, further adjustments made if so) must be traced.

D_{LCO} corrected for hemoglobin [R06-2002]:

- Males: D_{LCO} corrected for Hb = D_{LCO} measured $\times$[(10.22 + Hb)/1.7Hb]
- Females: D_{LCO} corrected for Hb = D_{LCO} measured $\times$[(9.38 + Hb)/1.7Hb]

Whereas Hb is expressed in $g \bullet dL^{-1}$.

The following rules will apply for the selection of D_{LCO} data: For D_{LCO} the mean value from three (if feasible; at least two are required) technically acceptable attempts will be used. Repeatability criteria for D_{LCO} according to American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines [R06-2002] have to be met.

5.6 BODY PLETHYSMOGRAPHY

Body plethysmography will be done in line with ATS/ERS standards [R08-1121], after salbutamol (albuterol), using the device of the investigational site for assessment of lung volumes and capacities.
The measurement of functional residual capacity (FRC) will be repeated at least 3 times, until 3 obtained FRC values show ≤ 5% variability.
Expiratory reserve volume (ERV) will be measured immediately after the FRC, followed by slow inspiratory vital capacity (IVC) manoeuver, all performed as ‘‘linked’’ manoeuvers (i.e. without the subject coming off the mouthpiece prior to the completion of the maneuvers). COPD patients who cannot perform linked manoeuvers will be instructed to have few cycles of quiet breathing before initiation of the ERV/IVC manoeuvers.
Mean FRC value of at least 3 technically satisfactory FRC measurements, linked to the technically satisfactory ERV and IVC manoeuvers used for calculating the RV and TLC will be reported. Residual volume (RV) will be calculated as a difference between the reported FRC value and the mean of the technically acceptable ERV measurements, linked to technically acceptable FRC determinations. Total lung capacity (TLC) will be calculated by adding the reported value for RV and the largest of the technically acceptable IVCs. Inspiratory capacity (IC) will be derived from IVC and ERV, and IC/TLC will be calculated. RV % predicted will also be reported.

5.7 MEDICAL EVENTS OF SPECIAL INTEREST (MESI)

The term MESI relates to any specific event, including an exacerbation of a pre-existing condition that has been identified at the study level as being of particular interest for prospective monitoring and assessment within this study, e.g. the potential for being related to the underlying COPD disease based on current scientific knowledge. Additional (other) events might be reported at the discretion of the investigator and are then also considered

MESI. Occurrence of a MESI will be captured and assessed during screening (after subject signs inform consent) and observational period until the subject individual study completion/ discontinuation. These events can be detected during study procedures (e.g. physical examination, laboratory results) at clinic visits or might be reported by the subject and will be recorded on a specific eCRF.
If such abnormalities already pre-exist prior to study inclusion they will be considered as baseline conditions and recorded on a separate eCRF.

The following disorders are considered MESIs:

5.7.1 Respiratory Disorders

- Pneumonia
- Pulmonary fibrosis
- Chronic respiratory failure
- Asthma-chronic pulmonary disease overlap syndrome
- Obstructive sleep apnoea
- Bronchiectasis
- Pleural effusion
- Lung Cancer
- COPD exacerbation
- Other (at the discretion of the investigator)

5.7.1.1 Definition and assessment of COPD exacerbations

For the purpose of this study, a COPD exacerbation is defined as a complex of lower respiratory events / symptoms (increase or new onset) related to the underlying COPD, with duration of three days or more.
A complex of lower respiratory events / symptoms is defined as at least two of the following:

- Shortness of breath
- Sputum production (volume)
- Change in sputum colour
- Cough
- Wheezing
- Chest tightness

“Onset of exacerbation” will be defined as the onset of first recorded symptom. The “end of exacerbation” will be decided by the investigator based on clinical judgment.

Exacerbations will be classified as follows:

Mild:	a new prescription or increased usage of maintenance bronchodilator only
Moderate:	patient receiving an exacerbation-related prescription of oral corticosteroids and/ or antibiotic not requiring hospitalisation
Severe:	COPD-related hospitalisation including emergency room visit

In the situation of hospitalisation associated with COPD exacerbation, the information collected should include the start date of all COPD-related hospitalisations as well as the discharge date from the hospital or equivalent.

Information regarding exacerbations will be collected by the investigators during the visits and telephone calls, and recorded in the eCRF. During all telephone calls and clinic visits, the same questions regarding exacerbation will be addressed for collecting exacerbation-related details and then recorded in the eCRF.

For all patients (completed/discontinued) the COPD exacerbation collection period of interest will be the screening and observational phase ending at Visit 7/ discontinuation visit.

If subjects are hospitalized, the study site will be responsible for collecting and reviewing pertinent medical records so that an informed judgment can be made as to the primary cause for admission.

5.7.2 Cardiovascular disorders

- Angina pectoris
- Ischaemic heart disease (including myocardial infarction)
- (Arterial) Hypertension (including pulmonary (arterial) hypertension)
- Hypotension
- Aneurysm
- Syncope
- Cardiac arrhythmia
- Heart failure (including congestive heart failure)
- Cerebrovascular disease
- Other (at the discretion of the investigator)

5.7.3 Metabolic/ Digestive disorders

- Diabetes mellitus
- Obesity
- Hyper-/Dyslipidaemia
- Cholecystitis
- Cholecystolithiasis
- Colitis (including Ulcerative colitis)
- Gastro-oesophageal reflux disease (GERD)
- Other (at the discretion of the investigator)

5.7.4 Neurological/psychiatric disorders

- Dementia
- Cognitive impairment
- Depression
- Anxiety
- Other (at the discretion of the investigator)

5.7.5 Other disorders

- Osteo-articular disorders (osteoporosis, rheumatoid arthritis, osteoarthritis)
- Other (at the discretion of the investigator)

5.8 BIOMARKER ASSESSMENTS

Pre-specified biomarkers will be analyzed in several biofluids at Visits 2 to 7. [redacted]

[redacted]

Whole blood
Total and differential cell counts in blood, which are assessed within the safety lab assessments, will also be assessed as biomarkers.

Blood will be collected to enable DNA analyses. The DNA sample will be used to determine the A1AT genotype.

[redacted]

Sputum Subset
At those sites selected to collect induced sputum samples, sputum will be processed according to the manual filed in the ISF to generate different sputum samples [redacted]

[redacted]

[redacted]

5.8.1 Biomarker sample collection

5.8.1.1 Blood collection

Blood samples will be taken at time points indicated in the flowchart.

[redacted]

Detailed instructions for biomarker blood sampling, processing, storage and shipment of the different biofluids are provided in the site's ISF.

[redacted]

[redacted]

5.8.1.2 Collection of sputum (in a subset of subjects only)

Induction and collection of sputum will be done in all subjects at selected sites only and samples will be taken at time points indicated in the flowchart.

In addition, subjects who have signed informed consent might be asked to provide an induced test sputum sample at the screening visit in order to assess the sputum processing capabilities at the investigational site. In this case the test sputum induction should take place at least 20 days prior to the first subject performing Visit 2 at the site.

The provided sputum samples will be obtained and processed according to the manual for sputum induction and processing provided in the ISF. The processing of sputum samples should start immediately, but no later than 1 hour after the sample has been taken.

Sputum induction will be started following all other visit assessments and should be done with the subjects being in a state of bronchodilation.
Patients are allowed to take their usual COPD medication before sputum induction. In addition, pre-treatment with salbutamol (albuterol) should be repeated if time between morning administration of salbutamol (albuterol) for post-bronchodilator PFT measurement and start of sputum induction is exceeding 4 hours.

Subjects who are not able to produce an acceptable sputum sample at Visit 2 and Visit 2 Retest as determined by the central overread will continue in the study, however, no sputum induction should be performed for the remainder of the study (from Visit 3 to Visit 7/discontinuation).

Detailed instructions for sputum induction and processing, storage and shipment are provided in the site's ISF.

5.8.2 Methods and timing of sample collection

All biomarker samples will be collected according to the flowchart.
Detailed instructions for biomarker sampling, sample processing, storage and shipment are provided in the ISF.

5.8.3 Analytical determinations

The analytical methods for the analysis of biomarkers will be given in detail in an analytical report.

5.8.4 Biobanking

All biomarker samples (will be used for further unspecified analysis to establish a better understanding of COPD and other respiratory diseases. The study samples will be discarded after completion of the additional investigations. These further scientific evaluations will be described in the subject information sheet and will be part of the informed consent.

5.9 ASSESSMENT OF SAFETY

5.9.1 Physical examination

A physical examination will be carried out at visits 1, 5, 6, and 7. In addition further physical examination should be performed if clarification of AEs is necessary.
All clinically significant findings at screening will be documented on the source documents and recorded in the eCRF as baseline conditions.

