NOVARTIS

Clinical Development

QVA149 (Indacaterol maleate / Glycopyrronium bromide)

Clinical Trial Protocol CQVA149ADE05 / NCT02442206

A randomized, double-blinded, single-center, placebo controlled, cross-over study to assess the effect of QVA149 (indacaterol maleate / glycopyrronium bromide) on cardiac function in patients with chronic obstructive pulmonary disease (COPD)

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List of abbreviations

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATS/ERS	American Thoracic Society/European Respiratory Society
BDI	Baseline Dyspnea Index
BTPS	normal body temperature (37°C), ambient pressure, saturated with water vapor
CAT	COPD assessment test
eCRF	electronic Case Report/Record Form
CCV	Cardio- and Cerebro-Vascular events
CPO	Country Pharma Organization
CRO	Contract Research Organization
CT	Computed tomography
DS&E	Drug Safety & Epidemiology
ECG	Electrocardiogram
EDC	Electronic Data Capture
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
FDC	Fixed-dose combination
FEV_1	Forced Expiratory Volume in 1 second
FRC	Functional Residual Capacity
FVC	Forced Vital Capacity
IC	Inspiratory capacity
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IOS	Impulse Oscillometry
i.v.	intravenous
IRB	Institutional Review Board
LABA	Long acting beta 2 agonist
LAMA	Long acting muscarinic antagonist

LV	Left ventricular
mMRC	Modified Medical Research Council mMRC Dyspnea Scale
MRI	Magnetic Resonance Imaging
o.d.	once a day
p.o.	oral
PP	per protocol
PSW	Premature Study Withdrawal
RVol	Residual Volume
RV	Right ventricular
SABA	Short acting beta2 agonist
SAE	Serious adverse event
SAMA	Short acting muscarinic antagonist
SDDPI	Single Dose Dry Powder Inhaler
SmPC	Summary of Product Characteristics
sRAW	Specific Airway Resistance
SUSAR	Suspected Unexpected Serious Adverse Reactions
TD	Study treatment discontinuation
TDI	Transitional Dyspnea Index
TLC	Total lung capacity

Glossary of terms

Assessment	A procedure used to generate data required by the study
Control drug	Drugs(s) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch	The planned stage of the subjects' participation in the study. Each epoch serves a purpose in the study as a whole. Typical epochs are: determination of subject eligibility, wash-out of previous treatments, exposure of subject to treatment or to follow-up on subjects after treatment has ended.
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug" or "investigational medicinal product."
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This *includes* any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally *does not include* other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage
Medication number	A unique identifier on the label of each investigational/study drug package in studies that dispense medication using an IRT system
Subject Number	A number assigned to each patient who enrolls into the study
Part	A subdivision of a single protocol into major design components. These parts often are independent of each other and have different populations or objectives. For example, a single dose design, a multiple dose design that are combined into one protocol, or the same design with different patient populations in each part.
Period	A subdivision of a cross-over study
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all investigational/study treatment administration and all assessments (including follow-up)
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study/investigational treatment was discontinued whichever is later
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), active drug run-ins or background therapy
Study/investigational treatment discontinuation	Point/time when patient permanently stops taking study/investigational treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points

Amendment 3

Amendment rationale

The protocol is being amended to implement the possibility of re-screening patients that failed the screening phase (before Visit 4) due to increased blood pressure (mean sitting systolic blood pressure >160 mmHg and/or mean sitting diastolic blood pressure > 90 mmHg as per exclusion criterion 7). For those patients where the antihypertensive therapy is being initiated or intensified and leads to a controlled disease status a re-screening can be considered. Re-screening is permitted to occur at V2, 4 weeks after change of antihypertensive medication. This scenario is described in Section 4.2.

Changes to specific sections of the protocol are shown by track changes in the track changes version of the protocol, ~~using strike-through red font~~ for deletions and red underlined for insertions.

The changes in this amended protocol are substantial. An approval of this amended protocol by the Institutional Review Board (IRBs/Independent Ethics Committee (IECs) and Health Authorities prior to implementation is required.

Summary of previous amendments

Amendment 2 (dated July 14th, 2015)

Amendment rationale

The protocol is being amended to additionally implement fluorine-enhanced (^{19}F) MRI-technique as an optional measurement to assess regional pulmonary ventilation during steady-state breathing. This method is complementary to the currently implemented MRI and allows getting further insights into the functional pulmonary effects of a dual bronchodilator therapy. This might also help to better understand the cardio-pulmonary interaction. Hence, an additional explorative objective is included on page 14 and Section 2.3, the assessment schedule is described in Section 6 (Table 6-1) and the method and rational is explained in Section 6.4.1.

Additional changes to the protocol

A full list of parameters that will be captured and documented in the eCRF is attached to this amended protocol:

Appendix 8: MRI parameters

Appendix 9: Echocardiography parameters

Section 5.5.1: clarification was added that Visit numbers in the eCRF are suffixed by “a” if it is passed for the second time due to re-screening of the patient.

Changes to specific sections of the protocol are shown by track changes in the track changes version of the protocol, ~~using strike through red font~~ for deletions and red underlined for insertions.

The changes in this amended protocol are substantial. An approval of this amended protocol by the Institutional Review Board (IRBs/Independent Ethics Committee (IECs) and Health Authorities prior to implementation is required.

Amendment 1 (dated May 11th, 2014)

Amendment rationale

The protocol is being amended to primarily include echocardiographic measures as additional explorative objectives. Echocardiography is widely used and accepted as a clinical method of choice to determine ventricular diastolic function and thus serves as a complementary method to MRI in this mechanistic study to comprehensively evaluate the effect of dual bronchodilation on cardiac function. Additional explorative objectives are included on page 13 and Section 2.3, the assessment schedule is described in Section 3.1. and 6 (Table 6-1, 6-2) and the method and rational is explained in Section 6.4.5 and 6.4.10, respectively.

In addition, to account for blood pressure changes as potential con-founder of ventricular function, blood pressure will be measured 4 times during MRI and mean will be considered during data analysis (see Section 6.4.1 and 9.4.4).

Some changes to the exclusion criteria on page 12 and in Section 4.2 were made:

- to allow patients with stents to be enrolled in the study as stent material does not interfere with MRI and the indication for stent implantation does not *per se* influence the outcome of the study unless significant ischemic cardiac changes are present. For these cases exclusion criterion #4 will be applied.
- to exclude patients with uncontrolled hypertension from the study
- to allow patients with a history of hypersensitivity to i.v. contrast medium to participate in the study. In case patients suffer from such a hypersensitivity, the last MRI protocol sequence that require i.v. contrast medium will not be performed (see also Section 6.4.1).

Additional changes to the protocol

Section 3.1, 6 (Table 6-1) and 6.5.3: height will be determined and documented at Visit 1 instead of Visit 3 as this information is crucial to determine FEV 1 % predicted at Screening.

Section 3.1, 6 (Table 6-1) and 6.5.3: weight will additionally be measured at Visit 1 to allow calculation of the BMI.

Section 3.1, 6 (Table 6-1) and 6.2: bodyplethysmography will also be performed after inhalation of salbutamol at Visit 3 to better characterize patients.

Section 3.1 and 6 (Table 6-1): inclusion of device and inhalation technique training at Visit 4.

Section 4.2: the start to re-enter the study after allowed re-screening is defined as Visit 2.

Section 5.5.4: the time interval for taking study medication at Visits 4 and 6 is prolonged due to the inclusion of echocardiography as additional efficacy measure.

Section 5.5.9: COPD Exacerbation definition and reporting is inserted.

Section 6 (Table 6-1) and 6.5.4: the time-point at which hematology and blood chemistry will be performed during the study is described more precisely.

Section 6.4.1: additional changes to the MRI protocol are made to optimize measurements.

Section 6.5.2: a description of how to take mean sitting blood pressure at Visit 3 is included.

In addition some minor inconsistencies within the text or typos are corrected.

The changes in this amended protocol are substantial. An approval of this amended protocol by the Institutional Review Board (IRBs/Independent Ethics Committee (IECs) and Health Authorities prior to implementation is required.

Protocol synopsis

Protocol number	CQVA149ADE05
Title	A randomized, double-blinded, single-center, placebo controlled, cross-over study to assess the effect of QVA149 (indacaterol maleate/glycopyrronium bromide) on cardiac function in patients with chronic obstructive pulmonary disease (COPD)
Brief title	Effect of QVA149 (indacaterol maleate/glycopyrronium bromide) on cardiac function in COPD patients
Sponsor and Clinical Phase	Novartis 4
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of the study is to evaluate the effect of dual bronchodilation with QVA149 on cardiac and lung function parameters in hyperinflated COPD patients.
Primary Objective(s) and Key Secondary Objective	To determine the effect of once-daily QVA149 compared with placebo on left ventricular enddiastolic volume as measured by MRI after 2 weeks of treatment.
Secondary Objectives	Objective 1: To evaluate the effects of QVA149 compared to placebo on lung function parameters as measured by forced spirometry 75 min post-dose (FEV_1 and FVC) and bodyplethysmography 60 min post-dose (inspiratory capacity (IC), total lung capacity (TLC), residual volume (RVol) and specific airway resistance (sRaw), functional residual capacity (FRC)) measured after 14 days of treatment Objective 2: To evaluate right and left ventricular ejection fraction measured by MRI after 14 days of treatment Objective 3: To evaluate right and left ventricular endsystolic volumes measured by MRI after 14 days of treatment Objective 4: To evaluate right ventricular enddiastolic volume measured by MRI after 14 days of treatment Objective 5: To evaluate cardiac output measured by MRI after 14 days of treatment
Study design	This is a randomized, double-blinded, single-center, placebo controlled, cross-over study to assess the effect of a two weeks therapy each with QVA149 versus placebo on cardiac function.

Population	The study population will consist of 62 hyperinflated adults age 40 years and older, with a residual volume (RVol) >135% predicted, a smoking history of at least 10 pack years and a clinical diagnosis of COPD.
Inclusion criteria	1. Male or female subjects, aged ≥ 40 years 2. Patients with airflow limitation indicated by a post-bronchodilator FEV_1 <80% of the predicted normal value and a post-bronchodilator $FEV_1/FVC<0.7$ at Visit 3. Post-bronchodilator refers to within 10-15 min of inhalation of 400µg (4x100 µg) of salbutamol. 3. Current or ex-smokers who have a smoking history of at least 10 pack years. (Ten pack-years are defined as 20 cigarettes a day for 10 years, or 10 cigarettes a day for 20 years etc.) 4. Able and willing to give written informed consent 5. Hyperinflated patients with RVol>135% predicted as measured at Visit 3
Exclusion criteria	1. Patients on LABA or LAMA treatment at Visit 1. Those patients may enter the study after LABA or LAMA withdrawal during a 14-day wash-out period before Visit 3. 2. History of one COPD exacerbation that required treatment with antibiotics, systemic steroids (oral or intravenous) or hospitalization 3 months prior to Visit 2. 3. More than one COPD exacerbation that required treatment with antibiotics, systemic steroids (oral or intravenous) or hospitalization within 6 months prior to Visit 2. 4. Patients who have clinically significant cardiovascular abnormalities, which could interfere with the assessment of the study treatment (such as but not limited to cardiac arrhythmias, heart failure with left ventricular ejection fraction <40% as determined by MRI scan at Visit 4, unstable ischemic heart disease, NYHA Class III/IV left ventricular failure, history of myocardial infarction 6 months prior to Visit 2) 5. Patients with a known history or current atrial fibrillation to be confirmed by ECG. 6. Patients with pacemaker or bypass 7. Patients with a mean sitting systolic blood pressure >160 mmHg and/or mean sitting diastolic blood pressure > 90 mmHg at Visit 3

	8. Patients whose QTcF measured at Visit 3 is >450 ms for males and >470 ms for females
Investigational and reference therapy	• QVA149 capsules for inhalation • Placebo to QVA149 capsules for inhalation
Efficacy assessments	• Right and left ventricular enddiastolic volume • Right and left ventricular endsystolic volume • Right and left ventricular ejection fraction • Cardiac output • Lung function measured by spirometry and bodyplethysmography
Safety assessments	none
Other assessments	• Average physical activity level (as average number of steps at a time/day) • Regional lung ventilation and perfusion • Pulmonary parenchymal blood flow • Biventricular cardiac mass • Impulse oscillometry (IOS) • Health status (CAT) • Dyspnea (BDI/TDI) • Left and right ventricular diastolic function • Left and right ventricular systolic function • Pulmonary arterial pressures • Regional lung ^{19}F gas wash-out time
Data analysis	The primary and secondary objectives will be analyzed by comparing treatments in an analysis of variance (ANOVA) model with the factors center, period, patient within center and treatment. Raw- as well as adjusted (LS-) means will be provided as point estimates for the pair wise treatment contrast. A two-sided, 95% confidence interval and a p-value for the null hypothesis of no treatment difference will be calculated. Additionally unadjusted descriptive statistics (mean, SD, range) will be provided for each treatment and for the treatment contrast.
Key words	QVA149, cardiac function, ventricular enddiastolic volume, hyperinflated COPD patients

1 Introduction

1.1 Background

Heart disease and chronic obstructive pulmonary disease (COPD) are leading causes of mortality that often co-exist: clinical or subclinical cardiovascular disease is increased in COPD patients, independently of risk factors shared by the two diseases [1].

In COPD patients, hyperinflation is a major lung functional abnormality, which is related to exercise limitations and mortality, with a higher RVol and a lower IC/TLC as independent predictors of all-cause and respiratory mortality in COPD [2, 3].

Hyperinflation can result from increase in airways resistance (e.g. airway narrowing), lung compliance (e.g., emphysema), or both [4]. FRC and TLC are thought to be more sensitive to changes in lung elastic recoil from emphysema [4, 5], whereas RVol is considered a better metric of hyperinflation with preserved lung elastic recoil but with airway narrowing [1]. As RVol is also the first lung volume to increase in COPD and is more sensitive to changes in the degree of airways obstruction than TLC, it may serve as an indicator for hyperinflation [6] and as an inclusion criterion for clinical trials.

In a large, population-based cohort, that was free of clinical cardiovascular disease, it was shown, that airflow obstruction as measured by spirometry and extent of emphysema as measured by CT are inversely related to left ventricular end-diastolic volumes, stroke volume and cardiac output. Relationships were linear across a spectrum from normal lung structure and function to moderately severe airflow obstruction and emphysema. Several potential mechanisms contribute to impaired left ventricular filling in COPD patients. Alveolar hypoxia has been described to cause pulmonary-artery vasoconstriction and vascular remodeling, leading to increased pulmonary vascular resistance and impaired left ventricular filling in COPD patients with severe airway obstruction. Hyperinflation is another mechanism in severe COPD, which can cause intrathoracic pressure to exceed venous pressure, with reductions in the blood volumes of both ventricles [7].

Smith et al. postulated also, that the intrathoracic pressure impairs the venous return to the right heart, resulting in underfilling of the pulmonary veins and leading to reduced pulmonary vein dimensions in COPD patients. Thus, impaired left ventricular filling may be predominantly due to reduced left ventricular preload from upstream pulmonary causes [8].