After Visit 1, new findings or worsening of screening conditions will be reported as adverse event if they are, in the opinion of the investigator, associated with a study procedure as described in Section 5.9.6.
Body height will be determined on screening visit only (Visit 1). Body weight will be measured at Visit 1, 5, 6, and 7.
Body weight and height will be documented on the source documents and recorded in the eCRF. BMI will be calculated automatically on the eCRF (refer to Appendix 10.4.3)

5.9.2 Vital Signs

Vital signs (blood pressure, pulse rate) will be taken at Visit 1, 5, 6, and 7. Systolic and diastolic blood pressure (BP) and pulse rate (PR) will be measured after the subject has rested for at least 5 minutes in a supine position. All measurements of an individual subject shall be made using the same blood pressure recording instrument on the same arm. The method, the identifier of the blood pressure recording instrument and the arm must be recorded in the source documents.
The measured vital signs will be documented on the source documents and recorded in the eCRF.

5.9.3 Safety laboratory parameters

Safety laboratory parameters will be obtained from blood. A full panel of clinical laboratory tests (hematology, chemistry, and coagulation) will be done at Visit 1, 2, 5, 6, and 7. A reduced laboratory panel will be conducted at Visit 3 and 4 (see flowchart).
Detailed instructions for laboratory safety blood sampling, handling and shipment of samples will be provided in the ISF / laboratory manual.
A total amount of approximately 70 mL blood will be taken per subject (approximately 10 mL per visit) during the whole course of the study for laboratory parameters listed in Table 5.9.3: 1. The respective reference ranges will be provided in the Investigator Site File (ISF). Refer to the flowchart for time points. The date and exact blood collection times must be documented on the source documents.
The laboratory tests listed in Table 5.9.3: 1 will be performed by a central laboratory.

The central laboratory will send reports to the investigational site. It is the responsibility of the investigator/ sub-investigator to evaluate the laboratory reports. Abnormal findings as judged by the investigator will be reported as adverse events if they are associated with a study procedure (please refer to Section 5.9.6.2).
The central laboratory will transfer the results of the safety analysis to the sponsor.

Table 5.9.3: 1 Safety laboratory parameters and exploratory biomarkers obtained from blood and measured by the central laboratory

Category	**Test name**
Hematology	Hematocrit (Hct) * Hemoglobin (Hb) * Red Blood Cell Count / Erythrocytes *(inclusive MCV (mean corpuscular volume), MCH (mean corpuscular hemoglobin) and MCHC (Mean Cellular Hemoglobin Concentration))** Reticulocyte Count * [redacted] Platelet Count / Thrombocytes *
[redacted]	[redacted]
Coagulation	Activated Partial Thromboplastin Time (= aPTT) Prothrombin Time (Quick and INR) [redacted]
Enzymes	SGOT SGPT Alkaline Phosphatase (AP/ALP) Creatine Kinase (CK) CK-MB if CK is elevated Gamma-Glutamyl Transferase (GGT/γ-GT) Lactic Dehydrogenase (LDH) Lipase Amylase
Substrates	Glucose (fasted) Creatinine * Bilirubin Total Bilirubin Direct Protein, Total [redacted] Uric Acid
Electrolytes	Calcium Sodium Potassium Magnesium

* Parameters to be analyzed on the reduced safety panel.

5.9.4 Electrocardiogram

A 12-lead ECG will be performed at Visit 1 (only for screening purposes, no data collected apart findings to be reported as baseline condition), visit 5, 6, and visit 7.
12-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using the ECG machine of the investigator site. ECG-records will be stored at the investigational site.

The ECGs will be recorded for about 10-second duration after the subject has rested for at least 5 minutes in a supine position. Electrode placement will be performed according to the Wilson method (precordial leads) and Goldberger and Einthoven (limb leads).
The ECG records will be evaluated for pathological results by the investigator or a designee. Abnormal findings as judged by the Investigator/Sub-Investigator will be reported as adverse events if they are associated with a study procedure (please refer to Section 5.9.6.2).
Any ECG abnormalities will be carefully monitored by the investigator and, if necessary, the subject will be removed from the study and medically treated.

5.9.5 Pregnancy tests

Urine pregnancy tests will be done at visits 1, 2, 4, 5, 6, and 7 in the clinic in women of childbearing potential only. Women not of childbearing potential are defined as women who are postmenopausal (12 months with no menses without an alternative medical cause) or who are permanently sterilized (e.g. hysterectomy, bilateral oophorectomy or bilateral salpingectomy). Tubal ligation is NOT a method of permanent sterilisation. If the urine pregnancy test is positive, subjects will be discontinued from the study (refer to Section 3.3.5.1), and should be asked if they agree to receive phone calls for Vital Status and COPD exacerbation status collection (for timepoints refer to Section 6.2.2: Vital Status and COPD exacerbation status collection (Phone Call)). The decision must be documented in the subjects' charts.

5.9.6 Assessment of adverse events

Adverse events will be collected and assessed as outlined below.

5.9.6.1 Definitions of AEs

Adverse event
An adverse event (AE) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient or clinical investigation subject undergoing a study procedure (e.g. MRI with a contrast agent) according to the study protocol.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with a study procedure, whether or not considered related to the study procedure.

Serious adverse event
A serious adverse event (SAE) is defined as any AE which:

- results in death
- is life-threatening

- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability or incapacity
- is a congenital anomaly/birth defect
  or
- is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardize the subject and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions

Life-threatening in this context refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.

For Japan only: the following events will be handled as "deemed serious for any other reason":

AEs which possibly lead to disability will be reported as SAEs.

Intensity of AEs
The intensity of the AE should be judged based on the following:

Mild:	Awareness of sign(s) or symptom(s) that is/are easily tolerated
Moderate:	Enough discomfort to cause interference with usual activity
Severe:	Incapacitating or causing inability to work or to perform usual activities

Causal relationship of AEs
Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Yes:	There is a reasonable causal relationship between a study procedure and the AE.
No:	There is no reasonable causal relationship between a study procedure and the AE.

5.9.6.2 Adverse event collection and reporting

AE Collection and Reporting
The following must be collected and documented on the appropriate eCRF by the Investigator:

- From signing the informed consent onwards until individual subject's Visit 7/ discontinuation visit:
  All AEs (serious and non-serious), which are associated with any study procedure.

The Investigator should enter SAEs, and non-serious AEs which are relevant for the SAE immediately (within 24 hours) into the eCRF. The same timeline applies if SAE follow-up information becomes available.

Information required
For each AE, the Investigator should provide the information requested on the appropriate eCRF pages.

The Investigator should determine the causal relationship to the study procedures outlined under Section 6.2.

All (S)AEs, including those persisting after individual subject's study completion of study must be followed up until they have resolved, have been sufficiently characterized, or no further information can be obtained.

Reporting of related Adverse Events associated with any BI drug

The investigator is encouraged to report all adverse events related to any BI drug according to the local regulatory requirements for spontaneous AE reporting at the investigator's discretion by using the locally established routes and AE report forms. The term AE includes drug exposure during pregnancy, and, regardless of whether an AE occurred or not, any abuse, off-label use, misuse, medication error, occupational exposure, lack of effect, and unexpected benefit.

5.10 PULSE OXIMETRY

Oxygen saturation (SpO_2) will be measured by non-invasive pulse oximetry using the pulse oximetry measurement device of the investigational site. All recordings shall be made using the same pulse oximetry measurement device per site on the same finger of the subject. The identifier of the pulse oximetry measurement device must be recorded in the source documents as well as the finger used. Refer to flowchart for time points.
Subjects will be asked not to use nail polish or acrylic nails to optimize the pulse oximeter measurement.
The measured SpO_2 values will be documented on the source documents and recorded in the eCRF.

5.11 SYMPTOM QUESTIONNAIRES

5.11.1 mMRC

The Modified Medical Research Council Dyspnoea Scale (mMRC) [R00-0206] should be completed by COPD patients as the first questionnaire during a study visit, prior to the CAT and SGRQ, pulmonary function testing and all other procedures. The mMRC will be completed at Visit 1, 2, 5, 6, and 7.
The mMRC uses a simple grading system to assess a patient´s level of dyspnoea. All questions relate to everyday activities and are generally easily understood by patients. Scores range from 0 (none) to 4 (very severe) and are usually obtained in a few seconds.

5.11.2 COPD Assessment Test (CAT)

The CAT [R12-1915] should be completed by COPD patients after the mMRC and prior to the SGRQ, pulmonary function testing and all other procedures. The CAT will be completed at Visit 2, 5, 6, and 7.

The CAT is designed to measure health status impairment in COPD and consists of 8 uni-dimensional items with scores ranging from 0 to 5 (0 = no impairment). An overall score is calculated by adding the score from each item. The CAT is provided on paper (appendix 10.1). Patients should be by themselves in a quiet place when they complete the questionnaire. The investigator (or designated site personnel) should check that all items have been completed by the patient, but the response to each item should not be questioned. Challenges to inconsistent responses (e.g. a really pronounced outlier) should only be done very infrequently and with very careful consideration. The scores will then be transcribed into the eCRF by the Investigator (or designated site personnel). The original will be retained at the site.