Jörgensen et al. described this as intrathoracic hypovolemia which decreases biventricular preload in patients with hyperinflated lungs and severe emphysema [9].

Consistent with this framework, Watz et al. described a significantly impaired left ventricular diastolic filling pattern and an impaired global right ventricular function in hyperinflated patients, characterized by IC/TLC<=0.25. This supports the concept of reduced preload condition in patients with COPD, as left ventricular isovolumetric relaxation time was unaffected by hyperinflation, indicating no relationship to left ventricular distensibility (i.e. stiff myocardium) [10].

A very recent study showed that hyperinflated patients – defined as TLC>110% predicted – have lower cardiac output, LV end diastolic volume and RV end diastolic volume, whereas the ejection fraction remained unchanged [11].

Until now, there is only very limited data available on the effect of bronchodilators, leading to reduced hyperinflation, on cardiac function. It has been shown, that treatment with tiotropium improved pulmonary arterial systolic pressure and E/e' ratio measured with tissue Doppler imaging. This suggests attenuation of air trapping, being associated with an improvement of right ventricular overload and left ventricular diastolic dysfunction [12].

Ultibro® (indacaterol/glycopyrronium) is an inhaled, once-daily dual bronchodilator containing a fixed dose combination of the long-acting β2-agonist indacaterol and the long acting muscarinic antagonist glycopyrronium. It is prescribed for the treatment of chronic obstructive pulmonary disease (COPD).

In phase III studies, Ultibro® significantly improved FEV_1 compared to indacaterol, glycopyrronium or tiotropium alone. These improvements in lung function, which were rapid in onset and maintained during long-term treatment, were generally associated with significant improvements not only in dyspnea, health status, COPD exacerbation risk, patient symptoms, and rescue medication use [13], but also in reducing static hyperinflation as measured by static inspiratory capacity and residual volume [14].
The hypothesis of this study is that Ultibro® potentially has a positive effect on cardiac function by decreasing airflow obstruction. This might result in an improvement of hyperinflation, altered pulmonary parenchymal blood flow, which is associated with an improved LV enddiastolic volume. This study is designed to evaluate the effect of a 2-week-treatment with Ultibro® on cardiac function evaluated by magnetic resonance imaging (MRI) [15; 16].

1.2 Purpose

The purpose of this mechanistic study is to determine whether QVA149 110/50 µg o.d. (compared to placebo) has a positive effect on cardiac function by decreasing airflow obstruction in hyperinflated COPD patients. Completion of the study will help to understand the effects of dual bronchodilation by QVA149 on cardiovascular parameters, which are impaired in COPD patients and are therefore co-existing risk factors.

2 Study objectives

2.1 Primary and key secondary objective

To determine the effect of once-daily QVA149 (110/50 µg o.d.) compared with placebo on left ventricular enddiastolic volume as measured by MRI after 2 weeks of treatment in hyperinflated COPD patients.

2.2 Secondary objectives

- To evaluate the effects of QVA149 compared to placebo on lung function parameters after 14 days of treatment, as measured by:

- Forced spirometry (75 min post-dose)
  - FEV_1 and FVC
- Bodyplethysmography (60 min post-dose):
  - inspiratory capacity (IC)
  - total lung capacity (TLC)
  - residual volume (RVol)
  - specific airway resistance (sRaw)
  - functional residual capacity (FRC)

To evaluate the effects of QVA149 compared to placebo on cardiac parameters, as measured by MRI after 14 days of treatment:

- right and left ventricular ejection fraction
- right and left ventricular endsystolic volumes
- right ventricular enddiastolic volume
- cardiac output

2.3 Exploratory objectives

To explore the change in:

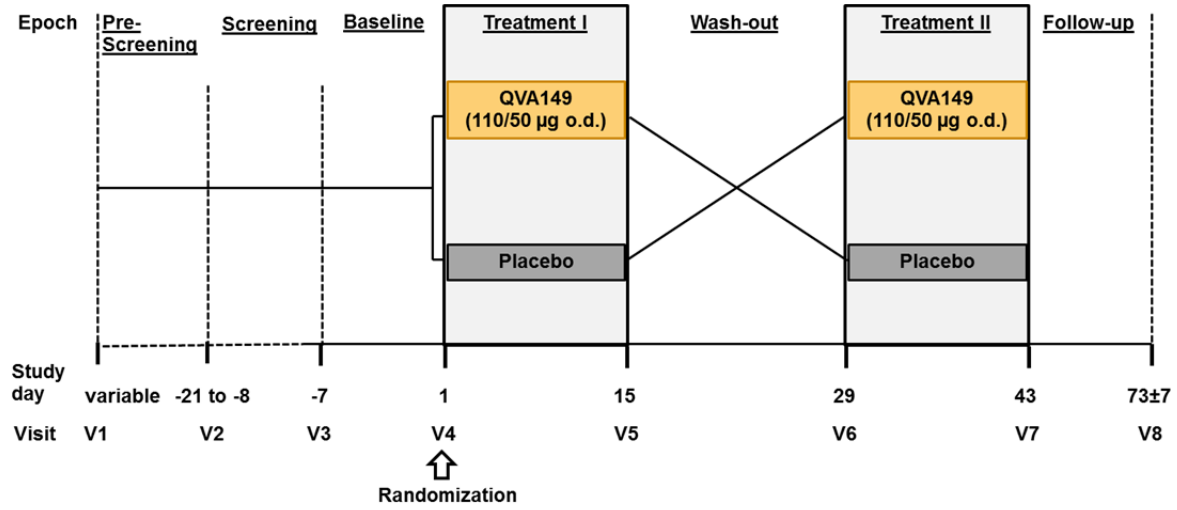
- health status (CAT questionnaire)
- dyspnea (BDI/TDI questionnaire)
- average physical activity level (as average number of steps at a time/day)
- biventricular cardiac mass, measured by MRI
- pulmonary parenchymal blood flow measured by MRI
- regional lung ventilation and perfusion measures (OTF, oxygen transfer function) using oxygen-enhanced T1 mapping MRI
- airway function using impulse oscillometry (IOS)
- left and right ventricular diastolic function measured by echocardiography
- left and right ventricular systolic function measured by echocardiography
- pulmonary arterial pressures measured by echocardiography
- regional lung ^{19}F gas wash-out time measured by MRI (as optional measurement in a subgroup of patients)

3 Investigational plan

3.1 Study design

This will be a randomized, double-blinded, placebo controlled, single-center, two period crossover study to compare the effects of a 2 week therapy each with QVA149 versus placebo. The study duration will be about 13 weeks (see Figure 3-1 Study outline). The study consists of six epochs: a variable Pre-Screening epoch, a Screening epoch (depending on washout required for prior medications), a Baseline epoch necessary to collect baseline data, two cross-over treatment periods (Treatment I and II) separated by a wash-out epoch and a follow-up epoch.

Figure 3-1 Study outline



Visit 1 (Pre-Screening)

At Visit 1, the informed consent will be obtained to assess whether patients might be eligible for this study. Current COPD medications, inclusion/exclusion criteria, COPD exacerbation history as well as smoking history will be reviewed. Patient demographics and medical history including history of cardiovascular (CV) risk factors will be assessed. Forced spirometry will be performed after intake of salbutamol to assess reversibility. The interval between Visit 1 and Visit 2 is variable and can take up to several months, depending on free MRI capacity slots.

Visit 2 (Screening)

At Visit 2 current COPD medications, inclusion/exclusion criteria as well as COPD exacerbation history will be reviewed. Medical history including history of cardiovascular (CV) risk factors will be assessed and if necessary, arrangements will be made to adjust prohibited COPD therapy (see Table 5-2). Patients on fixed-dose combination of long-acting beta2 agonists/inhaled corticosteroid (LABA/ICS) therapy must be switched to the equivalent dose of ICS monotherapy and salbutamol as rescue medication. This switch and wash-out of prior medication period has to be finished until Visit 3. However, during the treatment period

salbutamol is only to be applied for rescue ("when required") use. The interval between Visit 2 and Visit 3 is an individual run-in period (depending on the required wash-out time of the pre-medication), used to assess eligibility of patients for the study. Depending on the current medication the run-in period can be reduced to the wash-out period specified in Table 5-1 and Table 5-2.

Visit 2 is optional (not mandatory) and can be omitted if the patient can already be washed-out at Visit 1 and if subsequent MRI capacities are available. If Visit 2 is omitted, rescue medication should already be dispensed at Visit 1. All inclusion and exclusion criteria referring to Visit 2 are then related to Visit 1.

Visit 3 (Baseline)

Patients will commence a Baseline period for 7 days. The modified Medical Research Council (mMRC) as well as the COPD Assessment Test (CAT) will be collected. Patients will be re-assessed for the inclusion/exclusion criteria. Physical examination, weight, vital signs, ECG and blood analysis will be collected and a urine pregnancy test applied for women with child-bearing potential. Bodyplethysmography (before and after salbutamol inhalation) and impulse oscillometry will be performed to collect lung function data. Forced spirometry will be measured before and after salbutamol inhalation to assess reversibility. The Actibelt will be distributed to assess baseline physical activity (for 1 week) of patients after the wash-out period.

Visit 4 (Randomization – Beginning of Treatment I)

The questionnaires CAT and BDI will be completed prior to any other study assessment. The Actibelt will be returned and data will be transferred. ECG, vital signs and lung function measurements (impulse oscillometry, bodyplethysmography and spirometry) will be collected. Patients will undergo MRI investigation and inclusion/exclusion criteria will be re-assessed. Echocardiography will be performed. Patients that are eligible for the study will first be trained on the device and correct inhalation technique and then be randomized to either receive QVA149 in treatment period I followed by placebo in treatment period II or the same treatment in reverse order in an allocation ratio of 1:1. Patients will again receive the Actibelt and will be asked to wear it to measure physical activity throughout the entire treatment period I.

Patients must be instructed NOT to take their study medication at home on the day of the site visit as this will be administered at the site and – unless absolutely necessary – NOT to take rescue salbutamol within 6 hours of the start of each visit.

Visit 5 (End of Treatment I)

All questionnaires will be completed first. The Actibelt will be returned and data will be transferred. Vital signs, blood analysis and lung function measurements (impulse oscillometry, bodyplethysmography and spirometry) will be collected. Patients will undergo MRI and echocardiography investigations and receive their Actibelt for use during the wash-out period.

Visit 6 (Beginning of Treatment II)

All questionnaires will be completed first. The Actibelt will be returned and data will be transferred. Comparable to beginning of treatment I, ECG, vital signs, lung function measurements, MRI and echocardiography will be performed. In the second treatment period, all subjects will receive the other treatment (i.e. patients receiving QVA149 in treatment period I will receive placebo in treatment period II and patients receiving placebo in treatment period I will receive QVA149 in treatment period II). Patients will be asked to wear the Actibelt throughout the entire treatment period II.

Visit 7 (End of Treatment II)

Questionnaires will be completed and the Actibelt returned for data transfer. Physical examination, vital signs, blood analysis and lung function measurements (impulse oscillometry, bodyplethysmography and spirometry) will be collected and a urine pregnancy test applied for women with child-bearing potential. Patients have to return unused medication and will undergo final MRI and echocardiography investigations. At the time of study completion or early termination, all patients will be placed on the appropriate COPD treatment as prescribed by the investigator.

Visit 8 (Safety-Follow-up telephone call, 30 days after end of study)

All adverse events with a date of onset up to 30 days following the last dose of study drug must be reported.

The total time on study for each patient is (maximal 21 days screening/baseline) + (14 days treatment x 2=28 days) + (14 days washout) + safety follow-up (30 days) = 93 days plus the variable pre-screening period, where patients are maintained on their prior medication.

Drop-out Visit (Patient who discontinue the study)

Patient discontinuing the study shall perform all assessments as in Visit 7 marked with an asterix in the assessment schedule.

3.2 Rationale of study design

A randomized, blinded, cross-over design (rather than a parallel group design) was chosen because within-patient variability for the parameters assessed in this trial is expected to be less than between-patient variability thus allowing greater precision to be achieved whilst exposing a smaller number of patients to trial treatment and assessments. All measured treatment effects are expected to be completely reversible, therefore a cross-over design is a feasible alternative.

A washout period of 14 days between two treatment periods seems to be sufficient to avoid any “carry-over” effects and to restore potential structural changes of the heart.

3.3 Rationale of dose/regimen, route of administration and duration of treatment

The dose, dose regimen and route of administration of QVA149 (Ultibro®) is in accordance with product labeling. The selection of QVA149 dose (110/50 µg once daily) was based on data from the QAB149 and NVA237 monotherapy programs. Those programs identified the doses as 150 µg once daily for QAB149 and 50 µg once daily for NVA237. However, in formulating the QVA149 combination product, an increase in fine particle (respirable) fraction was observed for the QAB149 component (compared with the monotherapy). As a consequence, to ensure that the fine particle dose of QAB149 delivered to the lung from the combination matches that delivered from the monotherapy, the dose for the QAB149 component of QVA149 has been reduced to 110 µg.

A treatment duration of 2 weeks (14 days) was selected as the minimum required to detect functional changes in cardiac activity that are due to a decrease of intrathoracic pressure as a result of bronchodilation resulting in reduced hyperinflation.

3.4 Rationale for choice of comparator

The use of placebo control is justifiable, as it is unknown whether the dual bronchodilator QVA149 will show an effect on cardiovascular parameters, such as right and left ventricular enddiastolic volumes. It is important to note that the term “placebo” used in the context of this study refers to a placebo control that will be added to the well-established COPD background therapy with salbutamol as rescue medication and inhaled corticosteroid treatment (if applicable).

3.5 Purpose and timing of interim analyses/design adaptations

Not applicable

3.6 Risks and benefits

The risk to subjects in this trial will be minimized by compliance with all of the eligibility criteria determined as inclusion/exclusion criteria and by close clinical monitoring. Although altering the current COPD medication regimen during the screening period at the beginning of the study carries an inherent risk of a decline in lung function, this period is short. Patients will be exposed to a placebo period and a washout period between treatments. Providing the patients with rescue medication for use as needed throughout study and permitting them to continue on ICS treatment throughout the study, mitigates these risks.

Patients will be monitored closely by the investigator to ensure that the patients’ COPD remains adequately controlled. If patients experience a COPD exacerbation during the treatment period they will be treated as deemed appropriate by the investigator and discontinued from the study.

Repetitive lung function measurement maneuvers during the study can lead to cough, shortness of breath, dizziness, or exhaustion. Since the patient only carries out forced maneuvers during clinic visits (not at home), these are performed under medical supervision

to ensure availability of immediate aid if required. The assessments are infrequent, small in number, and part of the regular medical assessments of this patient population.

The risks of side effects from the study medication are those known for the compound QVA149. The most frequently reported side effects to date are upper respiratory tract infection, nasopharyngitis, cough, oropharyngeal pain and headache. Further information can be obtained from the QVA149 Investigator's Brochure.

The potential benefit for the patient lies in a thorough medical evaluation of the patients' disease and close clinical monitoring for the duration of the study.

4 Population

The study population will consist of 62 adult males and females aged 40 years and older, with a clinical diagnosis of COPD (GOLD 2014) and a smoking history of at least 10 pack years. It is anticipated that approximately 400 patients will need to be pre-screened in order to randomize 62 patients into 2 treatment sequences of the study with a randomization ration of 1:1. Drop-outs will not be replaced.

4.1 Inclusion criteria

Patients eligible for inclusion in this study have to fulfill **all** of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Male or female subjects, aged ≥ 40 years, giving written Informed Consent and who are willing and capable to comply with all study procedures.
3. Patients with stable COPD according to the current GOLD guidelines (GOLD 2014).
4. Patients with airflow limitation indicated by a post-bronchodilator FEV1 <80% of the predicted normal value and a post-bronchodilator FEV1/FC<0.7 at Visit 3. Post-bronchodilator refers to within 10-15 min after inhalation of 400 µg (4x100 µg) of salbutamol.
5. Current or ex-smokers who have a smoking history of at least 10 pack years. (Ten pack-years are defined as 20 cigarettes a day for 10 years, or 10 cigarettes a day for 20 years etc.)
6. Hyperinflated patients with RVol>135% predicted as measured at Visit 3, before intake of salbutamol.

4.2 Exclusion criteria

Patients fulfilling **any** of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

1. Patients with conditions contraindicated for treatment with, or having a history of reactions/hypersensitivity to any of the following inhaled drugs, drugs of a similar class or any component thereof
   - anticholinergics
   - long and short acting beta-2 agonists
   - sympathomimetic amines
   - lactose or any of the other excipients
2. Patients with a history of long QT syndrome or whose QTcF (Fredericia method) measured at Visit 3 is prolonged (>450 ms for males and >470 ms for females). These patients should not be re-screened.
3. Patients who have a clinically significant abnormality on the ECG at Visit 3, who in the judgment of the investigator would be at potential risk if enrolled into the study. These patients should not be re-screened.
4. Patients who have clinically significant cardiovascular abnormalities, which could interfere with the assessment of the study treatment (such as but not limited to cardiac arrhythmias, heart failure with left ventricular ejection fraction < 40 % as determined by MRI scan at Visit 4, unstable ischemic heart disease, NYHA Class III/IV left ventricular failure, history of myocardial infarction 6 months prior to Visit 2)
5. Patients with a known history or current atrial fibrillation to be confirmed by ECG at Visit 3.
6. Patients with pacemaker or bypass.
7. Patients with a mean sitting systolic blood pressure >160 mmHg and/or mean sitting diastolic blood pressure > 90 mmHg at Visit 3. These patients will be permitted to be re-screened after having achieved controlled disease status following initiation or intensification of antihypertensive therapy. Re-screening can start at Visit 2, 4 weeks after change of antihypertensive medication.
8. Past or present disease, which as judged by the investigator, may affect the outcome of this study. These diseases include, but are not limited to history of hepatic disease, renal disease, hematological disease, neurological and psychiatric disease, endocrine disease or pulmonary disease other than COPD (including but not confined to tuberculosis, bronchiectasis, cystic fibrosis, pulmonary hypertension, sarcoidosis, interstitial lung disease or lung fibrosis).
9. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
10. Patients with narrow-angle glaucoma, symptomatic benign prostatic hyperplasia or bladder-neck obstruction or severe renal impairment (GFR<30 mL/min/1.73 m^2) including those with end-stage renal disease requiring dialysis or urinary retention. Benign Prostatic Hyperplasia (BPH) patients who are stable on treatment can be considered.
11. Patients with Type I or uncontrolled Type II diabetes.
12. Patients with active/ clinical history of asthma.

13. Patients unable to undergo MRI scans, including claustrophobia or presence of any metal objects within the patient, preventing from MRI scan (e.g. pacemaker, aneurysm clips). A separate MRI patient informed consent form including MRI safety will be signed by the patient before each MRI exam.
14. History of lower respiratory tract infection within four weeks prior to Visit 2 and between Visit 2 and Visit 4. These patients will not be eligible, but will be permitted to be re-screened 4 weeks after the resolution of the respiratory tract infection and can re-start at Visit 2.
15. History of one COPD exacerbation that required treatment with antibiotics, systemic steroids (oral or intravenous) or hospitalization within 3 months prior to Visit 2.
16. More than one COPD exacerbation that required treatment with antibiotics, systemic steroids (oral or intravenous) or hospitalization within 6 months prior Visit 2.
17. Patients who develop a COPD exacerbation between Visit 2 and Visit 4 will not be eligible but will be permitted to be re-screened after a minimum of 3 months after the resolution of the COPD exacerbation and can re-start at Visit 2.
18. Patients requiring long term oxygen therapy on a daily basis for chronic hypoxemia.
19. Patients with active pulmonary tuberculosis, unless confirmed by imaging in the last year to be no longer active.
20. Patients with pulmonary lobectomy or lung volume reduction surgery or lung transplantation.
21. Patients with a diagnosis of alpha 1 anti-trypsin deficiency.
22. Patients with a body mass index (BMI) of more than 40 kg/m^2.
23. Patients participating in or planning to participate in the active phase of a supervised pulmonary rehabilitation program during the study
24. Patients who are, in the opinion of the investigator known to be unreliable or non-compliant.
25. Relevant history of drug or alcohol abuse as judged by the investigator.
26. Suspected inability to understand the protocol requirements, instructions and study-related restrictions, the nature, scope, and possible consequences of the study
27. Use of other investigational drug (approved or unapproved) at the time of enrollment, or within 30 days or 5 half-lives of Visit 1, whichever is longer.
28. Patients receiving any medications in the classes listed in Table 5-1 and Table 5-2.
29. Patients receiving medications in the classes listed in Table 5-3 should be excluded unless the medication has been stable for the specified period and the stated conditions have been met.
30. Women who are pregnant or breast feeding (pregnancy defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 5mIU/ml)).
31. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective contraception (Pearl Index <1*) during

the study and up to at least 4 weeks after the end of treatment. **UNLESS** they meet the following definition of post-menopausal: 12 months of natural (spontaneous) amenorrhea **OR** 6 months of spontaneous amenorrhea with serum FSH levels >40mIU/m **OR** 6 weeks after surgical bilateral oophorectomy (with or without hysterectomy).
* Examples of particularly reliable methods with Pearl Index (PI) <1, according to guidelines of Deutsche Gesellschaft für Gynäkologie und Geburtshilfe:
- Combination pill with estrogen and gestagen (no mini-pill, PI=0.1-0.9)
- Vaginal ring (NuvaRing®, PI=0.65 uncorr.; 0.4 corr.)
- Contraceptive patch (EVRA®, PI=0.72 uncorr.; 0.9 corr.)
- Estrogen-free ovulation inhibitors (Cerazette®, PI=0.14)
- Progestin-containing contraceptives (Implanon®, PI=0-0.08)
- Intra-uterine progestine device (Mirena®, PI=0.16)

Oral contraceptives without estrogen (e.g. "mini-pills"), nonsynthetic progesterone only IUDs, female condoms, cervical shield, periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Fertile males, defined as all males physiologically capable of conceiving offspring UNLESS the patient and his partner agree to comply with acceptable contraception, including a combination of male condom and spermicidal gel.

5 Treatment

5.1 Protocol requested treatment

5.1.1 Investigational treatment

- **QVA149** 110/50 µg capsules for inhalation supplied in blisters, delivered via Novartis single dose dry powder inhaler (SDDPI).
- **Placebo** to QVA149 capsules for inhalation supplied in blisters, delivered via Novartis single dose dry powder inhaler (SDDPI). Placebo QVA149 inhalation capsules will be equally matched in size, shape and color to QVA149 110/50 µg inhalation capsules.

The use of spacers is not permitted for study medication at any time during the study However, assessment of reversibility at Visit 1 can be performed via spacer (not reversibility at Visit 3).

Under no circumstances is an alternative inhalation device to be used for the administration of the above mentioned active or placebo capsules.

All therapies will be supplied by Novartis, providing sufficient quantity of medication to last each patient between clinical visits.

5.1.2 Additional study treatment

No additional treatment beyond investigational treatment is requested for this trial.

5.2 Treatment arms

Patients will be assigned to one of the following two treatment sequence arms in a ratio of 1:1.

Treatment sequence I: QVA149 (110/50 µg) o.d. (Day 1-15) followed by Placebo o.d. (Day 29-43).

Treatment sequence II: Placebo o.d. (Day 1-15) followed by QVA149 (110/50 µg) o.d. (Day 29-43).

5.3 Treatment assignment, randomization

At Visit 4 an eligible patient will be given the lowest available randomization number. This number assigns the patient to one of the treatment sequences. The investigator will enter the randomization number on the eCRF.

The randomization numbers will be generated using the following procedure to insure that treatment assignment is unbiased and concealed from patients and investigator staff. A randomization list will be produced by or under the responsibility of Novartis Biometry using a validated system ensuring assignment of treatment sequences to randomization numbers in the specified ratio.

The randomization scheme will be reviewed and approved by a member or delegate of the Novartis Biometry Randomization Group.

5.4 Treatment blinding

Patients, investigator staff, persons performing the assessments, sponsor staff and data analysts will remain blind to the identity of the treatment from the time of randomization until database lock, using the following methods: 1) Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study. 2) The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, taste.

Unblinding will only occur in the case of patient emergencies (see Section 5.5.10), and at the conclusion of the study.

5.5 Treating the patient

5.5.1 Patient numbering

Each patient is uniquely identified by a Patient-ID Number which is composed by the site number assigned by Novartis and a sequential subject number assigned by the investigator

(per allocation card or equivalently). Once assigned to a patient, the Patient-ID Number will not be reused.

Upon signing the informed consent form, the patient is assigned the next sequential number as given by the investigator using the next blank CRF book available from the EDC system.

If a screened patient fails to be randomized or enrolled for any reason, the reason will be entered on the Screening Failure Log CRF.

If a patient will be re-screened, some visits have to be passed for the second time. In the eCRF system the respective data will be captured under the Visit number suffixed by "a".

5.5.2 Dispensing the investigational treatment

The site will be supplied by Novartis with study drug in identically-appearing packaging.

QVA149 110/50 µg and matching placebo will be supplied as medication packs containing blister strips of capsules and SDDPI devices, as each SDDPI device should only be used for 30 days. Each medication pack contains 2 blister strips à 20 capsules for inhalation and one SDDPI device, sufficient to last until the end of the respective treatment period.

One component of the packaging has a 2-part label. Each part of this label contains sequentially increasing randomization numbers (corresponding to treatment sequences according to the confidential randomization list). Investigator staff will identify the study drug to dispense to the patient using the randomization number and the visit number on the label. Immediately before dispensing study drug to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) containing that patient's unique patient number.

5.5.3 Handling of study treatment

5.5.3.1 Handling of investigational treatment

Investigational treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Upon receipt, all investigational treatment should be stored according to the instructions specified on the drug labels. Clinical supplies are to be dispensed only in accordance with the protocol.

Medication labels will be in German and comply with the legal requirements of Germany. They will include storage conditions for the drug, but no information about the patient except for the randomization number.

The investigator must maintain an accurate record of the shipment and dispensing of investigational treatment in a drug accountability log. Monitoring of drug accountability will be performed by the field monitor during site visits and at the completion of the trial. Patients will be asked to return all unused investigational treatment and packaging at the end of the study or at the time of discontinuation of investigational treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused investigational treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

5.5.3.2 Handling of other study treatment

Not applicable.

5.5.4 Instructions for prescribing and taking study treatment

Patients will be required to take their study medication once a day between 7:00 and 11:30 +/- 30 minutes. Patients will be instructed to come to the clinic in appropriate time to complete pre-dosing assessments and to allow randomized study medication to be taken in the morning between 07:00 and 13:30 (Visits 4 and 6) and between 07:00 and 11:30 (Visits 5 and 7), respectively. Patients must be instructed to withhold the use of short acting beta2 agonists (rescue medication) for at least 6 hours prior to all clinic visits, unless the use is absolutely necessary.

Capsules should only be removed from the blister immediately before dosing.

At Visit 4, patients will be randomized to one of two treatment sequences.

Patients will be instructed on how to use the study treatment SDDPIs devices. Additional SDDPI devices and placebo capsules will be provided for training and demonstration purposes.

At Visits 4, 5, 6 and 7 (randomized treatment) **the study medication will be administered in the clinic by the site personnel** after completion of all pre-dose procedures between 07:00 and 13:30 (Visits 4 and 6) and between 07:00 and 11:30 (Visits 5 and 7),respectively. Patients shall refrain from the inhalation of study drug at home prior to each scheduled Visit.

The site staff should call the patient two days prior to Visits 3, 4, 5, 6 and 7 to remind them to take their study medication only on the day before the scheduled visit (only relevant for Visits 4, 5, 6 and 7) and to abstain from taking rescue medication (salbutamol) within 6 hours of the start of the visit.

If study drug is inhaled at home, at the day of Visit 4, 5, 6 and 7, the visit should be rescheduled to the next possible date.

The investigator should promote compliance by instructing the patient to take the study drug exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient should be instructed to contact the investigator if he/she is unable for any reason to take the study drug as prescribed.

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF (eCRF).

The storage conditions for study drug will be described on the medication label

5.5.5 Permitted dose adjustments and interruptions of study treatment

No adjustments to the study drug dosage or schedule are permitted, other than temporarily interrupting study medication during the treatment period as a result of an adverse event (including mild COPD exacerbations), if necessary.

Patients that experience a moderate to severe COPD exacerbation (see Section 5.5.9) **must be discontinued from study medication and the trial immediately**.

Any interruption of study medication should be for the shortest time period possible and any interruption of study medication for more than 3 consecutive days should be discussed with the local Novartis Clinical Monitor to review the patient's eligibility to continue in the trial.

These changes must be recorded in the Dosage Administration Record CRF (eCRF).

5.5.6 Rescue medication

At the start of screening (Visit 2), all patients will be provided with a short acting beta2 agonist (salbutamol) which they will be instructed to use throughout the trial as rescue medication. Salbutamol (100 µg) will be supplied to the investigator sites locally by Novartis. In case Visit 2 is omitted, salbutamol will be dispensed at Visit 1. During the treatment period salbutamol should be taken as rescue (when required) purposes only. No other rescue treatment is permitted. Nebulized salbutamol is not allowed as rescue medication.

In order to standardize measurements, patients must be instructed to abstain from taking rescue medication (salbutamol) within 6 hours of the start of each visit where spirometry is being performed unless absolutely necessary. If rescue medication is taken within 6 hours prior to spirometry at Visit 3, 4, 5, 6 and 7, the visit should be rescheduled to the next day if possible. The investigator must use their judgment when deciding how many times a visit for an individual patient should be rescheduled.

In the event that a patient uses a dose of rescue medication during any visit, but after echocardiography assessment was performed, the visit should continue as planned. If the patient uses a dose of rescue medication within 6 hours before MRI measurement, the visit should be rescheduled.

The approximate time of rescue medication intake will be captured in the eCRF if taken during one of the above study visits.

5.5.7 Concomitant treatment

The investigator should instruct the patient to notify the study site about any new medications he/she takes after the patient was enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study must be recorded on the Concomitant medications/Significant non-drug therapies eCRF page.