5.11.3 Saint George's Respiratory Questionnaire (SGRQ)

The SGRQ [R96-0686] should be completed by COPD patients after the CAT test during a study visit, prior to pulmonary function testing and all other procedures. The SGRQ will be completed at Visit 2, 5, 6, and 7.
The SGRQ is designed to measure health impairment in patients with COPD. It is divided into two parts. Part I produce the Symptoms score, and Part 2 the Activity and Impacts scores. A Total score is also produced.
Part 1 (Questions 1 to 8) covers the patient's recollection of their symptoms over a preceding period that may range from 1 month to 1 year. It is not designed to be an accurate epidemiological tool; its purpose is to assess the patient's perception of their recent respiratory problems. The original version was validated using a 12-month recall period. A 3-month recall period has been used very satisfactorily. In summary, the 3-month and 1-year versions provide the best properties, with no specific advantages to either.
Part 2 (questions 9 to 16) addresses the patients' current state (i.e. how they are these days). The activity score just measures disturbances to patient's daily physical activity. The Impacts score covers a wide range of disturbances of psycho-social function. Validation studies showed that this component relates in part to respiratory symptoms, but it also correlates quite strongly with exercise performance (6-minute walk test), breathlessness in daily life (MRC breathlessness score) and disturbances of mood (anxiety and depression). The Impacts score is, therefore, the broadest component of the questionnaires, covering the whole range of disturbances that respiratory patients experience in their lives.
Details of the SGRQ are provided in appendix 10.2.

5.12 6 MINUTE WALK TEST (6 MWT)

The 6 MWT should be done according to ATS guideline [R03-0725]. Testing should be performed at Visits 1, 2, 6, and 7 in a location where a rapid, appropriate response in the event of an emergency is possible (see ATS guideline for other technical aspects, e.g. choice of location, required equipment, etc.).

Supplies that must be available include oxygen, sublingual nitroglycerine, aspirin, and salbutamol (albuterol) in metered dose inhaler or nebulizer. A telephone or other means should be in place to enable a call for help.

If a patient is on chronic oxygen therapy, oxygen should be given at their standard rate or as directed by a physician.

A physician is required to be present for the first test (at Visit 1) and for subsequent tests, as needed.

Reasons for immediately stopping a 6 MWT include the following:

- Chest pain
- Intolerable dyspnea
- Leg cramps
- Staggering
- Diaphoresis
- Pale or ashen appearance.

The distance walked will be measured in meters (m) and will be recorded. If the test is stopped prematurely, the distance (m), the duration (min), and the reason for stopping will be recorded.

5.13 APPROPRIATENESS OF MEASUREMENTS

The majority of measurements performed during this study are standard measurements and will be performed in order to monitor safety aspects or assess study objectives in an appropriate way.
[redacted] The frequency and intensity of the procedures was determined to guarantee a successful assessment of study parameters and to put study subjects at low risk.
Chest CT is the current gold standard to assess lung density or loss of lung density, i.e. emphysema, and airway disease, which cannot be done by other techniques including other imaging modalities such as MRI. [redacted].

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

The study consists of a screening period and an observational period. Following the screening period (up to 28 days long), subjects will enter the observational period at Visit 2. Clinic visits and phone calls will be scheduled as per flowchart.

Subjects should make all efforts to complete the study. Investigators should encourage adherence to the protocol procedures. All subjects should adhere to the visit schedule as specified in the flowchart. Any deviations from the planned visit schedule should be documented.

6.1.1 Rescheduling clinic visits and study procedures

6.1.1.1 Diet and life style restrictions

Diet and life style restrictions are necessary for subjects' safety and study assessments. Clinic visits involving a PFT may be rescheduled twice within the permitted time windows due to lack of dietary and life style restrictions. If possible, subjects should be contacted by telephone within 3 days before the clinic visit to remind them about the visit schedule and the restrictions.

6.1.1.2 Sputum induction (at selected sites only)

Sputum induction at Visit 2 can be rescheduled up to 3 days. If the subject is unable to produce an adequate sample of the sputum or a sputum sample of acceptable quality at visit 2 (after feedback from the vendor), repeat sputum induction should be performed. An interval of at least 3 full days and up to 21 days should be observed between repeat sputum induction procedures. All other Visit 2 procedures should have been completed on the originally scheduled Visit 2 date.

If sputum induction procedure at Visit 2 needs to be repeated, subject will complete only the sputum induction procedure at the repeat visit. In this case, sputum induction should be started within 15 min to 4 hours after salbutamol (albuterol) inhalation. Salbutamol (albuterol) can be self-administered by the subject under the supervision of the staff performing the sputum induction according to the inhalation procedure described for the post-bronchodilator testing (four separate doses at approximately 30 sec interval, see Section 5.4).

Sputum induction procedures at Visits 3 - 7 will not be repeated if the subject is unable to produce sputum or if the sputum sample quality is not acceptable. If the sputum induction and processing procedure cannot be scheduled during the regular study Visits 3 to 7, it should be rescheduled within 21 days after the visit. In this case, administration of salbutamol (albuterol) should be performed prior to the procedure.

6.1.1.3 Imaging assessments (chest CT and MRI)

If chest CT and (if applicable) MRI cannot be performed at the day of the scheduled visit the imaging assessment can be rescheduled up to 14 days after the visit. In this case imaging assessments should be performed 15 min to 4 hours after salbutamol (albuterol) inhalation. Salbutamol (albuterol) can be self-administered by the subject under the supervision of the staff performing the imaging assessments according to the inhalation procedure described for the post-bronchodilator testing (four separate doses at approximately 30 sec interval, see Section 5.4).

6.1.1.4 COPD exacerbation and respiratory tract infection

If a patient experiences a COPD exacerbation or respiratory tract infection during the screening period, Visit 2 will be postponed until 4 weeks following recovery from the exacerbation or infection. Screening period may be extended up to eight weeks if the patient experiences a COPD exacerbation or respiratory tract infection during the screening period (refer to Section 4.2.2.1).

If patient has a COPD exacerbation or respiratory tract infection during the observational period, study visits will be rescheduled. Please discuss with the Local Clinical Monitor.

6.1.1.5 Rescheduling clinic visits during the screening period

In general, the screening period can be extended for administrative reason, e.g. (extended travel, life events or if lab results are not yet available). The delay should be kept as short as possible and if longer than additional 4 weeks, please contact the Local Clinical Monitor. A re-screening visit can be considered.

6.1.1.6 Rescheduling clinic visits during the observational period

All clinic visits should be completed at the time window allowed in the flowchart.

If a clinic visit after Visit 2 is out of the time window allowed by the protocol, subsequent visits should occur at the originally scheduled date. Any clinic visits outside the time window allowed by the protocol should be discussed with the Local Clinical Monitor. All subjects are expected to complete the observational period.

6.2 DETAILS OF STUDY PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

An informed consent will be obtained prior to subject's participation in the study. Considering the number and complexity of study procedures and the duration of the study, the subjects should be given sufficient time to discuss concerns, potential benefits and risks, and obligations. Restrictions according to Section 4.2.2 are allowed only after the subject signs the informed consent. If the subject is willing to provide a sample for unspecified pharmacogenomic testing, a separate consent must be obtained. If the subject is willing to participate in the MRI subset (only at selected study sites) a separate consent must be

obtained. Each subject will be assigned a unique subject number and once the subject signed informed consent, enrollment will be recorded in eCRF.

At Visit 1, demographics, medical history (including baseline conditions), physical examination, BMI, vital signs (including pulse oximetry) and eligibility criteria will be assessed. Concomitant therapy, smoking status, MESI and AE (if study procedure related) will be recorded. Subjects will be provided with a reminder diary (see Section 3.1.1).
Visit 1 should be scheduled to start in the morning between 6:00 am and 9:00 am. Restriction check, pregnancy test (if applicable) and IRT subject visit registration should be done first. The sequence of procedures will be mMRC, followed by ECG and pre PFT. Post PFTs should be done prior to post D_{LCO}. 6 MWT should be performed after post PFTs/D_{LCO}. Blood samples for safety laboratory and PGx testing should be collected after the ECG procedure is completed.
Instructions for shipping of laboratory samples will be provided in the manual.
If the subject has met all the eligibility criteria, Visit 2 will be scheduled.

Discontinuation during the screening period
If subjects discontinue from the study during the screening period, no additional clinic visits are required, and they will be marked as screen failures.

Subjects who were discontinued during screening period under the criteria of the former protocol version can re-enter the study if they meet the amended inclusion/exclusion criteria. In this case, the subject will receive a new subject number and be treated like a new subject (e.g. new informed consent).

Re-screening
Subjects may be re-screened once with approval from the Local Clinical Monitor (subjects keep the original subject number). Subjects who met all inclusion criteria but failed first screening due to acute medical conditions that have since been resolved or those who failed to comply with diet and life style restrictions will be good candidates for re-screening. If other reasons apply, please contact your local CML. The re-screening visit should be entered as a separate visit in in the eCRF.