The following adjustments to patients who are treated with ICS are required:

- Patients taking inhalative corticosteroids (either as a monotherapy or as a fixed-dose combination of a LABA and ICS) for at least 30 days prior to Visit 2, shall continue

inhaling the ICS at an equivalent dose and dosing regimen for the duration of the study. The LABA-component, in case of a fixed-dose combination, must be discontinued at least 14 days prior to Visit 3. All other patients taking ICS intermittently or less than 30 days shall discontinue ICS inhalation.

- If, in the judgment of the investigator, it is necessary to increase the ICS dose of a patient between Visit 2 and Visit 4 in order to stabilize the patient, this patient will be considered a screening failure. The patient may be re-screened when the ICS dose required for the stable maintenance of the patient's condition has been established and he/she has been stable under this regimen for at least 1 month before being re-screened. Patients being re-screened do not have to undergo Visit 1, but can immediately start with Visit 2. During the treatment period of the study (Visit 4 until Visit 7), patients shall be maintained on an unchanged ICS regimen.

5.5.8 Prohibited Treatment

Use of the treatments displayed in Table 5-1 **and** Table 5-2 **is NOT allowed to be taken during the study.** The medications in Table 5-3 are only permitted under the circumstances given. Each concomitant drug must be individually assessed against all exclusion criteria and the tables below to see if it is allowed. If in doubt the investigator should contact the Novartis medical monitor before randomizing a patient or allowing a new medication to be started.

Table 5-1 Prohibited Concomitant Medications[1]

Class of Medication	Minimum cessation period prior to baseline visit (Visit 3)
Non-potassium sparing diuretics (unless administered as a fixed-dose combination with a potassium conserving drug	7 days
Non-selective systemic beta-blocking agents[2]	7 days
Cardiac anti-arrhythmics Class Ia	7 days
Cardiac anti-arrhythmics Class III	7 days, amiodarone 3 months
Other drug with potential to significantly prolong the QT interval	14 days or 5 half-lives, whichever is longer
Tricyclic antidepressants	14 days
All antipsychotic agents (first, second and third generation, inclusive of atypical antipsychotics)	14 days
Combinations of antipsychotic agents with antidepressants are prohibited	
Serotonin Noradrenaline Reuptake Inhibitors (SNRIs)	14 days
Other noradrenaline reuptake inhibitors	14 days
Monoamino-oxidase inhibitors	14 days
Live attenuated vaccine	30 days
Macrolide antibiotics	30 days

Class of Medication	Minimum cessation period prior to baseline visit (Visit 3)
Systematic Mast cell stabilizers (e.g., cromoglycate, nedocromil, ketotifen)	7 days
Systemic anticholinergics	7 days
IgE inhibitors (e.g., Xolair)	6 months
Leukotriene antagonists and leukotriene synthesis inhibitors	7 days

[1]This table is to be used as a guide only and not considered all-inclusive. Medications should be assessed for adherence to the indication, compatibility with the study aims, study medication, study-related procedures, and other inclusion/ exclusion criteria.
[2]Selective ß1-blocking agents are permitted.

The washout of these prohibited medications is not to be encouraged.

Table 5-2 Prohibited COPD related medications during the trial[1]

Class of Medication	Minimum washout period prior to baseline visit (Visit 3)
Short-acting β_2 agonists (SABA) (other than study rescue medication)	6 hr
Short acting anticholinergics (SAMA)	8 hr
Fixed combinations of short-acting β_2 agonists and short-acting anticholinergics (SABA/SAMA)	8 hr
Long-acting β_2 agonists (LABA)	14 days
Fixed combinations of long-acting β_2 agonists and inhaled corticosteroids (LABA/ICS)	14 days (LABA) - Must be switched to the nearest equivalent dose of inhaled corticosteroid monotherapy
Long-acting anticholinergics (LAMA)	14 days
Inhaled corticosteroids (intermittent use)	14 days
Oral Phosphodiesterase-IV inhibitor	7 days
Xanthines (any formulation)	7 days
Parenteral or oral corticosteroids (allowed for the treatment of COPD exacerbation)	30 days
Intra-muscular depot corticosteroids	3 months

[1]These tables are to be used as a guide only and not considered all-inclusive. Medications should be assessed for adherence to the indication and other inclusion/exclusion criteria. These medications are also prohibited if administered for other indications.

Table 5-3 Medications allowed under certain conditions[1]

Class of Medication	Condition under which medication is permitted
Selective Serotonin Reuptake Inhibitors	Stable dose for at least 30 days prior to screening (Visit 2) and during the study.
Inhaled corticosteroids (stable long-term regimen)	Stable dose for at least 30 days prior to

Class of Medication	Condition under which medication is permitted
	screening (Visit 2) and during the study.
Intra-nasal corticosteroids	Stable dose for at least 30 days prior to screening (Visit 2) and during the study
H_1-antagonists	Stable dose for at least 5 days prior to screening (Visit 2) and during the study. (except mizolastin or terfenadine)
Inactivated influenza, pneumococcal or any other inactivated vaccine	Not administered within 48 hours prior to a study visit

[1]These tables are to be used as a guide only and not considered all-inclusive. Medications should be assessed for adherence to the indication and other inclusion/exclusion criteria.

5.5.9 Discontinuation of study treatment and premature patient withdrawal

Study drug must be discontinued and the patient withdrawn from the trial if the investigator determines that continuing it would result in a significant safety risk for that patient. The following circumstances **require** study drug discontinuation:

- Withdrawal of informed consent
- Pregnancy
- Adverse events for which continued inhalation of the study treatment would be detrimental
- Abnormal test procedure results indicating risk for the patient on continued inhalation of the study drug
- If patient experiences a **moderate or severe COPD exacerbation during the study** (i.e. between Visit 4-7)
- If in the judgement of the investigator, the patient has had excessive use of rescue medication (more than 8 puffs a day), the investigator should assess whether it is safe for the patient to continue in the study.

Protocol deviations should not lead to patient withdrawal unless they indicate a significant risk to the patient's safety.

In addition to these requirements for study drug discontinuation, the investigator should discontinue study drug for a given patient if, on balance, he/she believes that continuation would be detrimental to the patient's well-being.

Patients may voluntarily withdraw from the study for any reason at any time. Patients may be considered withdrawn, if they state an intention to withdraw, or fail to return for visits, or become lost to follow up for any other reason.

If premature withdrawal occurs for any reason, the patient should return to the clinic as soon as possible for an End of Study Visit. The investigator must make every effort to determine the primary reason for a patient's premature withdrawal from the study and record this information on the End of Treatment eCRF.

The last date of study treatment intake should be entered into the Study Completion CRF and the reason for discontinuing the study should be given on the comments page. If a patient who discontinued study treatment performed all scheduled study procedures and measurements (up to Visit 7), he/she will be counted as a study completer.

Patients who are prematurely discontinued/ withdrawn from the study will not be replaced.

5.5.10 Emergency breaking of treatment assignment

Emergency breaking of the assigned treatment code should only be undertaken when it is essential to treat the patient safely and efficaciously. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Two complete sets of emergency code break cards are provided by Novartis Pharma GmbH. One set is to be retained by Novartis Pharma GmbH and one set is to be distributed to the investigator.

They must be stored in a secure place but accessible in case of emergency. The investigator will receive a blinded code break card for each patient, with the details of drug treatment covered by a sealed tear-off cover. In an emergency, the tear-off cover can be removed to determine the treatment. The tear-off covers are not to be removed for any reason other than an emergency. When the investigator removes the tear-off cover he/she must note the date, time, and reason for removing it and retain this information with the case report form documentation. The unblinded treatment code should not be recorded on the eCRF. The investigator must also immediately inform the Novartis Monitor that the code has been broken.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the emergency code breaks for his/her patients at the site. The investigator will inform the patient how to contact his/her backup in cases of emergency when he/she is unavailable. The protocol number, study drug name if available, patient number, and instructions for contacting the German Novartis affiliated company (or any entity to which it has delegated responsibility for emergency code breaks) will be provided to the patient in case emergency unblinding is required at a time when the investigator and backup are unavailable. As per Novartis SOPs it is one of the primary responsibilities of each investigator to be available in case of an urgent emergency unblinding for one of his/her patients. He or she need to provide a telephone number by which he or she can be reached throughout the trial in case of an emergency unblinding request for one of his patients (e.g. a mobile number).

5.5.11 Study completion and post-study treatment

The study will be considered completed for an individual patient when he/she completes Study Visit 7. Completion of the study will be when all randomized patients have completed Study Visit 7 or have been withdrawn.

Patients completing Visit 7 will not be given further access to study drug.

The investigator also must provide follow-up medical care for all patients who completed the study or who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

5.5.12 Early study termination

The study can be terminated at any time for any reason specified in the clinical trial study contract, by Novartis. Should this be necessary, the patient should be seen as soon as possible and treated for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The sponsor will be responsible for informing IRBs and/or ECs of the early termination of the trial.

6 Visit schedule and assessments

Table 6-1 lists all of the assessments and indicates with an "X" the visits when they are performed. Patients should be seen for all visits on the designated day or as close to it as possible.

Patients who discontinue study treatment before completing the study should be scheduled for a visit as soon as possible, at which time all of the assessments listed for Visit 7 marked with an asterix in the assessment schedule will be performed. At a minimum, they will be contacted for safety evaluations during the 30 days following the last dose of study treatment, including final contact at the 30-day point. Documentation of attempts to contact the patient should be recorded in the patient record.

All data obtained from the assessments listed in Table 6-1 and described in detail in the subsections below must be supported in the patient's source documentation. Assessments that generate data for database entry and which are recorded on eCRFs are listed using the eCRF name. Assessments that are transferred to the database electronically (e.g., laboratory data) are listed by test name.

Table 6-1 Assessment schedule

Epoch	Pre-Screening	Screening	Baseline	Treatment Period I		Washout	Treatment Period II		FUP
Study day	**variable**	**-21 to -8**	**-7**	**1**	**15[1]**	**16-28[1]**	**29**	**43[1]**	**73±7**
Visit number	**1**	**2**	**3[2]**	**4[2]**	**5[2]**		**6[2]**	**7[2]**	**8[3]**
Signed Informed consent	X								
Medical history, demographics	X	X							
Incl./excl. criteria	X	X	X	X					
Height	X								
Weight	X		X					X*,**	
Current medication review/ adjustment	X	X							
Review concomitant medications			X	X	X		X	X*,**	X
Smoking history/status	X								
Dispense ß2-agonist (rescue, as required)		X[7]	X	X	X		X		
Physical exam			X					X*,**	
Vital signs			X	X	X		X	X*,**	
ECG			X	X			X	X*,**,[8]	
Hematology			X		X			X*,**	
Blood chemistry			X	X	X		X	X*,**	
Pregnancy Test (urine)			X					X*,**	
Impulse oscillometry			X	X	X		X	X*	
Spirometry				X	X		X	X*	
Reversibility	X[4]		X						
Bodyplethysmography			X[9]	X	X		X	X*	
Randomization				X					
Device and inhalation training				X					
Dispense study medication				X			X		
Administration study drug at visit				X	X		X	X*	
Collect study medication					X			X*,**	
Review use of study medication					X			X*,**	
MRI[5]				X	X		X	X*	
^{19}F MRI[10]					X			X	
Echocardiography				X	X		X	X*	
Activity tool training			X						
Provide activity measuring tool			X	X	X		X		
Return activity measuring tool				X	X		X	X*,**	

Epoch	Pre-Screening	Screening	Baseline	Treatment Period I		Washout	Treatment Period II		FUP
Study day	**variable**	**-21 to -8**	**-7**	**1**	**15[1]**	**16-28[1]**	**29**	**43[1]**	**73±7**
Visit number	**1**	**2**	**3[2]**	**4[2]**	**5[2]**		**6[2]**	**7[2]**	**8[3]**
mMRC[6]			X						
CAT[6]			X	X	X		X	X*,**	
BDI/ TDI [6]				X	X		X	X*,**	
Adverse events				X	X		X	X*,**	X
Serious adverse events	X	X	X	X	X		X	X*,**	X
Call patient approx.-2days: to remind them to abstain from rescue medication/not to take study drug at home[8] on the day of the next visit			X	X	X		X	X*	
Study termination									X

* These assessments should be done for patients who prematurely withdraw, but are willing to perform end of study visit including all relevant assessments and study drug inhalation
** These assessments should also be done for patients who discontinue study drug

1 Patients should be seen for all visits as close as possible, with a tolerance of ± 3 days. The treatment periods as well as the wash-out period have to be at least 14 days
2 Impulse oscillometry, bodyplethysmography, spirometry, MRI and echocardiography (can be performed on separate days within 48 hours); initial measurements at beginning of each treatment period (Visit 4 and Visit 6) shall be performed pre-dose (i.e. before study medication intake); whereas final measurements at the end of each treatment period (Visit 5 and Visit 7) shall be performed post-dose (i.e. after study medication intake), specifically 45 min (±15 min) post-dose for impulse oscillometry, 60 min (±15 min) post-dose for bodyplethysmography, 75 min (±15 min) post-dose for spirometry,2 hours (±30 min) post-dose for MRI and 4 hours (±30 min) post-dose for echocardiography.
3 Telephone call
4 Abbreviated reversibility only with post-dose measurement after inhalation of salbutamol (4*100 µg salbutamol or reduced dose, depending on prior medication intake of patient)
5 MRI will include the anatomical and functional assessment of the heart and lungs (i.e. right and left ventricular mass and function, and perfusion MRI of the lung parenchyma for pulmonary parenchymal blood flow and regional ventilation measures).
6 Questionnaires will include modified Medical Research Council (mMRC), COPD Assessment Test (CAT) and Baseline/Transition Dyspnea Index, which are to be completed before all other measurements.
7 Short-acting ß2-agonist will be dispensed as rescue medication on Visit 1 if Visit 2 is omitted.
8 ECG is no mandatory assessment at Visit 7 and should only be done for patients who prematurely withdrew or discontinued study drug intake.
9 Bodyplethysmography will be performed pre-and post-inhalation of salbutamol
10 ^{19}F-enhanced MRI sequence will be an optional measurement that require separate patient consent. The sequence will be captured after the MRI anatomical and functional assessment of the heart and lung.

Table 6-2 Timed Assessments

	Time-point[1]	CAT	BDI/ TDI	Impulse oscillometry	Bodyplethysmography	Spirometry	MRI	Echocardiography
Visit 4 (Day 1)	**to be completed first**	X	X					
	before randomization			X	X	X	X	X
	0 min	**RANDOMIZATION**						
Visit 5 (Day 14)	**to be completed**	X	X					

	Time-point[1]	CAT	BDI/ TDI	Impulse oscillometry	Bodyplethys mography	Spirometry	MRI	Echocardio graphy
	first							
	0 min	**Study drug intake**						
	45 min			X				
	1 h				X			
	1 h 15 min					X		
	2 h						X	
	4 h							X

	Time-point[1]	CAT	BDI/ TDI	Impulse oscillometry	Bodyplethys mography	Spirometry	MRI	Echocardio graphy
Visit 6 (Day 29)	**to be completed first**	X	X					
	before study drug intake			X	X	X	X	X
	0 min	**Study drug intake**						
Visit 7 (Day 42)	**to be completed first**	X	X					
	0 min	**Study drug intake**						
	45 min			X				
	1 h				X			
	1 h 15 min					X		
	2 h						X	
	4 h							X

[1] Time-points relative to the scheduled dose at visit unless otherwise specified.