6.2.2 Observational period and Study Completion

Eligibility criteria that apply at Visit 2 must be re-checked before proceeding with Visit 2.

The observational period begins after the subject completes Visit 2 and ends after completion of Visit 7 at Week 156 or after the discontinuation visit. Procedures listed under each visit in the flowchart should be completed. Visit windows should be adhered as specified in the flowchart.

All visits during the observational period should be scheduled to start in the mornings according to Visit 1. Restriction check, smoking status, pregnancy test (if applicable) and IRT subject visit registration should be done first. Other checks include review of concomitant medication, MESI and AE. Physical examination and vital sign assessment (including pulse oximetry) will be performed additionally at Visits 5, 6, and 7.

The sequence of procedures will be the completion of the questionnaires mMRC, CAT and SGRQ, followed by ECG and pre PFT. Post PFTs should be done prior to post D_{LCO}/bodyplethysmography. Chest CT (and MRI, if applicable) should be performed between 1h and 4h after the end of the salbutamol (albuterol) administration (post-bronchodilator testing) at timepoints indicated in the flowchart. 6 MWT should be performed after post PFT/D_{LCO}/bodyplethysmography. Blood samples for safety and biomarker assessment should be collected after the ECG procedure is completed. Collection of induced sputum (if applicable) should be the last procedure. A spirometric device will be used to perform the PFTs and monitor subject's lung function during sputum induction. The BODE index will be calculated at visit 2, 6, and 7 in patients with COPD/COPD and A1ATD only.

If the scheduled visit does not occur within the protocol allowed time window, follow instructions provided in Section 6.1.1 for rescheduling. Unscheduled visits may be arranged if necessary and the procedures completed during the unscheduled visit will depend on the circumstances under which the visit was scheduled.

Telephone contacts between clinic visits

Study sites will follow up subjects and collect information by telephone interviews at the dates indicated in the flowchart and will perform an IRT subject visit registration call. A subjects' reminder card will be provided to assist their memory recall in terms of respiratory symptoms, COPD exacerbations, hospitalization or interim health care visits, and concomitant therapy.

At each telephone contact, the investigator or delegate will review with the subject new occurrences of MESI (including COPD exacerbation: new occurrence of exacerbation, respiratory symptoms, COPD exacerbation-related hospitalization and other pertaining information) and will record it in the eCRF. If subjects are hospitalized, the study site might consider collecting and reviewing pertinent medical records (hospital records, telephone or written correspondence with primary physicians, discharge summaries, and death certificates) so that an informed judgment can be made as to the primary cause for admission.

In case of hospitalizations, subjects will be encouraged to promptly inform the study site prior to their regularly scheduled telephone interviews.

Details of all COPD exacerbations will be captured in the source notes.

Study Completion

Visit 7/ discontinuation visit will mark the end of the study period, and the subject has completed the study.

Discontinuation during the observational period

If a subject discontinues from the study during the observational period, the subject should be asked to come to the site for a discontinuation visit at the time of the next scheduled visit. The subject will undergo the procedures of this particular visit as outlined in the flowchart. If not possible, the subject should be encouraged to at least undergo the procedures for safety assessments. Women who become pregnant should undergo the procedures for safety assessments only.

Vital Status and COPD exacerbation status collection (Phone Call):
The objective of the phone call is to collect information on vital status (dead or alive) and COPD exacerbation status (COPD exacerbation status only in patients with COPD and patients with COPD and A1AT deficiency) in the time interval between the subjects' discontinuation date from the observational period and their hypothetical Visit 7 date. No other MESI will be collected during the phone call.
Depending on the point in time when the subject discontinues, the vital status and COPD exacerbation status collection phone call will be scheduled as follows:

Discontinuation date between Visit 2 and 5 will result in 3 telephone calls:

1. First collection: predicted 52 weeks (D364 ± 14) from Visit 2
2. Second collection: predicted 104 weeks (D728 ± 14) from Visit 2
3. Third collection: predicted 156 weeks (D1092 ± 14) from Visit 2

Discontinuation date between Visit 5 and 6 will result in 2 telephone calls:

1. First collection: predicted 104 weeks (D728 ± 14) from Visit 2
2. Second collection: predicted 156 weeks (D1092 ± 14) from Visit 2

Discontinuation date between Visit 6 and 7 will result in 1 telephone call:

1. First collection: predicted 156 weeks (D1092 ± 14) from Visit 2

If death occurs, the investigator will review the circumstances, including the relevant medical records to ascertain the most likely primary cause, if possible. Vital status and COPD exacerbation status information will be collected in accordance with national ethical and regulatory guidelines.

The purpose of the Vital Status and COPD exacerbation status collection will be explained to subjects prior to their participation in the study and will be part of the written informed consent.

Informed consent procedure and Vital Status and COPD exacerbation status information collection:
All subjects should be asked again at the timepoint of discontinuation, if they still agree to participate in the Vital Status and COPD exacerbation status collection part of the study. The decision must be documented in the subjects' charts.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

[redacted]

[redacted]

All subjects entering the study will be included in the analyses. Protocol violations will be defined in TSAP. Per-protocol set will be defined accordingly thereafter.

7.2 NULL AND ALTERNATIVE HYPOTHESES

No statistical hypotheses in a confirmatory sense are planned. All statistical tests are exploratory.

7.3 PLANNED ANALYSES

Variables to be analyzed are:

- Soluble biomarkers: assessments are made from blood sample (whole blood, serum, and plasma), and induced sputum. [redacted]. See Section 5.8 for details.
- Imaging biomarkers: assessments are made from CT and MRI. [redacted] See Sections 5.2 and 5.3 for details.
- Clinical and disease progression biomarkers: assessments are standard clinical measurements for patients with COPD. Examples are FEV_1, mMRC, or 6 MWT. See Sections 5.4, 5.5, 5.6, 5.10, 5.11 and 5.12 for details.
- Medical events of special interest: they include pre-defined disorders and their intensities (additional other events might be reported at the discretion of the investigators). Examples are COPD exacerbations, heart failure or obesity. See Section 5.7 for details.
- Safety assessments: They include, for example, laboratory parameters, adverse events and their intensities. See Section 5.9 for details.

Subjects' demographics and medical history are summarized. They may be included in regression models to adjust for potential confounding.

7.3.1 Primary analyses

7.3.1.1 Descriptive and Summary Statistics

Continuous variables are characterized by their distributional summary statistics. Ordinal, counts, and categorical variables are summarized by counts and frequencies. Statistics are computed for each subject group (healthy subjects, GOLD 1, GOLD 2, GOLD 3, and COPD with A1ATD), and for all subjects combined when appropriate.

For variables measured for more than once during the course of the study, descriptive statistics are provided at each time point. In addition, if they are continuous, changes from baseline are calculated by subtracting baseline values from post-baseline values. Summary statistics are presented for each change by each subject group and by all subjects combined. Their 95% confidence intervals are also presented.

Summary plots such as histograms, barplots, or boxplots are produced as visual aids for understanding the distributions of these variables.

7.3.1.2 Correlations

Correlations between different biomarkers and between biomarkers and clinical assessments are estimated using Pearson or Spearman correlations for each subject group and for all subjects combined. Correlations between changes from baseline of the biomarker values are similarly estimated. Scatterplots are produced in addition.

7.3.1.3 ANOVA Models and Logistic regression for Baseline Biomarker Values

Baseline values are defined as the last measurement taken by the end of Visit 2.

To compare baseline biomarkers and clinical assessments across subject groups, analysis of covariance (ANOVA) models for continuous variables and logistic regressions for ordinal and categorical variables will be conducted. Demographic variables and baseline disease status are adjusted to account for potential imbalance in baseline values. A detailed list of covariates will be discussed in TSAP.

7.3.1.4 Predictive models

To examine the predictive potential of the biomarkers—soluble, imaging and physiological—in clinical outcomes, e.g. FEV_1 decline at week 56, separate regression models are fitted for the clinical assessments using changes from baseline at each post-baseline time-point while adjusting for baseline covariates.

[redacted]

[redacted]

[redacted]

7.3.1.5 Repeated Measurement Models for Changes in Biomarkers Over Time

Repeated measurement models are fitted for selected biomarkers and clinical assessments. This method provides a time profile and an overall trend for changes in these assessments.

[redacted]

7.3.2 Secondary analyses

Exploratory statistical regression and prediction models will be developed for clinical assessments based on biomarker values alone, and based on biomarker values in conjunction with established baseline covariates. Their performances will be evaluated. Different approaches such as penalized regression models, recursive partitioning, or classification and regression tree (CART) methods will be investigated.

[redacted]

7.3.4 Safety analyses

All subjects enrolled will be included in the safety analysis. In general, safety analyses are descriptive in nature and are based on BI standards. No hypothesis testing is planned. Adverse events (AEs) will be coded using the latest version (at the time of database lock) of Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Standard BI summary tables and listings will be produced by subject groups.

Statistical analysis and reporting of AEs will focus on AEs that are study procedure related as judged by the investigators and medical events of special interest (MESI) as defined in Section 5.7.

Frequency, severity, and causal relationship of AEs will be tabulated by system organ class and preferred term after coding according to the latest version of MedDRA. Frequency of MESIs will be tabulated by disorder.

Laboratory data will be analyzed both quantitatively as well as qualitatively. The latter are done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be highlighted in the listings. Subject groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

Vital signs, physical examinations, or other safety-relevant data observed at screening, baseline, during the course of the study and at the end-of-study evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

7.3.5 Pharmacokinetic analyses

Not applicable

7.3.6 Pharmacogenomic analyses

Genomic parameters are assessed at baseline only. They may be adjusted in the aforementioned statistical models as baseline covariates.

7.4 INTERIM ANALYSES

An interim analysis will be conducted after data from the 52-week and 104-week assessment are available for at least 70% of subjects entered in the study. An interim database lock will occur. The interim analysis will be conducted by the trial team. Detail of the planned statistical analyses will be defined in the TSAP. No separate CTR will be provided. Results of this analysis will be stored.

[redacted]

[redacted]

7.5 HANDLING OF MISSING DATA

Missing data may be imputed if deemed necessary. Details will be discussed in the Trial Statistical Analysis Plan (TSAP).

7.6 RANDOMISATION

Not applicable.

7.7 DETERMINATION OF SAMPLE SIZE

Due to the exploratory nature of the study, power computations are focused on attaining desired precisions for biomarker estimates and relevant clinical assessments in all COPD patient groups except for the A1ATD group.

Calculations are performed in SAS 9.3 using PROC POWER procedure. By assuming up to a 20% dropout rate, at least 100 subjects are expected to contribute to the analysis at the end of 3-year study period. The computations are thus based on 100 subjects in each COPD patient group.

7.7.1 Power computation based on FEV_1 annual decline

Available information reports standard deviations (SD) of annual FEV_1 decline ranging from about 20 mL/year [P12-04707] to over 60 mL/year [R15-3625].

Using this information, with a planned 100 subjects in each group, the following table provides the coverage probability for the half-width of a 95% confidence interval (CI) for the decline of FEV_1 for a given SD. For example, if the observed SD is 50 mL/year, and the true half-width of the CI is 11 mL/year, with 100 subjects, the probability that the observed CI will cover the true CI is 93.8% (see highlighted cells in Table 7.7.1: 1).

Table 7.7.1: 1 Coverage probability of 95% confidence intervals (alpha = 0.05, n = 100)

	Half-width of a 95% CI									
SD	6	7	8	9	10	11	12	13	14	15
25	0.998	>.999	>.999	>.999	>.999	>.999	>.999	>.999	>.999	>.999
30	0.557	0.993	>.999	>.999	>.999	>.999	>.999	>.999	>.999	>.999
35	0.026	0.557	0.983	>.999	>.999	>.999	>.999	>.999	>.999	>.999
40	<.001	0.048	0.557	0.97	>.999	>.999	>.999	>.999	>.999	>.999
45	<.001	<.001	0.072	0.557	0.954	>.999	>.999	>.999	>.999	>.999
50	<.001	<.001	0.003	0.097	0.557	0.938	0.998	>.999	>.999	>.999
55	<.001	<.001	<.001	0.006	0.122	0.557	0.921	0.996	>.999	>.999

Table 7.7.1: 1 (cont.) Coverage probability of 95% confidence intervals (alpha = 0.05, n = 100)

	Half-width of a 95% CI									
SD	6	7	8	9	10	11	12	13	14	15
60	<.001	<.001	<.001	<.001	0.011	0.146	0.557	0.905	0.993	>.999
65	<.001	<.001	<.001	<.001	<.001	0.018	0.168	0.557	0.889	0.988
70	<.001	<.001	<.001	<.001	<.001	0.001	0.026	0.189	0.557	0.873

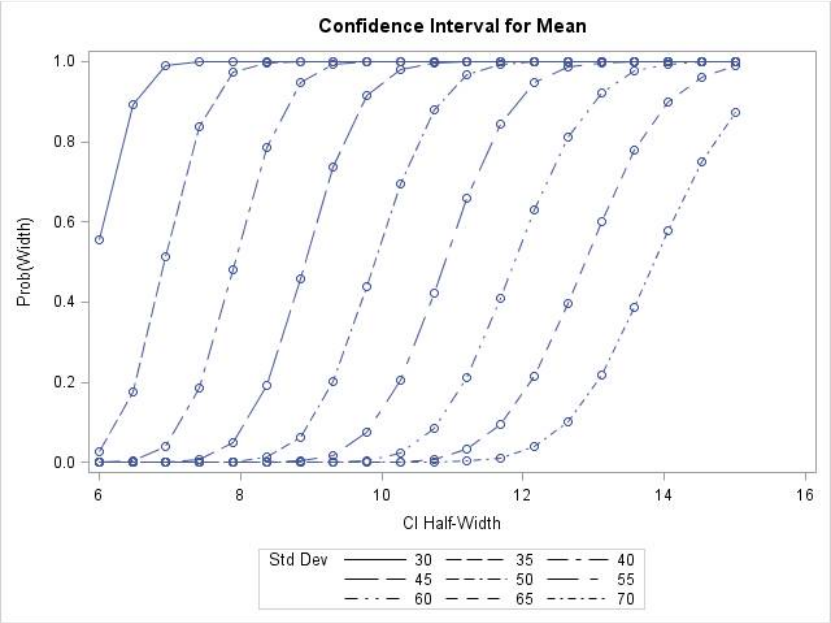


Figure 7.7.1: 1Visual presentation of Table 7.7.1: 1

7.7.2 Power computation based on PD15 decline

Reported SD on annual PD15 decline, a CT parameter, ranges from 3.4 to 5.5 unit [P15-06332] [R15-3199]. Using the same assumptions as before, Table 7.7.2: 1 contains probability coverage of a true CI for a given SD for 100 subjects.

Table 7.7.2: 1 Coverage probability of 95% confidence intervals (alpha = 0.05, n = 100)

	Half-width of a 95% CI										
SD	0.55	0.6	0.65	0.7	0.75	0.8	0.85	0.9	0.95	1	1.05
2.5	0.938	0.998	>.999	>.999	>.999	>.999	>.999	>.999	>.999	>.999	>.999
3	0.146	0.557	0.905	0.993	>.999	>.999	>.999	>.999	>.999	>.999	>.999
3.5	0.001	0.026	0.189	0.557	0.873	0.983	0.999	>.999	>.999	>.999	>.999
4	<.001	<.001	0.005	0.048	0.226	0.557	0.846	0.97	0.997	>.999	>.999
4.5	<.001	<.001	<.001	<.001	0.011	0.072	0.257	0.557	0.822	0.954	0.993
5	<.001	<.001	<.001	<.001	<.001	0.003	0.021	0.097	0.284	0.557	0.801
5.5	<.001	<.001	<.001	<.001	<.001	<.001	<.001	0.006	0.033	0.122	0.306
6	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	0.002	0.011	0.048

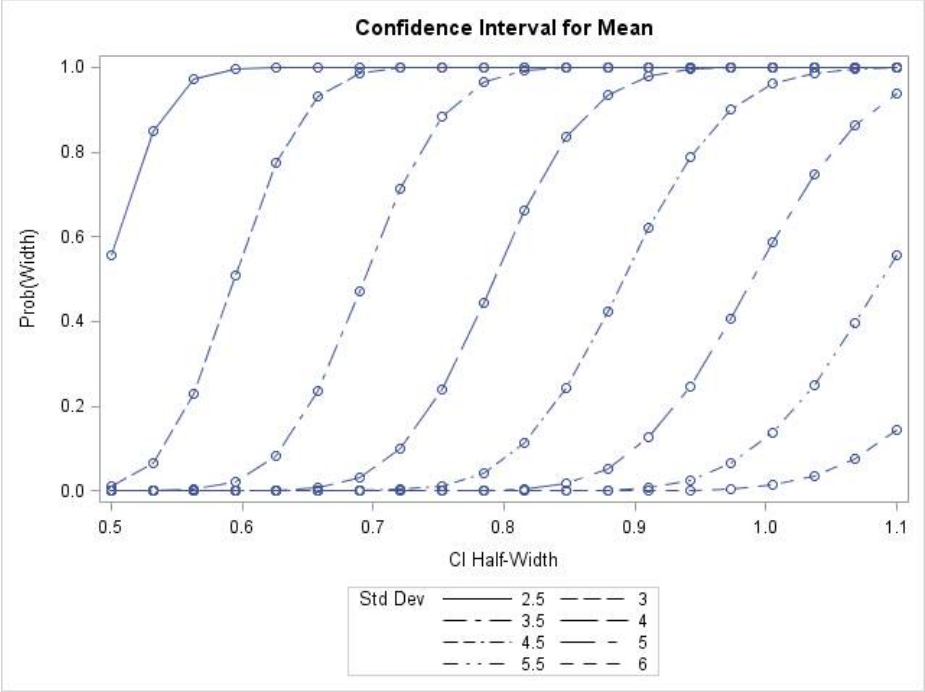


Figure 7.7.2: 1Visual presentation of Table 7.7.2: 1

7.7.3 Power Computation based on Partial Pearson Correlation Coefficients

In addition, with 100 subjects in each group by allowing for up to 15 covariates, a partial Pearson correlation coefficient of 0.30 can be declared significant with 80% power between any two continuous variables (e.g. FEV_1 and a new biomarker) within the group. Table 7.7.3: 1 below provides additional details.