6.1 Information to be collected on screening failures

Only demography data, the reason for failing (screening failure log) are collected for those patients who fail to enter the treatment phase.

Potential serious adverse events and hospitalizations which may have occurred from time of signing informed consent until screening failure time should be documented in the patient medical records. Reporting of potential SAE during this time period should be followed as described in Section 7.2.

6.2 Patient demographics/other baseline characteristics

The following demographics / baseline characteristics will be collected and recorded in the eCRF:

- Year of birth
- Age

- Sex
- Height
- Weight
- Date of diagnosis of COPD
- Relevant medical history, including any documented exacerbation of COPD that occurred during the previous year
- Smoking History (e.g., one pack year = 20 cigarettes/day x 1 year)
- Prior concomitant medications (COPD related and non-COPD related)
- Baseline physical examination (not databased other than in context of relevant medical history)
- Vital signs at Visit 3
- ECG finding at Visit 3
- Laboratory: Hematology and blood chemistry at Visit 3
- Pregnancy test (dipstick at Visit 3, if applicable)
- Pre- and post-dose bronchodilator spirometry at Visit 3 (FEV_1 and FVC)
- Pre- and post-dose bodyplethysmography at Visit 3 (IC, FRC, sRAW, TLC, RVol)

6.3 Treatment exposure and compliance

All medications taken after the start of study drug, the reason for prescribing the medication, and the start and end dates will be collected in the source documents and recorded on the respective pages of the eCRF.

The time of study drug administration at each dosing visit will be collected on the eCRF. The date and time of the last use of study drug will be recorded on the study completion page.

Study drug compliance will be assessed by the investigator and/or center personnel at designated visits by recording capsule counts from the previously dispensed blister strips for the Novartis SDDPI. This information should be captured in the source documentation at each visit. The total number of doses of study drug administered since the last dispensing visit will be recorded at Visits 5 and 7 for each patient on the eCRF.

6.4 Efficacy

6.4.1 Magnetic resonance imaging (MRI)

The MRI exam will be conducted at a 1.5T system. The patient will change clothes and leave metallic belongings outside the scanner room. A G20 sized venous cannula (pink) will be placed in the antecubital fossa. MRI compatible ECG electrodes will be placed on the thoracic wall of the patient. During 100% oxygen delivery, O_2 and CO_2 will be continuously monitored.

The MRI assessment will include the anatomical (HASTE, VIBEUTE sequences) and functional assessment of the heart (SSFP cine MRI) and lungs (Dynamic contrast enhanced MRI, FLASH T1 mapping at room air and 100% oxygen, GRE MRI).

The MRI protocol consists of:

MRI Sequence	Orientation	Breathing	Purpose	time (min)
T1 GRE	triplane	inspiration	localiser	1
True FISP	axial	free breathing	anatomy ECG gated	1
True FISP	coronal	free breathing	anatomy ECG gated	1
UTE (Siemens WIP)	3D	free breathing	anatomy	8
Measure blood pressure (1)				
T1 GRE	oblique	inspiration	cardiac localiser	1
True FISP	4chamber view	inspiration	cardiac function ECG gated	1
True FISP	2 chamber view	inspiration	cardiac function ECG gated	1
True FISP	short axis view	inspiration	cardiac function ECG gated	10
GRE Phase contrast	Mitral valve	free breathing	flow venc 130	2
GRE Phase contrast	septum	free breathing	flow venc 30	2
GRE Phase contrast	main PA	free breathing	flow venc 150	2
Measure blood pressure (2)				
T1 GRE	coronal	free breathing	ventilation 3 slices	3
T1 GRE	saggital	free breathing	ventilation 2 slices	2
T1 GRE FLASH	coronal	inspiration	T1 mapping room air 3 slices 1st time	1
T1 GRE FLASH	coronal	inspiration	T1 mapping room air 3 slices 2nd time	1
Oxygen mask on				2
HASTE	coronal	free breathing	wash in O2 (turn100% oxygen on)	5
T1 GRE FLASH	coronal	inspiration	T1 mapping oxygen 3 slices 1st time	1
GRE Phase contrast	main PA	free breathing	flow venc 150	2
T1 GRE FLASH	coronal	inspiration	T1 mapping oxygen 3 slices 2nd time	1
HASTE	coronal	free breathing	wash out O2 (turn oxygen off)	5
Measure blood pressure (3)				
Oxygen mask off				2
TWIST-VIBE	coronal	inspiration/shallow breathing	lung perfusion	1
contrast agent 0.04 mmol/kg Dotarem© iv at 5cc/sec				
TWIST-VIBE	coronal	inspiration/shallow breathing	lung perfusion	2
Measure blood pressure (4)				
Sum (min)				58

A detailed exam protocol including all scan parameters will be available on the MRI system at the CRC Hannover. The estimated total time for the MRI procedure is 1.5 h.

The following parameters will be measured and evaluated with specific software:

- Right and left ventricular enddiastolic volume
- Right and left ventricular ejection fraction
- Right and left ventricular endsystolic volumes
- Cardiac output
- Right and left ventricular cardiac mass
- Pulmonary parenchymal blood flow
- Regional lung ventilation and perfusion measures (oxygen transfer function) using oxygen-enhanced T1 mapping MRI

All MRI parameters will be assessed by one radiologist blinded to procedure sequences. A list of parameters that will be captured in the eCRF is attached to this protocol in Appendix 8. The exclusion criteria 4 (patients with heart failure with left ventricular ejection fraction <40%) will be determined by MRI scan at Visit 4. This ejection fraction should be assessed by one

experienced radiologist, which not necessarily has to be the radiologist evaluating all MRI parameter.

During MRI systolic and diastolic blood pressure will be measured 4 times as depicted in the MRI protocol above: at the beginning and the end of the cardiac sequence, after oxygen perfusion and finally at the end of all MRI sequences.

In case a patient has a history of hypersensitivity to i.v. contrast medium, the last MRI sequence that require i.v. application of contrast medium will not be performed.

Optional fluorine (^{19}F) –enhanced MRI measurement

The fluorine-enhanced MRI technique uses an inert perfluoropropane/oxygen (79%/21%) gas mixture as contrast agent to assess regional ventilation dynamics in the lungs during steady-state breathing. It will be performed at Visit 5 and Visit 7 subsequent to the described anatomical and functional MRI measurements above.

Every patient will receive a separate patient information on this MRI method and has to give separate written informed consent before this assessment is being performed. In case a patient would not fit into the specially equipped MRI-system due to the body size, the investigating radiologist will not perform the ^{19}F MRI.

During ^{19}F MRI procedure, O_2 and CO_2 will be continuously monitored.

The ^{19}F MRI protocol is as follows:

19 F Protocol	Patient has a 7 min break outside the MRI scanner. During this time the 19F coil setup takes place.			
MRI Sequence	**Orientation**	**Breathing**	**Purpose**	**time (min)**
T1 GRE	triplane	inspiration	localiser	1
3D Vibe	axial	inspiration	anatomy	1
3D Vibe	coronal	inspiration	anatomy	1
Mask on. Oxygen and carbon dioxide monitoring setup. 1 min 100 % oxygen breathing prior to 19F/oxygen gas mixture inhalation				4
3D GRE	coronal	inspiration	monitor 19F gas distribution in the lung	1
3D GRE	coronal	inspiration	monitor 19F gas distribution in the lung	1
3D GRE	coronal	inspiration	monitor 19F gas distribution in the lung	1
3D GRE	coronal	free beathing	19 F gas washout	5
Sum (min)				15

The estimated total time for the ^{19}F MRI procedure is 25 min.

The following parameter (see also Appendix 8) will be measured and evaluated with specific software by one radiologist blinded to procedure sequences:

- regional lung 19F gas wash-out time

6.4.2 Bodyplethysmography

Constant-volume bodyplethysmography will be used to assess the following parameters:

- Total Lung Capacity (TLC)
- Inspiratory Capacity (IC)
- Residual Volume (RVol)
- Specific Airway Resistance (sRaw) and
- Functional Residual Capacity (FRC)

Bodyplethysmography maneuvers must be first explained to the patient and then practiced until consistently reproducible efforts can be made by the patient. Further practices can be scheduled after the completion of all assessments at Visit 3 if required.

The instructions for bodyplethysmography and the maximal flow-volume loop measurements are as follows:

Specific airway resistance (sRaw) measurement: After having the maneuver explained to the subject, resting tidal breathing will commence. As soon as a stable end-expiratory lung volume level and a stable tidal volume are achieved at least five pressure-flow curves will be collected to determine the specific airway resistance (sRaw), which is entered as the effective resistance (sReff) in the eCRF.

The slopes for the pressure-flow loops should be calculated such that the effective resistance is estimated (sReff). Artefacts will be deleted, but no corrections will be performed. At least 5 acceptable measurements should be taken. The median is reported as sReff in the eCRF.

FRC measurements: After a few breaths, the shutter of the bodyplethysmograph will be closed and the subject will continue to breathe against the closed shutter at a breathing frequency of about 0.5 – 1 per second for an additional few breaths during which the pressure-volume loops will be collected and FRC obtained. Three acceptable shutter maneuvers will be performed. The difference of the FRC measurements should be ≤5% (difference between highest and lowest value, divided by the mean should be less than 0.05).

Linked maneuvers to assess inspiratory capacity (IC) and slow vital capacity (SVC): Linked maneuver will be performed to assess IC and SVC. After a shutter, the patient should fill up his or her lungs slowly and completely to reach a plateau at the TLC level, and then exhale fully and slowly to the level of RVol with verbal encouragement. The exhaled volume is the slow vital capacity (SVC). The exhalation should be no longer than 15 s or fulfill the end-of-test criterion, which is less than 20 ml volume change in two consecutive seconds. At least three linked maneuvers will be performed, with a difference of max. 150 ml between highest and second highest SVC measurement, as well as IC measurement.

The following values are transferred to the eCRF:

- sReff: median of five acceptable measurements
- FRC: mean of three reproducible values (reproducible defined as: difference between highest and lowest value, divided by the mean should be less than 0.05)
- IC: highest of three reproducible values (reproducible defined as: difference of max. 150 ml between highest and second highest IC)
- SVC: highest of three reproducible values (reproducible defined as: difference of max. 150 ml between highest and second highest SVC)

In case the values are not reproducible, three acceptable measurements should be taken instead.

TLC will be calculated by the eCRF (TLC = FRC mean + highest IC)
RVol will be calculated by the eCRF (RVol = TLC – highest SVC)

All volumes will be reported in liters (L) under BTPS conditions (body temperature (37°C), ambient pressure, saturated with water vapor.

To avoid exhaustion of the patients due to multiple lung function tests and potential influence on MRI assessment, at least 3 acceptable lung function tests up to a maximum of five lung function tests need to be performed only at each timepoint.

Spirometry equipment and performance of spirometric testing must be in accordance with ATS/ERS standards [21]. The spirometer should be calibrated every morning before taking any spirometric measurements for this study. Calibration reports should be stored as source data.

6.4.3 Spirometry assessments

Please refer to the latest version of the Spirometry Guidance, in Appendix 3 and Table 6-2 for full details on scheduling and performing spirometry.

At Visit 3, spirometry measurements will be taken to assess patient's eligibility for the study and to assess the post bronchodilation FEV_1. The reversibility test should be performed as follows:

A baseline spirometry assessment should be performed after a washout period of at least:

- 6 h for short-acting ß2-agonist
- 8 h for short-acting anticholinergic

Administer 4*100 µg of salbutamol following the completion of the baseline assessment, which is pre-dose FEV_1 measurement. A second spirometry assessment is then performed 15 min thereafter.

Spirometry performance should be in accordance with ATS standards [21]. For all clinic spirometry assessments, three acceptable maneuvers (a maximum of 5 maneuvers) should be performed for each time-point. The FEV_1, FVC values recorded in the eCRF must be the highest values measured irrespective of whether or not they occur on the same curve.

This study will utilize the spirometric predication equation standards for the European Community for Coal and Steel for predicted normal spirometry values [22].

All displaceable volumes will be reported in liters (L) at the following conditions: normal body temperature (37°C), ambient pressure, saturated with water vapor (BTPS). In addition the spirometer should be calibrated every morning before taking any spirometric measurements for this study. Calibration reports should be stored as source data.

6.4.4 Impulse oscillometry

The impulse oscillometry system (IOS) is a sensitive and noninvasive method to assess pulmonary function during tidal breathing [23]. It is used to assess resistance and reactance in subjects with airway obstruction. It can provide separate measurements for both large and small airways function [24].

The following parameters will be assessed:

- Resistance (R5, R20, R5-20, kPa L-1 s-1);

- Reactance (X5, kPa L-1 s-1).

- Area of reactance (AX, Hz kPa L-1 s-1).

During the measurement, the patient sits upright, head straight or slightly extended. The patient should hold his hands tightly against his cheeks. The lips will be firmly closed around the mouthpiece and the mouthpiece will be held tightly between the teeth with the tongue kept beneath the mouthpiece.

After about 15 to 30 seconds tidal breathing, measurement will be performed for at least 60 seconds. At least three measurements will be performed. Spikes (indicative of glottis closure or swallowing) should be removed from the data manually prior to analysis but the data can still be analyzed.

The variation for R5 and R20 should be < 15%. In case the variation is higher, up to 5 measurements can be performed at the discretion of the investigator. The mean value of at least 3 measurements should be reported for R5, R20, R5-20, X5, AX.

Daily calibration with the necessary standard resistors will be performed and information on temperature and humidity will be collected. Calibration reports will be stored as source data.

6.4.5 Echocardiography

Echocardiography is the current standard examination tool for the diagnosis of diastolic dysfunction. An echocardiography will be performed at Visits 4, 5, 6, and 7 according to standard recommendations by the German Society of Cardiology.

The following parameters will be assessed:

- parameters of left and right ventricular diastolic function
- parameters of left and right ventricular systolic function
- parameters of pulmonary arterial pressure

A detailed list of parameters that will be captured in the eCRF is attached to this protocol in Appendix 9.

Due to an expected limitation in the acoustic window, examination of diameters, volumes, and ejection fraction will not be performed as this is part of analyzes done by MRI. All echocardiography investigations will be performed by the same investigator blinded to procedure sequences. The estimated total measurement time depending on the quality of acoustic window is about 20-40 min.

6.4.6 Activity with Actibelt

At Visits 3, 4, 5 and 6 each patient will be provided with an Actibelt device to measure physical activity. Patients may also require another, flexible Actibelt to wear in the evening/ at night. The Actibelt device to be used in this study is the Actibelt from TRIUM Analysis Online GmbH (München, Germany). Patient will be instructed to wear the accelerometer device continuously day and night with the exception of the time spent for personal hygiene. The Actibelt will be brought to the Visits 4, 5, 6 and 7 and the Actibelt recording box has to be recharged. At the same time, the data from the Actibelt recording box will be downloaded to the local computer of the study site, copied to a SD-card and transferred to the data management system from TRIUM.