Table 7.7.3: 1 Power for a given Pearson correlation coefficient (alpha = 0.05, two-sided tests, n = 100)

Partial Pearson correlation	# of partial variables			
	0	5	10	15
0.25	0.715	0.692	0.668	0.643
0.30	0.865	0.847	0.827	0.805
0.35	0.951	0.941	0.929	0.914
0.40	0.987	0.983	0.978	0.971

The results from these calculations indicate the study has adequate power to estimate the biomarker values from the assessments described in previous sections.

8. INFORMED CONSENT, DATA PROTECTION, STUDY RECORDS

The study will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP), the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997), relevant BI Standard Operating Procedures (SOPs), and relevant regulations.

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the subject.

The Investigator will inform the Sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol or of ICH GCP.

The rights of the investigator and of the sponsor with regard to publication of the results of this study are described in the investigator contract. As a rule, no study results should be published prior to finalization of the Clinical Study Report.

The certificate of insurance cover is made available to the Investigator and the subject, and is stored in the ISF (Investigator Site File).

8.1 STUDY APPROVAL, SUBJECT INFORMATION, AND INFORMED CONSENT

This study will be initiated only after all required legal documentation has been reviewed and/or approved/confirmed by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and/or competent authority (CA) as applicable according to national and international regulations. The same applies for the implementation of changes introduced by amendments.
Prior to subject participation in the study, written informed consent must be obtained from each subject (or the subjects' legally accepted representative) according to ICH / GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional subject information form retained by the Investigator as part of the study records. A signed copy of the informed consent and any additional subject information must be given to each subject or the patient's legally accepted representative.

The Investigator (or delegate, if locally applicable) must give a full explanation to study subjects including the items listed below in association with the use of the subject information form, which is prepared avoiding the use of technical terms and expressions. The subject must be given sufficient time to consider participation in the study. The Investigator (or delegate, if locally applicable) obtains written consent of the subject's own free will with the informed consent form after confirming that the subject understands the contents. The Investigator (or delegate, if locally applicable) must sign (or place a seal on)

and date the informed consent form. If a study collaborator has given a supplementary explanation, the study collaborator also signs (or places a seal on) and dates the informed consent.
Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this study may be conducted by the Sponsor, Sponsor's designees, or by IRB / IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the Investigator's study-related files and correspondence, and the informed consent documentation of this clinical study.

8.3 RECORDS

Electronic Case Report Forms (eCRF) for individual subjects will be provided by the Sponsor.

8.3.1 Source documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
Data reported on the eCRF must be consistent with the source data or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study; current medical records must also be available.
For eCRFs all data must be derived from source documents.

8.3.2 Direct access to source data and documents

The Investigator / institution will permit study-related monitoring, audits, IRB / IEC review and regulatory inspection, providing direct access to all related source data / documents. eCRF and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the Sponsor's clinical study monitor, auditor and inspection by health authorities (e.g. FDA). The Clinical Research Associate (CRA) / on site monitor and auditor may review all eCRF, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 8.3.1.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

8.4.1 Expedited reporting to health authorities and IEC / IRB

There will be no global expedited reporting of adverse events in this study. If applicable, expedited reporting of serious adverse events to health authorities and IEC / IRB will be done according to local regulatory requirements.

8.5 STATEMENT OF CONFIDENTIALITY

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Subject confidentiality will be ensured by using Subject identification code numbers. Treatment data may be given to the subjects' personal physician or to other appropriate medical personnel responsible for the subject's welfare. Data generated as a result of the study need to be available for inspection on request by the participating physicians, the Sponsor's representatives, by the IRB / IEC and the regulatory authorities if applicable.

8.6 END OF STUDY

The end of the study is defined as the last subject completing Visit 7, the last visit of the observational phase.
The IEC / competent authority in each participating EU member state will be notified about the end or early termination of the study as applicable according to national regulations.

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10. APPENDICES

10.1 COPD ASSESSMENT TEST™ (CAT)

Your name:

Today's date:

CAT
COPD Assessment Test

How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

Example: I am very happy 0 X 2 3 4 5 I am very sad

			SCORE
I never cough	0 1 2 3 4 5	I cough all the time	
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	My chest is completely full of phlegm (mucus)	
My chest does not feel tight at all	0 1 2 3 4 5	My chest feels very tight	
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up a hill or one flight of stairs I am very breathless	
I am not limited doing any activities at home	0 1 2 3 4 5	I am very limited doing activities at home	
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	I am not at all confident leaving my home because of my lung condition	
I sleep soundly	0 1 2 3 4 5	I don't sleep soundly because of my lung condition	
I have lots of energy	0 1 2 3 4 5	I have no energy at all	
			TOTAL SCORE

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10.2 SAINT GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)

What is the St George's Respiratory Questionnaire?

The SGRQ is designed to measure health impairment in patients with asthma and COPD. It is also valid for use in bronchiectasis and has been used successfully in patients with kyphoscoliosis and sarcoidosis. It is not suitable for cystic fibrosis. It is in two parts. Part I produces the Symptoms score, and Part 2 the Activity and Impacts scores. A Total score is also produced.
Part 1 (Questions 1 to 8) covers the patients' recollection of their symptoms over a preceding period that may range 1 month to 1 year. It is not designed to be an accurate epidemiological tool; its purpose is to assess the patient's perception of their recent respiratory problems. The original version was validated using a 12-month recall period. More recently a 1 month recall version (appropriately worded) has been validated. This has slightly weaker psychometric properties than the 12-month version and produces a marginally lower Symptom score and Total score.
Part 2 (Questions 9 to 16) addresses the patients' current state (i.e. how they are these days). The Activity score just measures disturbances to patients' daily physical activity. The Impacts score covers a wide range of disturbances of psycho-social function. Validation studies showed that this component relates in part to respiratory symptoms, but it also correlates quite strongly with exercise performance (6-minute walking test), breathlessness in daily life (MRC breathlessness score) and disturbances of mood (anxiety and depression). The Impacts score is, therefore, the broadest component of the questionnaires, covering the whole range of disturbances that respiratory patients experience in their lives.

How should it be administered?

The questionnaire should be completed in a quiet area free from distraction and the patient should ideally be sitting at a desk or table. Explain to the patient why they are completing the questionnaire, and how important it is for us to understand how they feel about their illness and the effect it has on their daily life. Ask the patient to complete the questionnaire as honestly as possible and stress that there are no right or wrong answers; simply the answer that the patient feels applies to them. Explain that they must answer every question and that someone will be close at hand to answer any queries.

The SGRQ is designed as a supervised self-administered questionnaire. This means that the patients should complete the questionnaire themselves but someone should be available to give advice if it is required. The patient's responses should not be influenced by the opinions of family, friends or members of staff. The questionnaire is designed to elicit the patient's opinion of his/her health, not someone else's opinion of it. If the spouse or partner has accompanied the patient they should be asked to wait in a separate area. Similarly, do not allow patients to take the SGRQ home to be completed since you cannot be sure that it will be completed without the help of family or friends.

It is very important, once the patient has finished, that you check the questionnaire to make sure a response has been given to every question and return it the patient for completion of missed items, before the patient leaves.

What should I do about queries regarding completion of the questionnaire?

If a patient asks for help with a question, do not provide an answer for them. The point of the questionnaire is to get an understanding of how the patient views his or her illness. It is appropriate to clarify a question but not to provide an answer. Questions may be read aloud if patients have difficulty with reading, but the responses must be theirs alone. If a patient gives an answer you disagree with it is not appropriate to challenge their response or to query it. It is their view of their condition we are interested in – no matter how strange the response!

The following are notes which may help you explain to patients what is required:

1. In Part 1 of the questionnaire, emphasize to patients that you are interested in how much chest trouble they have had over the last month.
2. Asthma and COPD can vary day-to day. In Part 2, we want to know about the patient's current state (these days).
3. A severe or very unpleasant attack of chest trouble (Part 1, Question 5) is any attack that could be described that way in the patient's own judgment. Not 'severe' as defined by medical staff.
4. For Question 7 emphasize that you are interested in the number of good days that they have had.
5. Question 10 regarding employment can cause patients some problems. We are interested in how a patient's chest trouble affects their current working life or how it affected life when they were working. For example, if a patient took early retirement because of their chest condition, the response would be 10a – 'My chest trouble made me stop work', if a patient's retirement was unrelated to their chest trouble, their response would be 10c 'My chest trouble does not affect my work'.
6. Questions 11 to 16 require a response to every question. It may be worth emphasizing this to the patient.
7. Many patients do not engage in physical activity. It is important to determine whether this is because they do not wish to (in which case the answer would be 'False') or cannot engage in these activities because of their chest trouble (in which case the answer would be 'True').
8. Medication questions refer to medications and treatments given for a patient chest disease and may interfere with their life if, for example, they are on oxygen support and have to carry it around with them.
9. It should be emphasized that responses to Question 15 are in terms of breathing difficulties and not any other problems. If patients do not engage in activities described in certain items, they should tick 'False'. Patients, who do not engage in these activities because they are limited by their breathlessness, should tick 'True'.

EXAMPLE OF QUESTIONNAIRE

PART 1

QUESTIONS ABOUT HOW MUCH CHEST TROUBLE YOU HAVE HAD OVER THE LAST MONTH. PLEASE TICK ONE BOX FOR EACH QUESTION.

	Most days a week	Several days a week	A few days a month	Only with chest infections	Not at all
Over the last month, I have coughed	☐	☐	☐	☐	☐
Over the last month, I have brought up phlegm (sputum)	☐	☐	☐	☐	☐
Over the last month, I have had shortness of breath	☐	☐	☐	☐	☐
Over the last month, I have had attacks of wheezing	☐	☐	☐	☐	☐

During the last month, how many severe or very unpleasant attacks of chest trouble have you had:
- More than 3 attacks …… □
- 3 attacks ……. □
- 2 attacks ……. □
- 1 attack …….. □
- No attacks ……... □

How long did the worst attack of chest trouble last: (Go to Question 7 if you had no severe attacks)
- 1 week or more …….. □
- 3 or more days ……... □
- 1 or 2 days ……. □
- Less than 1 day …….. □

Over the last month, in an average week, how many good days (with little chest trouble) have you had:
- No good days …….. □
- 1 or 2 good days …… □
- 3 or 4 good days …… □
- Nearly every day is good .□
- Every day is good ……... □

If you have a wheeze, is it worse in the morning:
- No ……. □
- Yes …… □

PART 2

SECTION 1:

HOW WOULD YOU DESCRIBE YOUR CHEST CONDITION? (PLEASE TICK IN ONE BOX ONLY)

The most important problem I have ..... □
Causes me quite a lot of problems ..... □
Causes me a few problems ..... □
Causes me no problems ..... □

IF YOU HAVE EVER HAD PAID EMPLOYMENT, PLEASE TICK ONE OF THESE

My chest trouble made me stop work altogether ..... □
My chest trouble interferes with my work or made me change my job ..... □
My chest trouble does not affect my work ..... □

SECTION 2:

QUESTIONS ABOUT WHAT ACTIVITIES USUALLY MAKE YOU FEEL BREATHLESS THESE DAYS. PLEASE TICK IN THE BOX EITHER TRUE OR FALSE, AS IT APPLIES TO YOU

Sitting or lying still ..... □ True □ False
Getting washed or dressed ..... □ True □ False
Walking around the home ..... □ True □ False
Walking outside on the level ..... □ True □ False
Walking up a flight of stairs ..... □ True □ False
Walking up hills ..... □ True □ False
Playing sports or games ..... □ True □ False

SECTION 3:

SOME MORE QUESTIONS ABOUT YOUR COUGH AND BREATHLESSNESS THESE DAYS.

PLEASE TICK IN THE BOX EITHER TRUE OR FALSE AS IT APPLIES TO YOU.

My cough hurts ..... □ True □ False
My cough makes me feel tired ..... □ True □ False
I am breathless when I talk ..... □ True □ False
I am breathless when I bend over ..... □ True □ False
My cough or breathing disturbs my sleep ..... □ True □ False

I get exhausted easily ..... □ True □ False

SECTION 4:

QUESTIONS ABOUT OTHER EFFECTS THAT YOUR CHEST TROUBLE MAY HAVE ON YOU THESE DAYS. PLEASE TICK IN THE BOX EITHER TRUE OR FALSE AS IT APPLIES TO YOU.

My cough or breathing is embarrassing in public..... □ True □ False
My chest trouble is a nuisance to my family, friends or neighbours ..... □ True □ False
I get afraid or panic when I cannot get my breath ..... □ True □ False
I feel that I am not in control of my chest problem ..... □ True □ False
I do not expect my chest to get any better ..... □ True □ False
I have become frail or an invalid because of my chest..... □ True □ False
Exercise is not safe for me..... □ True □ False
Everything seems too much of an effort..... □ True □ False

SECTION 5

QUESTIONS ABOUT YOUR MEDICATION. IF YOU ARE RECEIVING NO MEDICATION GO STRAIGHT TO SECTION 6.

My medication does not help me very much □ True □ False
I get embarrassed using my medication in public □ True □ False
I have unpleasant side effects from my medication □ True □ False
My medication interferes with my life a lot □ True □ False

SECTION 6

THESE ARE QUESTIONS ABOUT HOW MUCH YOUR ACTIVITIES MIGHT BE AFFECTED BY YOUR BREATHING. FOR EACH QUESTION PLEASE TICK IF TRUE IF ONE OR MORE OF THE PARTS OF THE QUESTION APPLIES TO YOU BECAUSE OF YOUR BREATHING. OTHERWISE ANSWER FALSE.

It takes a long time to get washed or dressed ..... □ True □ False
I cannot take a bath or shower, or I take a long time..... □ True □ False
I walk much slower than other people, or I stop for rests..... □ True □ False
Jobs such as housework take a long time, or I have to stop for rests..... □ True □ False
If I walk up one flight of stairs, I have to go slowly or stop..... □ True □ False
If I hurry or walk fast, I have to stop or slow down..... □ True □ False
My breathing makes it difficult to do things such as walk up hills
carrying things up stairs, light gardening such as weeding, dance,

play bowls, or golf..... □ True □ False

My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles per hour, play tennis or swim ..... □ True □ False

My breathing makes it difficult to do things such as very heavy manual work run, cycle, swim fast or play competitive sports ..... □ True □ False

SECTION 7

WE WOULD LIKE TO KNOW HOW YOUR CHEST TROUBLE USUALLY AFFECTS YOUR DAILY LIFE

I cannot play sports or games ..... □ True □ False

I cannot go out for entertainment or recreation ..... □ True □ False

I cannot go out of the house to do the shopping ..... □ True □ False

I cannot do housework..... □ True □ False

I cannot move far from my bed or chair ..... □ True □ False

HERE IS A LIST OF OTHER ACTIVITIES THAT YOUR CHEST TROUBLE MAY PREVENT YOU FROM DOING. (YOU DO NOT HAVE TO TICK THESE, THEY ARE JUST TO REMIND YOU OF WAYS IN WHICH YOUR BREATHLESSNESS MAY AFFECT YOU)

Going for walks, or walking the dog

Doing things at home or in the garden

Sexual intercourse

Going out to church, or place of entertainment

Going out in bad weather, or into smoky rooms

Visiting family or friends, or playing with children

PLEASE WRITE IN ANY OTHER IMPORTANT ACTIVITIES THAT YOUR CHEST TROUBLE MAY STOP YOU DOING

_____

_____

_____

NOW, WOULD YOU TICK IN THE BOX (ONE ONLY) WHICH YOU THINK BEST

DESCRIBE HOW YOUR CHEST AFFECTS YOU:

It does not stop me doing anything I would like to do..... □

It stops me doing one or two things I would like to do..... □

It stops me doing most of the things I would like to do..... □

It stops me doing everything I would like to do

10.3 MODIFIED MEDICAL RESEARCH COUNCIL DYSPNOEA SCALE (mMRC)

Modified Medical Research Council Dyspnoea Scale

Grade

0 "I only get breathless with strenuous exercise"

1 "I get short of breath when hurrying on the level or walking up a slight hill"

2 "I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level"

3 "I stop for breath after walking about 100 yards or after a few minutes on the level"

4 "I am too breathless to leave the house" or "I am breathless when dressing"

NB: This is the modified MRC scale that uses the same descriptors as the original MRC scale in which the descriptors are numbered 1-5. The modified MRC scale (0-4) is used for calculation of BODE index.

10.4 ADDITIONAL INFORMATION REGARDING IN/EX CRITERIA

10.4.1 Calculation of number of pack years

$$\text{Pack years} = \frac{\text{..... .. .. per day}}{20} \times \text{years of smoking}$$

10.4.2 Laboratory data

Subjects may not enter the observational part of the study without the availability of laboratory results at the actual study site (including pregnancy test).

10.4.3 Body Mass Index

$$\text{BMI} = \text{body weight [kg]} / \text{body height}^2 \text{ [m]}$$

10.4.4 Alpha1-antitrypsin deficiency

Genomic testing of A1ATD will be part of the centralized PGx testing at Visit 1. Inclusion/ stratification of subjects can be based on available test results or on PGx testing at Visit 1.