6.4.7 COPD Assessment Test (CAT)

The COPD Assessment Test (CAT) is a short instrument used to quantify the symptom burden of COPD and will be used to assess the health status of patients in this study (Jones et al. 2009a, Jones et al 2009b). It is completed by the patient at the beginning of the study visit before any other assessment to avoid influencing the responses. The CAT will be completed by the patient at the investigator's site at Visits 3, 4, 5, 6 and 7, or at the time of discontinuation for patients who prematurely withdraw from the study. There are 8 questions in the CAT. Patients should read the two statements for each item, and mark where on the scale (0-5) they fit. Scores for each of the eight items are summed to give an overall score (out of 40). A score of 0 indicates no impact of COPD on a person's life and a maximum score of 40 indicates a very high impact of COPD.

An example of the COPD Assessment Test (CAT) is provided in Appendix 5.

6.4.8 Modified Medical Research Council (mMRC) Dyspnea Scale

The modified Medical Research Council (mMRC) Dyspnea Scale (Mahler et al. 1984) is a five-item instrument to assess a patient's degree of breathlessness in relation to physical activity. Participants will be required to read a brief description of an activity and then select a statement that best describes their experience with dyspnea at Visit 3. The mMRC will be used for characterizing COPD patients.

An example of the mMRC Dyspnea Scale is provided in Appendix 6.

6.4.9 Baseline/Transition Dyspnea Indexes (BDI/TDI)

Patients should be interviewed by a trained assessor (in accordance with training materials provided by Novartis) who will grade the degree of impairment due to dyspnea at Visits 4, 6 (baseline dyspnea index) and at Visits 5, 7 (transition dyspnea index). If possible, the same assessor should complete both the BDI and TDI assessments for an individual patient, which should be undertaken prior to dosing at these visits.

The BDI must be administered at the beginning of the treatment period (Visits 4 and 6) and the TDI at the end of the treatment period (Visits 5 and 7). The BDI as well as the TDI must be completed prior to any spirometry assessment including taking of study medication.

An example of the BDI/TDI Dyspnea Index is provided in Appendix 4.

6.4.10 Appropriateness of efficacy assessments

The efficacy assessments planned for this study: spirometry, bodyplethysmography, impulse oscillometry, and patient symptoms (BDI/TDI, CAT) planned for this study are the standard ones in COPD clinical trials.

MRI assessments are applied, due to their high accuracy and reproducibility compared to echocardiography, allowing for a smaller sample size of patients to prove the hypothesis of improved leftventricular enddiastolic filling.

Echocardiography is applied as it is considered the current standard measure to particularly determine ventricular diastolic function and generates additional information on cardiac function complementary to MRI.

The Actibelt accelerometer is applied to assess the activity of the patient with high accuracy, as it is worn at the body's center of gravity.

6.5 Safety

For details on adverse event collection and reporting, refer to Section 7.

6.5.1 Physical examination

A physical examination is to be performed by the investigator at Visits 3 and 7 (or at early discontinuation) and will include the following:

General appearance, skin, neck, (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological.

Significant findings that are present prior to first intake of study drug must be included in the Relevant Medical History/Current medical Conditions screen on the patient's eCRF. Significant findings made after first intake of study drug which meet the definition of an Adverse Event must be recorded on the Adverse Event screen of the patient's eCRF. Further information for all physical examinations must be included in the source documentation at the study site and will not be recorded in the eCRF.

6.5.2 Vital signs

Vital signs will include pulse rate and systolic and diastolic blood pressure. All blood pressure measurements should be taken after the patient has rested for at least 5 min in a sitting position. At Visit 3 the mean sitting systolic and diastolic blood pressure of three consecutive measurements at 2 minute intervals will be captured to determine eligibility of the patient. Vital signs will be obtained at Visits 3, 4, 5, 6 and 7 or at premature discontinuation.

6.5.3 Height and weight

Height in centimeters (cm) will be measured at Visit 1 and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured at Visit 1, Visit 3 and again at Visit 7.

6.5.4 Laboratory evaluations

A blood sample will be collected for analysis at baseline Visit 3, Visits 4, 5, 6 and 7 or premature withdrawal. A central laboratory will be used for analysis of all specimens collected. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

Clinically notable laboratory findings are defined in Appendix 1.

6.5.4.1 Hematology

Glycosylated Hemoglobin (HbA1c), Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (% and absolute), and platelet count will be measured at Visits 3, 5 and 7 or premature withdrawal.

6.5.4.2 Clinical chemistry

Albumin, alkaline phosphate, total bilirubin, BUN, calcium, total cholesterol, LDH, magnesium, phosphate, sodium, potassium, creatinine, creatinine clearance (measured by GFR (MDRD formula)), γ-GT, blood glucose, total protein, AST and ALT will be measured at Visits 3, 5 and 7 or premature withdrawal. TSH will be measured only at Visit 3 and NT-proBNP will be measured at Visits 4, 5, 6, and 7 or premature withdrawal.

If the total bilirubin concentration is increased above 1.5 times the upper limit of normal range, total bilirubin should be differentiated into the direct and indirect reacting bilirubin.

The Laboratory will supply procedures for the preparation and collection of these samples.

All patients with laboratory tests containing clinically significant abnormalities should be followed regularly until the values return to within the normal ranges or until a valid reason other than drug-related adverse experiences is identified, even after the medication has discontinued.

6.5.5 Electrocardiogram (ECG)

ECGs should be free of baseline wander and noise. Prior to an ECG being performed, the ECG operator should check the tracing to ensure that it is of high quality.

A standard 12 lead ECG will be performed at Visits 3, 4 and 6 or premature discontinuation visit. Interpretation of the tracing must be made by a qualified physician and documented on the ECG section of the eCRF. Each ECG tracing should be labeled with the study code, patient number, date and time, and kept in the source documents at the study site. Clinically significant abnormalities should also be recorded on the relevant medical history/Adverse Events eCRF page. Please refer to the relevant exclusion criteria prior to randomization (Section 4.2). Clinically significant findings must be discussed with the Novartis Clinical

Monitor prior to enrolling the patient in the study. Values of >450 ms for males and >470 ms for females or an increase of ECG value of >30ms during the course of the study shall be confirmed by the Investigator, a cardiologist at the site or a cardiologist employed by Novartis.

ECGs must be performed only after subjects have been resting in the supine position for at least 5 minutes.

6.5.6 Pregnancy and assessments of fertility

In pre-menopausal women who are not surgically sterile a urine pregnancy test will be performed at Visit 3 and Visit 7 (tests provided by the Central Laboratory). A positive pregnancy test requires the patient to be discontinued from the trial. No assessments of fertility will be performed. Refer to Section 5.5.9 and Section 7.4 for more details. A urine pregnancy test is also required in the event of premature study withdrawal.

6.5.7 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/patient population.

6.6 Other assessments

No additional tests will be performed on patients entered into this study.

6.6.1 Resource utilization

Not applicable.

6.6.2 Health-related Quality of Life

Not applicable.

6.6.3 Pharmacokinetics

Not applicable.

6.6.4 Pharmacogenetics/pharmacogenomics

Not applicable.

6.6.5 Other biomarkers

Not applicable.

7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after first intake of study drug, even if the event is not considered

to be related to study drug. Therefore, an AE may or may not be temporally or causally associated with the use of an investigational product.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for labs and other test abnormalities are included in Appendix 1.

Adverse events should be recorded in the Adverse Events eCRF under the signs, symptoms or diagnosis associated with them accompanied by the following information.

- the severity grade
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities
- its relationship to the study treatment
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported.
- whether it constitutes a serious adverse event (SAE)
- action taken regarding study treatment
- whether other medication or therapies have been taken (concomitant medication/non-drug therapy)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

An SAE is any adverse event (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless

hospitalization is for*:*

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
- treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- social reasons and respite care in the absence of any deterioration in the patient's general condition

- is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 7.2.

All adverse events should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); study treatment dosage adjusted/temporarily interrupted; study drug(s) permanently discontinued; concomitant medication given; non-drug therapy given. The action taken to treat the adverse event should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment*,* the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

The investigator should also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information should be recorded in the investigator's source documents, however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

7.2 Serious adverse event reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days after the patient has stopped study participation (defined as time of last dose of study drug taken or last visit whichever is later) must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after the 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs (*either initial or follow up information)* is collected and recorded on the paper Serious Adverse Event Report Form. The investigator must assess the relationship to *each specific component of study treatment (if study treatment consists of several drugs)* complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours after awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department. The telephone and fax number of the contact persons in the local department of Drug Safety and Epidemiology, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site. Follow-up information should be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE

Follow-up information provided should describe whether the event has resolved or continues, if and how it was treated, whether the treatment code was broken or not and whether the patient continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the investigational treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same investigational treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

7.3 COPD Exacerbation

COPD exacerbations are defined as:

Worsening of 2 or more of the following major symptoms for at least 2 consecutive days:

• dyspnoea

• sputum volume

• sputum purulence

• AND requiring treatment with systemic corticosteroids and/or antibiotic.

OR

Worsening of any 1 major symptom together with any 1 of the following minor symptoms for at least 2 consecutive days:

• sore throat

• colds (nasal discharge and/or nasal congestion)

• fever without other cause

• increased cough

• increased wheeze

COPD exacerbations are considered of moderate severity if treatment with systemic corticosteroids and/or antibiotic was required and severe if hospitalization was required. An Emergency Room (ER) visit of longer than 24 hours will be considered a hospitalization.

An increase in ICS dose will not be considered as an exacerbation. A worsening of symptoms that does not meet the above symptom definition but is treated by the investigator with systemic corticosteroids or antibiotics or meets the symptom definition and does not get treated by the investigator is not considered moderate or severe COPD exacerbation for the study.

All COPD exacerbations, regardless of treatment, should only be recorded on the COPD exacerbation episode CRF and not on the Adverse Event Form CRF. In case of serious severity, it should be additionally reported on the Serious Adverse Event Form. Please refer to discontinuation criteria following moderate or severe exacerbations in Section 5.5.9.

7.4 Liver safety monitoring

Not applicable.

7.5 Pregnancy reporting

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner.

7.6 Prospective suicidality assessment

Not applicable.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit, a Novartis representative will review the protocol and eCRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

8.2 Data collection

Novartis will give the investigator site access to Electronic Data Capture (EDC) software that has been fully validated and conforms to 21 CFR Part 11 requirements.

Investigator site staff will not be given access to the EDC system until they have been trained. Designated investigator staff will enter the data required by the protocol into the Novartis eCRFs. Automatic validation programs check for data discrepancies in the eCRFs and, by generating appropriate error messages, allow modification or verification of the entered data by the investigator staff. The investigator must certify that the data entered are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

Data of the mMRC, the CAT and the BDI/TDI will be entered into the eCRF by investigator staff. The original version of the questionnaires will be stored at the investigational site as source documents.

8.3 Database management and quality control

Novartis staff or a designated CRO review the eCRFs entered by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and make any necessary changes to the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff or a designated CRO who will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

At the conclusion of the study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused drug supplies to Novartis. The occurrence of any protocol violations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made by Trial Statistician and Statistical Reporting and the Clinical Trial Leader.

8.4 Data Monitoring Committee

Not required.

8.5 Adjudication Committee

Not required.

9 Data analysis

9.1 Analysis sets

The data will be analyzed by Novartis and/or by the designated CRO. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

The **full analysis set (FAS)** will include all randomized patients who received at least one dose of randomized study drug. FAS will be used for the efficacy variables related to lung function and QoL-parameters.

The **per-protocol set (PP)** will include all patients in the FAS without any major protocol deviations. Major protocol deviations will be defined in the validation analysis plan (general) and in the protocol of the blind review meeting (details) prior to database lock and the un-

blinding of the study. PP will be used for the primary analysis of cardiac function parameters, were the aim is to explore mechanistic effects rather than on an estimate of effects achievable in clinical practice. Additionally PP analyses will be used for lung function- and QoL-parameters to support the respective FAS-findings.

The **safety set (SAF)** will include all patients who received at least one dose of study drug whether or not being randomized. Patients will be analyzed according to the treatment they received. The safety set will be used in the analysis of all safety variables.

Note that the FAS and safety set are the same except that the safety set allows the inclusion of non-randomized patients who received study drug in error. In addition, the FAS assigns randomized treatment and the safety set assigns received treatment.

9.2 Patient demographics and other baseline characteristics

Summary statistics will be presented for continuous demographic and baseline characteristic variables by treatment sequence for all subjects in the FAS. The number and percentage of subjects in each category will be presented for categorical variables for each treatment sequence and for all subjects.

9.3 Treatments

Duration of exposure to each of the study drugs during the treatment phase and compliance based on the returned medication will be summarized.

Summary data listings will be provided for concomitant therapy both prior to and after start of study drug administration. The WHO Drug Reference dictionary will be used for coding of medications.

9.4 Analysis of the primary variable

9.4.1 Variable(s)

The primary efficacy variable is the left ventricular enddiastolic volume assessed by MRI after 2 weeks of treatment (i.e. at visit 5 and 7 respectively).

9.4.2 Statistical model, hypothesis, and method of analysis

The primary analysis will be performed comparing treatments with respect to the primary efficacy variable in an analysis of variance (ANOVA) model with the factors center, period, patient within center and treatment. Raw- as well as adjusted (LS-) means will be provided as point estimates for the pair wise treatment contrast. A two-sided, 95% confidence interval and a p-value for the null hypothesis of no treatment difference will be calculated. Additionally unadjusted descriptive statistics (mean, SD, range) will be provided for each treatment and for the treatment contrast.

9.4.3 Significance Level: The significance level is 5% two-sided.Handling of missing values/censoring/discontinuations

As the aim of this study is explore mechanistic effects rather than to estimate effects achievable in clinical practice, the primary analysis will be conducted for the PP-Set. No missing values for the primary endpoint are expected for this set.

9.4.4 Supportive analyses

In case of serious deviations from the normality assumptions, a non-parametric comparison (signed-rank test) may be computed additionally.

The primary endpoint, the left ventricular enddiastolic volume may be affected by the patient's blood pressure. Blood pressure is not a 'classical' covariate, since it is measured after baseline and may itself be affected by the treatment given, therefore, this kind of confounding cannot validly be adjusted for in the primary analysis. However, as a secondary analysis and as an exploratory tool, the primary model will be re-calculated with systolic and diastolic blood pressure added as additional covariates. The mean over the four blood pressure measurements (beginning and the end of the cardiac sequence, after oxygen perfusion and finally at the end of all MRI sequences) will be used for this purpose.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

All secondary endpoints (lung function- and other cardiac function parameters) will be analyzed analogous to the primary endpoint. Exploratory endpoints and Qol-measurements will be analyzed descriptively; appropriate statistical tests for treatment comparisons may be defined in the Statistical Analysis Plan (SAP).

9.5.2 Safety variables

Safety assessments will be based mainly on the frequency of adverse events. Adverse events will be coded by primary system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA). All AEs will be assigned to the last treatment the patient received before AE start. In the data listings of adverse events, the severity of an AE, whether or not an AE is study drug related, and whether or not it is a serious AE, will be indicated. An adverse event related to study drug is defined as one considered by the investigator to have a suspected relationship with the study drug. The adverse events will be summarized by the number and percentage of patients in each primary system organ class and preferred term. For summaries by severity of event, the most severe occurrence for a particular preferred term will be used for a given patient. Summary tables of adverse events by treatment and severity will be provided. Multiple occurrences of the same AE or SAE in the same patient in one treatment period will be counted only once, using the worst severity and drug relationship. Data from other tests (e.g. ECG or vital signs) will be listed, notable values will be flagged, and any other information collected will be listed as appropriate.

For a given treatment period in this crossover design, the only adverse event that will be counted for that treatment will be treatment-emergent events. These events are those that

started after the start of that treatment period, or were present prior to the start of the treatment period but increased in severity, change from being not suspected to being suspected to the due to study drug, or developed into an SAE after the start of the treatment period.

9.5.3 Resource utilization

Not applicable.

9.5.4 Health-related Quality of Life

Not applicable.

9.5.5 Pharmacokinetics

Not applicable.

9.5.6 Pharmacogenetics/pharmacogenomics

Not applicable

9.5.7 Biomarkers

Not applicable

9.5.8 PK/PD

Not applicable.

9.6 Interim analyses

No interim analysis will be conducted.

9.7 Sample size calculation

A QVA149-placebo treatment difference in left ventricular enddiastolic volume (primary endpoint) of 4 ml is considered a sufficient magnitude of effect to reveal mechanistic aspects relevant for COPD patients. The effect size of 4 ml is estimated based on different publications comparing COPD patients with non-COPD patients or with patients of different percentage emphysema, demonstrating differences in LVEDV between 4 – 25 ml [7, 8, 17, 18].

The intraindividual standard deviation of 10 ml is based on Bellenger et al, who describes the interstudy variability within 7 days with an SD of 7.4 ml [19]. As the reproducibility of the method itself (2 measurements with a minimal time interval) is given with a SD of 6.7 ml, an overall SD for this trial is assumed to be 10 ml [20].

With a (within-patient-) standard deviation of 10 ml, 62 patients will be randomized initially with the intention that 52 patients complete the study with valid MRI-measurements. This samples size will provide 80% power to detect the difference as statistically significant at the 5% significance level (2 sided).

9.8 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local

regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

9.9 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

Novartis will provide to investigators in a separate document an informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study.

Women of child bearing potential should be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

9.10 Responsibilities of the investigator and IRB/IEC

The protocol and the informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC must be given to Novartis before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

9.11 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

10 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the trial to request approval of a protocol deviation, as requests to approve deviations will not be granted.

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Under no circumstances should an investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

10.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC. Only amendments that are required for patient safety may be implemented prior to IRB/IEC approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed within 10 working days or less, if required by local regulations.

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12 Appendix 1: Clinically notable laboratory values and vital signs

There are no specific criteria for this study, however, the Central Laboratory will flag laboratory values falling outside of the normal ranges on the Central Laboratory Report (which the investigator should review and sign off) and the investigator will report any values considered clinically significant in the eCRF.

The number (%) of patients with pulse rate of <40 and >130 bpm; systolic blood pressure of <75 and >200 mmHg; diastolic blood pressure of <40 and >115 mmHg will be summarized by treatment group.

Notable values for vital signs and change from baseline will be summarized. A notable value is defined as follows:

- Systolic blood pressure

"Low" criterion: <75 mmHg, or ≤90 mmHg and decrease from baseline ≥20 mmHg

"High" criterion: >200 mmHg, or ≥180 mmHg and increase from baseline ≥20 mmHg

- Diastolic blood pressure

"Low" criterion: <40 mmHg, or ≤50 mmHg and decrease from baseline ≥15 mmHg

"High" criterion: >115 mmHg, or ≥105 mmHg and increase from baseline ≥15 mmHg

- Pulse rate

"Low" criterion: <40 bpm, or ≤50 bpm and decrease from baseline ≥15 bpm

"High" criterion: >130 bpm, or ≥120 bpm and increase from baseline ≥15 bpm

For ECGs a notable QTc value is defined as a QTc interval of greater than 450 ms for males and 470 ms for females.

QTc will be calculated from the QT interval and RR (in seconds) using Fridericia's formula: QTc = QT / cube root (RR).

13 Appendix 2: GOLD guidelines (2014)

- Patient Group A – Low Risk, Less Symptoms

  Typically GOLD 1 or GOLD 2 (mild or moderate airflow limitation); and/or 0-1 exacerbation per year and not hospitalization for exacerbation; and CAT score <10 or mMRC grade 0-1.

- Patient Group B – Low Risk, More Symptoms

  Typically GOLD 1 or GOLD 2 (mld or moderate airflow limitation); and/or 0-1 exacerbation per year and no hospitalization for exacerbation; and CAT score ≥10 or mMRC grade ≥2.

- Patient Group C – High Risk, Less Symptoms

  Typically GOLD 3 or GOLD 4 (severe or very severe airflow limitation); and/or ≥2 exacerbations per year or ≥1 with hospitalization for exacerbation; and CAT score <10 or mMRC grade 0-1.

- Patient Group D – High Risk, More Symptoms

  Typically GOLD 3 or GOLD 4 (severe or very severe airflow limitation); and/or ≥2 exacerbations per year or ≥1 with hospitalization for exacerbation; and CAT score ≥10 or mMRC grade ≥2.

14 Appendix 3: Spirometry Guidance

Equipment

Spirometers must meet the specifications and performance criteria recommended in the American Thoracic Society (ATS)/European Respiratory Society (ERS) Standardization of Spirometry. Spirometers must have the capacity to print FVC tracings. All spirometry values should be reported at BTPS by the method established by the manufacturer.

Calibration

The spirometer should be calibrated every morning before any spirometric measurements for the study are performed. Calibration reports should be printed and stored as source data at the site.

Preparing the test subject

On study days when spirometry will be performed, patients should refrain from the following:

- Coffee, tea, chocolate, cola and other caffeine-containing beverages and foods and ice-cold beverages for 4 hours prior to spirometry
- Alcohol for 4 hours prior to spirometry
- Strenuous activity for 12 hours prior to spirometry
- Smoking within at least 1 hour of testing
- Exposure to environmental smoke, dust or areas with strong odors

Every effort should be made to assure consistent testing conditions throughout the study. A seated position with nose clips is recommended to reduce risks related to dizziness or syncope. When possible, spirometry should be conducted by the same technician using the same spirometer.

Performing Spirometry

The subject's age, height and gender will be recorded and entered into the eCRF, where the predicted normal values are lodged. It is important that the height is measured accurately at the study site. Spirometry, an effort-dependent test, requires careful instruction and cooperation of the subject. The technician should ensure a good seal around the mouthpiece, and confirm that the subject's posture is correct. The results of spirometry should meet the ATS/ERS criteria for acceptability and repeatability. Acceptability criteria should be applied before repeatability is determined.

Number of trials

Spirometric assessments will be performed in triplicate according to ATS/ERS standards. If a subject is unable to perform a single acceptable maneuver after 5 attempts, testing may be discontinued.

Acceptability

An acceptable maneuver has the following characteristics:

- No hesitation or false start;
- A rapid start;
- No cough, especially during the first second of the maneuver;
- No glottis closure or obstruction by tongue or dentures
- No early termination of exhalation (minimum exhalation time of 6 seconds is recommended, or no volume change for at least 1 second) or the subject cannot continue to exhale further

Repeatability

The 2 largest FVC and FEV_1 values from 3 acceptable maneuvers should not vary by more than 0.150 L.

Recording of data

The highest FEV_1 and FVC from any of the acceptable curves are recorded. (The highest FEV_1 and FVC may not necessarily result from the same acceptable curve).

Predicted normal

This study will utilize the spirometric predication equation standards for the European Community for Coal and Steel (Quanjer et al 1993).

Reversibility

All reversibility evaluations should follow the recommendations of the ATS/ERS Task force: Standardization of Lung Function Testing[1]. A pre-bronchodilator spirometry assessment should be performed after a washout period of at least:

- 6 h for short-acting β_2-agonists
- 8 h for short-acting anticholinergics
- 48 h for long-acting β_2-agonist
- 7 days for long-acting anticholinergic
- 7 days for indacaterol

Administer 400µg of salbutamol (4x100µg) following the completion of the pre-bronchdilator assessment. Post-bronchodilator spirometry assessment is then performed 10-15 minutes after administration of salbumatol.

Reversibility is calculated as:

$$100 \times \frac{FEV_1 \text{ (post-bronchodilator)} - FEV_1 \text{ (pre-bronchodilator)}}{FEV_1 \text{ (pre-bronchodilator)}}$$

Patients with COPD demonstrating a high reversibility may require further clinical evaluation by the investigator to rule out a diagnosis of asthma.

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15 Appendix 4: Baseline Dyspnea Index and Transition Dyspnea Index

(Samples of questionnaires provided here are for illustrative purposes only)

Dyspnea Index - Baseline
(Reproduced by kind permission of CHEST)

Functional Impairment

- ☐ Grade 4: *No Impairment*. Able to carry out usual activities and occupation without shortness of breath.
- ☐ Grade 3: *Slight Impairment*. Distinct impairment in at least one activity but no activities completely abandoned. Reduction, in activity at work *or* in usual activities, that seems slight or not clearly caused by shortness of breath.
- ☐ Grade 2: *Moderate Impairment*. Patient has changed jobs *and/or* has abandoned at least one usual activity due to shortness of breath.
- ☐ Grade 1: *Severe Impairment*. Patient unable to work *or* has given up most or all usual activities due to shortness of breath.
- ☐ Grade 0: *Very Severe Impairment*. Unable to work *and* has given up most or all usual activities due to shortness of breath.
- ☐ W: *Amount Uncertain*. Patient is impaired due to shortness of breath, but amount cannot be specified. Details are not sufficient to allow impairment to be categoried.
- ☐ X: *Unknown*. Information unavailable regarding impairment.
- ☐ Y: *Impaired for Reasons Other than Shortness of Breath*. For example, musculoskeletal problem or chest pain.

Usual activities refer to requirements of daily living, maintenance or upkeep of residence, yard work, gardening, shopping, etc.

Magnitude of Task

- ☐ Grade 4: *Extraordinary*. Becomes short of breath only with extraordinary activity such as carrying very heavy loads on the level, lighter loads uphill, or running. No shortness of breath with ordinary tasks.
- ☐ Grade 3: *Major*. Becomes short of breath only with such major activities as walking up a steep hill, climbing more than three flights of stairs, or carrying a moderate load on the level.
- ☐ Grade 2: *Moderate*. Becomes short of breath with moderate or average tasks such as walking up a gradual hill, climbing fewer than three flights of stairs, or carrying a light load on the level.
- ☐ Grade 1: *Light*. Becomes short of breath with light activities such as walking on the level, washing, or standing.
- ☐ Grade 0: *No Task*. Becomes short of breath at rest, while sitting, or lying down.
- ☐ W: *Amount Uncertain*. Patient's ability to perform tasks is impaired due to shortness of breath, but amount cannot be specified. Details are not sufficient to allow impairment to be categoried.
- ☐ X: *Unknown*. Information unavailable regarding limitation of magnitude of task.
- ☐ Y: *Impaired for Reasons Other than Shortness of Breath*. For example, musculoskeletal problem or chest pain.

Dyspnea Index - cont. - Baseline

Magnitude of Effort

☐ Grade 4: *Extraordinary*. Becomes short of breath only with the greatest imaginable effort. No shortness of breath with ordinary effort.

☐ Grade 3: *Major*. Becomes short of breath with effort distinctly submaximal, but of major proportion. Tasks performed without pause unless the task requires extraordinary effort that may be performed with pauses.

☐ Grade 2: *Moderate*. Becomes short of breath with moderate effort. Tasks performed with occasional pauses and requiring longer to complete than the average person.

☐ Grade 1: *Light*. Becomes short of breath with little effort. Tasks performed with little effort or more difficult tasks performed with frequent pauses and requiring 50-100% longer to complete than the average person might require.

☐ Grade 0: *No Effort*. Becomes short of breath at rest, while sitting, or lying down.

☐ W: *Amount Uncertain*. Patient's exertional ability is impaired due to shortness of breath, but amount cannot be specified. Details are not sufficient to allow impairment to be categorized.

☐ X: *Unknown*. Information unavailable regarding limitation of effort.

☐ Y: *Impaired for Reasons Other than Shortness of Breath*. For example, musculoskeletal problems or chest pain.

Dyspnea Index - Transition

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Change in Functional Impairment

- ☐ -3: *Major Deterioration*. Formerly working and has had to stop working *and* has completely abandoned some of usual activities due to shortness of breath.
- ☐ -2: *Moderate Deterioration*. Formerly working and has had to stop working *or* has completely abandoned some of usual activities due to shortness of breath.
- ☐ -1: *Minor Deterioration*. Has changed to a lighter job *and/or* has reduced activities in number or duration due to shortness of breath. Any deterioration less than preceding categories.
- ☐ 0: *No Change*. No change in functional status due to shortness of breath.
- ☐ +1: *Minor Improvement*. Able to return to work at reduced pace *or* has resumed some customary activities with more vigor than previously due to improvement in shortness of breath.
- ☐ +2: *Moderate Improvement*. Able to return to work at nearly usual pace *and/or* able to return to most activities with moderate restriction only.
- ☐ +3: *Major Improvement*. Able to return to work at former pace *and* able to return to full activities with only mild restriction due to improvement of shortness of breath.
- ☐ Z: *Further Impairment for Reasons Other than Shortness of Breath*. Patient has stopped working, reduced work, or has given up or reduced other activities for other reasons. For example, other medical problems, being "laid off" from work, etc.

Change in Magnitude of Task

- ☐ -3: *Major Deterioration*. Has deteriorated two grades or greater from baseline status.
- ☐ -2: *Moderate Deterioration*. Has deteriorated at least one grade but fewer than two grades from baseline status.
- ☐ -1: *Minor Deterioration*. Has deteriorated less than one grade from baseline. Patient with distinct deterioration within grade, but has not changed grades.
- ☐ 0: *No Change*. No change from baseline.
- ☐ +1: *Minor Improvement*. Has improved less than one grade from baseline. Patient with distinct improvement within grade, but has not changed grades.
- ☐ +2: *Moderate Improvement*. Has improved at least one grade but fewer than two grades from baseline.
- ☐ +3: *Major Improvement*. Has improved two grades or greater from baseline.
- ☐ Z: *Further Impairment for Reasons Other than Shortness of Breath*. Patient has reduced exertional capacity, but not related to shortness of breath. For example, musculoskeletal problem or chest pain.