10.4.5 Definition of ex-smokers

For the purpose of this study, an ex-smoker is defined as an individual (healthy subject or patient with COPD) who has quit smoking for at least 9 months.

10.5 INSTRUCTIONS FOR ASSESSMENTS

Spirometers, D_{LCO} device, body plethysmograph and their use, including daily calibration, must meet American Thoracic Society (ATS)/ European Respiratory Society (ERS) criteria.

10.6 COMPUTATION OF BODE INDEX

Table 10.6.:1 Variables and Point Values Used for the Computation of the Body Mass Index, Degree of Airflow Obstruction and Dyspnea, and Exercise Capacity (BODE) Index [R04-0879]

Variable	**Points on BODE Index**			
	0	1	2	3
FEV_1 (% of predicted)	≥65	50–64	36–49	≤35
Distance walked in 6 min (m)	≥350	250–349	150–249	≤149
MMRC dyspnea scale	0–1	2	3	4
Body-mass index	>21	≤21		

10.7 GLOMERULAR FILTRATION RATE (GFR)

Subjects, who are part of the MRI subset, must meet the MRI specific criteria outlined in Section 3.3.2.2 and 3.3.3.2. GFR must not be older than 14 days from the MRI assessment. Creatinine values are provided by the Central Lab, but not on the day of the blood draw. Note: If the MRI assessment at a visit is earlier than the availability of the creatinine value provided by the central lab, the creatinine value must be assessed locally. GFR can be calculated according to the local procedure.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CSP revision		07 OCTOBER 2015
EudraCT number		n/a
BI Study number		352.2069
BI Investigational Product(s)		n/a
Title of protocol		Observational study in healthy subjects and patients with COPD to assess the relationship between clinical, imaging and biomarker measurements, and progression of emphysema over two years.
To be implemented only after approval of the IRB / IEC / Competent Authorities		✓
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		n/a
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		n/a
Section to be changed	I) II) III) IV) V) VI) VII) VIII) IX) X)	Cover Page, Synopsis and section 3.1.1 Flowchart and footnotes 2.3, 5.9.1.1 3.1 3.2, 5.9 5.1.2 5.4, 5.6, 6.2.2 5.5, 5.6, 6.2.1, 6.2.2 6.1.1.2 10.6
Description of change	I) II) III) IV) V) VI) VII)	Deletion of Coordinating Investigator function A1ATD testing and DNA banking added Correction of blood volumes Clarification of procedures during phone calls Clarification of laboratory sampling Clarification of D_{LCO} assessments Specification of timing of PFT procedure

	VIII) IX) X)	Rearrangement of procedures D_{LCO} and bodyplethysmography Clarification of induced sputum procedure Addition of BODE index computation
Rationale for change	I) II) III) IV) V) VI) VII) VIII) IX) X)	Role change of Coordinating Investigator Clarification of laboratory samples (no addition of new procedures) Correction Inconsistent description Ambiguous description Correction Clarification Correction Inconsistency, omission Clarification

Number of global amendment		2
Date of CSP revision		15 DECEMBER 2015
EudraCT number		n/a
BI Study number		352.2069
BI Investigational Product(s)		n/a
Title of protocol		Observational study in healthy subjects and patients with COPD to assess the relationship between clinical, imaging and biomarker measurements, and progression of emphysema over two years.
To be implemented only after approval of the IRB / IEC / Competent Authorities		✓
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		n/a
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		n/a
Section to be changed	I) II) III) IV)	Cover Page Flowchart footnotes, protocol text (various sections) 3.3.3.1, 3.3.4.1 4.2.1

	V) VI) VII) VIII) IX) X) XI) XII) XIII)	5.2, 5.3 5.4 5.6 5.8 5.8.1.2 6.1.1.2 6.1.1.3 7.3.1.3, 7.3.1.5, 7.4 10.4.5
Description of change	I) II) III) IV) V) VI) VII) VIII) IX) X) XI) XII) XIII)	Correction of number of participating sites Text/word additions and corrections INCL 5: change of threshold value for FEV_1/FVC from LLN to 70% Separate mention of additional medication Detailed description of bronchodilation for imaging assessments and rescheduling Name change of reversibility testing and precision of salbutamol (albuterol) dosing Removal of shutter manoeuver [redacted] Addition of a description for quality check of sputum samples, precision of timing of sputum sample processing Precision of sputum assessment rescheduling Addition of rescheduling rules for imaging assessments Rewording of statistical method, addition of soluble biomarkers to the interim analysis Addition of ex-smoker definition
Rationale for change	I) II) III) IV) V) VI) VII) VIII) IX) X) XI) XII) XIII)	Update Clarifications and specifications Reconciliation Clarification Clarification Clarification Simplification Simplification Precision Precision Clarification Clarification, precision Clarification

Number of global amendment		3

Date of CSP revision		18 APRIL 2017
EudraCT number		n/a
BI Study number		352.2069
BI Investigational Product(s)		n/a
Title of protocol		Observational study in healthy subjects and patients with COPD to assess the relationship between clinical, imaging and biomarker measurements, and progression of emphysema over two years.
To be implemented only after approval of the IRB / IEC / Competent Authorities		yes
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		n/a
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		n/a
Section to be changed	I) II) III) VI) V) VI) VII) VIII) IX) X) XI) XII) XIII) XIV) XV) XVI) XVII)	Cover Page Synopsis Flowchart and footnotes Abbreviations 2.1, 2.2, 2.3 3.1, 3.2 3.3 4 5.3 5.4 – 5.7 5.8 5.9 6 7 8 9 10
Description of change	I) II) III) IV)	Addition of study name, other formal changes Formal changes related to changes in other sections Changes to the study design Addition of new abbreviations

	V)	Formal changes
	VI)	Change related to sputum procedure, addition of recruitment strategy
	VII)	Update of subject numbers, changes to INCL/EXCL
	VIII)	Minor additions and corrections
	IX)	[redacted]
	X)	Minor changes
	XI)	[redacted]
	XII)	Addition of creatinine to safety panel, clarification regarding pregnancy testing, adaptation for Japan, minor changes and corrections
	XIII)	Update of rescheduling rules for sputum assessment, extension of screening period in case of COPD exacerbations or RTI, new rescheduling rule for administrative reason, removal of pre DLCO and pre bodyplethysmography, new re-screening rule regarding previously screen-failed subjects, clarification regarding re-screening, minor changes and clarifications
	XIV)	Clarification regarding analysis, update of interim analysis, minor text changes
	XV)	Addition of text for Japan, minor changes
	XVI)	New R number for JRS
	XVII)	Addition of Section 10.7 GFR
Rationale for change	I)	Amendment
	II)	Amendment
	III)	Simplification of study design and clarifications
	IV)	Amendment
	V)	Alignment with other protocol sections
	VI)	Amendment
	VII)	Clarification, Facilitation of recruitment
	VIII)	Clarification
	IX)	Amendment, Clarification
	X)	Amendment, Clarification
	XI)	Amendment, Clarification
	XII)	Amendment, Clarification
	XIII)	Amendment, Clarification
	XIV)	Amendment, Clarification
	XV)	Amendment, Clarification

	XVI) XVII)	Amendment Clarification
		As there was a mistake in the header (wrong document date) which was corrected, there are two versions 4.0 in the system. No content changed.

Number of global amendment		4
Date of CSP revision		29 MAY 2018
EudraCT number		n/a
BI Study number		352.2069
BI Investigational Product(s)		n/a
Title of protocol		Observational study in healthy subjects and patients with COPD to assess the relationship between clinical, imaging and biomarker measurements, and progression of emphysema over three years.
To be implemented only after approval of the IRB / IEC / Competent Authorities		yes
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		n/a
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		n/a
Section to be changed	I) II) III) IV) V) VI) VII) VIII) IX) X) XI) XII)	Cover Page Synopsis Flowchart and footnotes Abbreviations 2.1, 2.2, 2.3 3.1, 3.2 5 6 7 8 9 2.3, 5.8
Description of change	I)-	Adaptations for new 3 year observational

	IX), XI) X) XII)	timepoint Specification of Investigator responsibilities during informed consent procedure Revision of blood sample volumes
Rationale for change	I)- IX), XI) X) XII)	Amendment Clarification to meet country requirements Correction

Number of global amendment		5
Date of CSP revision		24 FEB 2020
EudraCT number		n/a
BI Study number		352.2069
BI Investigational Product(s)		n/a
Title of protocol		Observational study in healthy subjects and patients with COPD to assess the relationship between clinical, imaging and biomarker measurements, and progression of emphysema over three years [FOOTPRINTS®].
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed	I) II) III) IV)	Cover Page Synopsis Section 5.3 and 7.4 Section 5.8
Description of change	I) II) III) IV)	Formal Changes Formal Changes [redacted] Changed wording regarding collection and analysis of biomarkers
Rationale for change	I) II) III) IV)	Amendment Amendment [redacted] Clarification