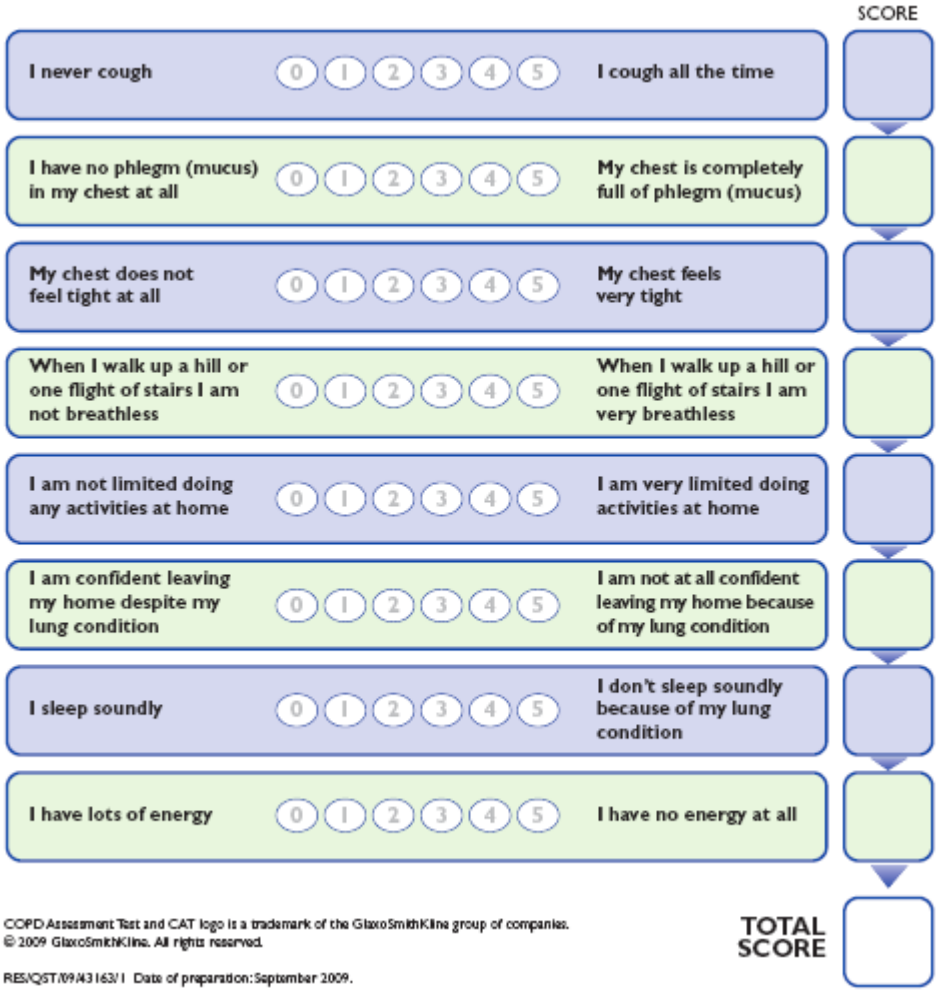
Dyspnea Index - cont. - Transition

Change in Magnitude of Effort

- ☐ -3: *Major Deterioration*. Severe decrease in effort from baseline to avoid shortness of breath. Activities now take 50-100% longer to complete than required at baseline.
- ☐ -2: *Moderate Deterioration*. Some decrease in effort to avoid shortness of breath, although not as great as preceding category. There is greater pausing with some activities.
- ☐ -1: *Minor Deterioration*. Does not require more pauses to avoid shortness of breath, but does things with distinctly less effort than previously to avoid breathlessness.
- ☐ 0: *No Change*. No change in effort to avoid shortness of breath.
- ☐ +1: *Minor Improvement*. Able to do things with distinctly greater effort without shortness of breath. For example, may be able to carry out tasks somewhat more rapidly than previously.
- ☐ +2: *Moderate Improvement*. Able to do things with fewer pauses and distinctly greater effort without shortness of breath. Improvement is greater than preceding category, but not of major proportion.
- ☐ +3: *Major Improvement*. Able to do things with much greater effort than previously with few, if any, pauses. For example, activities may be performed 50-100% more rapidly than at baseline.
- ☐ Z: *Further Impairment for Reasons Other than Shortness of Breath*. Patient has reduced exertional capacity, but not related to shortness of breath. For example, musculoskeletal problem ot chest pain.

16 Appendix 5: COPD Assessment Test (CAT)

(Sample of test provided here are for illustrative purposes only)



17 Appendix 6: modified Medical Research Council (mMRC) Dyspnea Scale

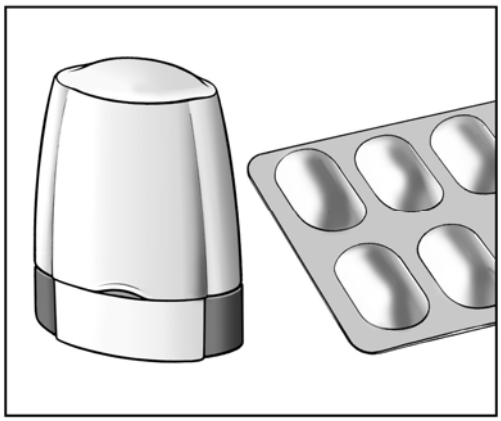
Medical Research Council (Mahler et al. 1984):

Grade	Symptoms
0	Not troubled by breathlessness except with strenuous exercise
1	Troubled by shortness of breath when hurrying on the level or walking up a slight hill
2	Walks slower than people of the same age on the level because of breathlessness or has to stop for breath when walking at own pace on the level
3	Stops for breath after walking about 100 yards (91 m) or after a few minutes on the level
4	Too breathless to leave the house or breathless when dressing or undressing

18 Appendix 7: Instructions for use of the SDDPI

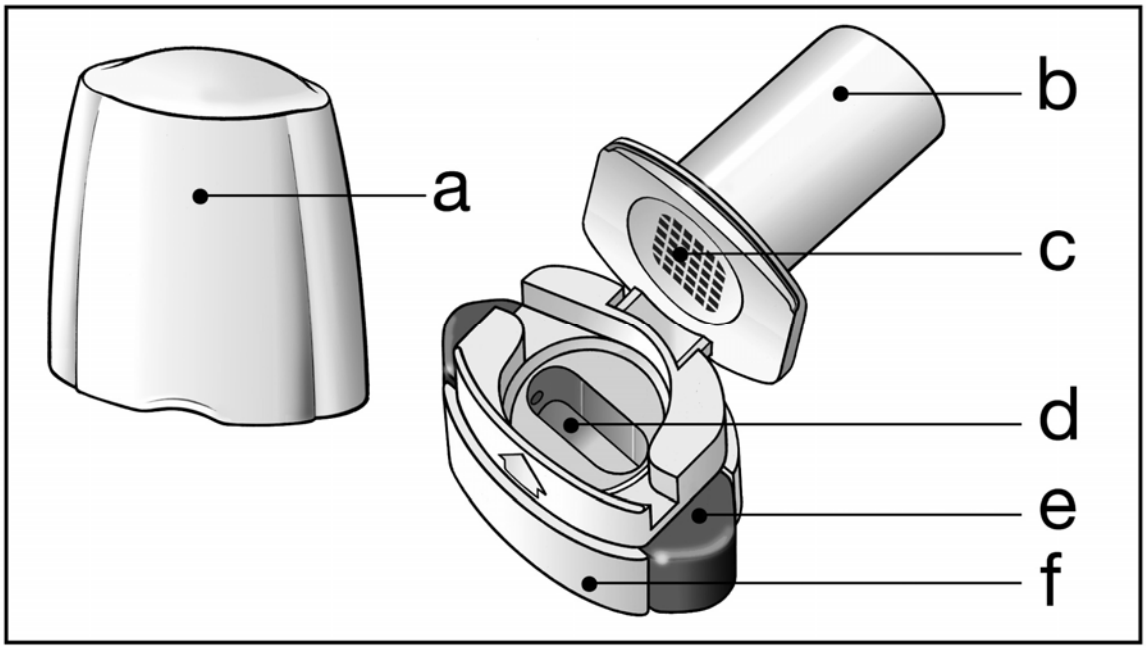
How to use the SDDPI

Your inhaler



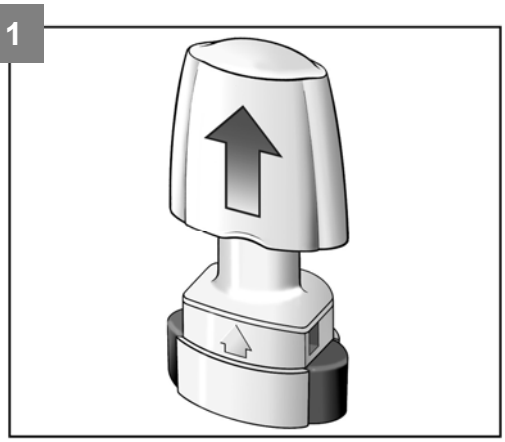
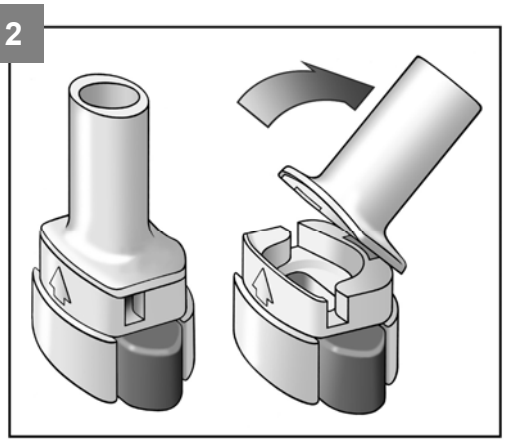
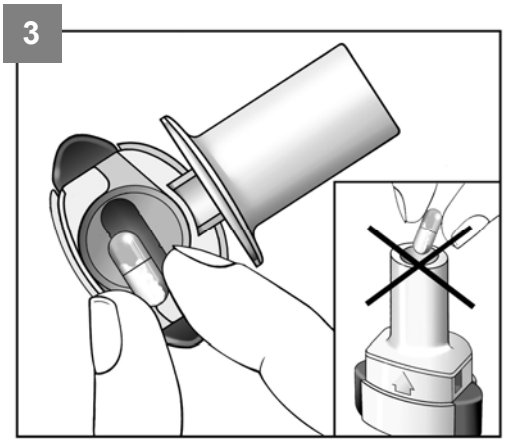
Your inhaler is designed to administer the study drug contained in the capsules. The capsules are packaged in blisters.

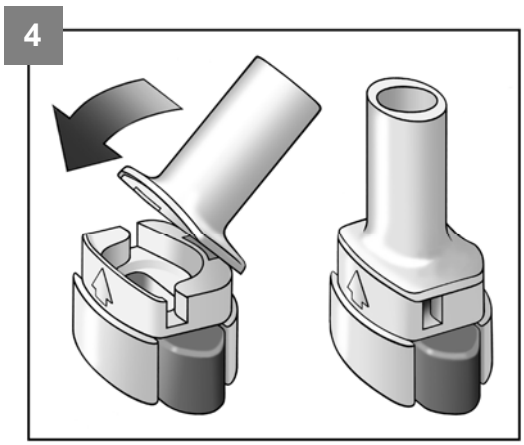
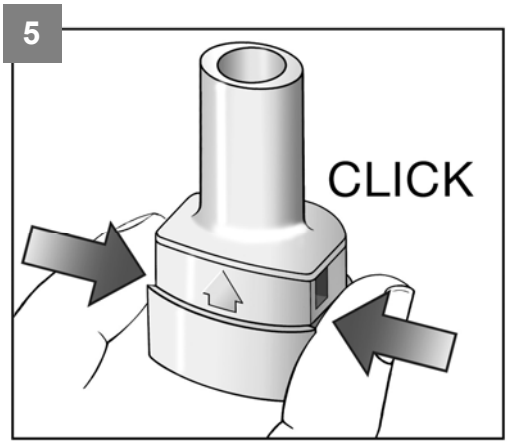
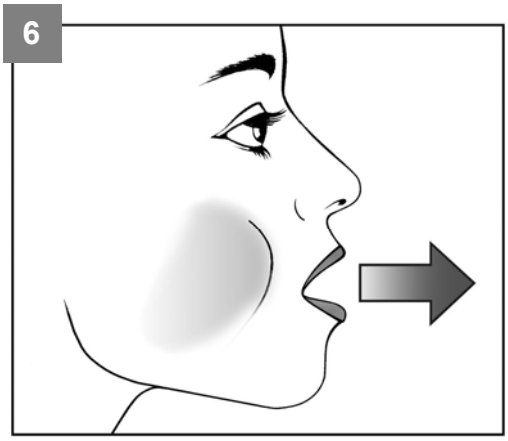
Do not swallow capsule.

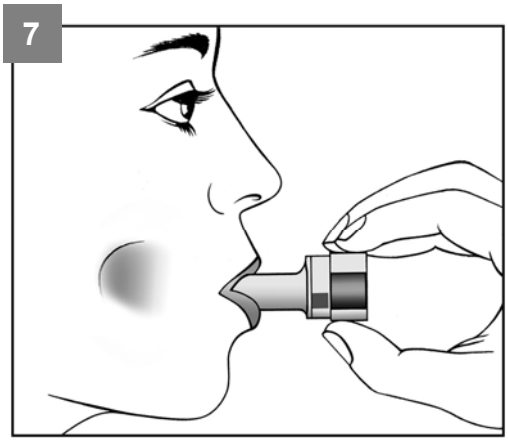
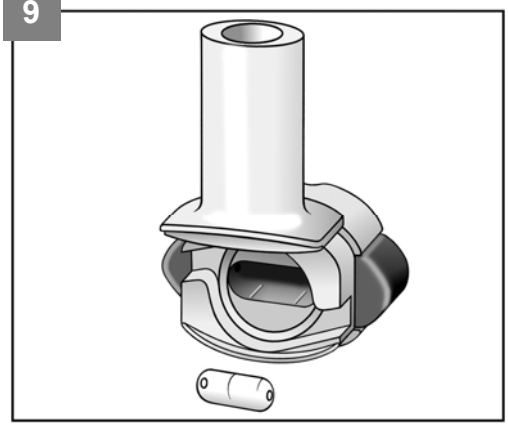


a	Cap	**d**	Capsule cavity
b	Mouthpiece	**e**	Button
c	Screen	**f**	Base

How to use your inhaler

1 	Pull off cap.
2 	Open inhaler: Hold the base of the inhaler firmly and tilt the mouthpiece in the direction of the arrow to open the inhaler.
3 	Insert capsule: **Immediately before use**, with dry hands, remove one capsule from the blister. Place the capsule into the capsule cavity. **Never place a capsule directly into the mouthpiece.**

	Close the inhaler: Close the inhaler fully. You should hear a ‘click’ as it fully closes.
	Pierce the capsule: Hold the inhaler upright. **Press both buttons fully one time.** You should hear a ‘click’ as the capsule is being pierced. Release the buttons fully. **Do not press the buttons repeatedly.**
	Breathe out: Before placing the mouthpiece in your mouth, breathe out fully. **Never blow into the mouthpiece**.

7 	Administer study drug: Before breathing in, place the mouthpiece in your mouth and close your lips around the mouthpiece. Hold the inhaler with the buttons to the left and right (not up and down). Breathe in rapidly and steadily, as deeply as you can. **Do not press the buttons**. As you breathe in through the inhaler, the capsule spins around in the cavity and you should hear a whirring noise. You will experience a sweet taste as the medicine goes into your lungs. If you do not hear a whirring noise, the capsule may be stuck in the capsule cavity. If this occurs, open the inhaler and carefully loosen the capsule by tapping the base of the device. **Do not press the buttons repeatedly** to loosen the capsule. Repeat steps 6 and 7 if necessary.
8 	**Continue to hold your breath** as long as comfortably possible while removing the inhaler from your mouth. Then breathe out. Open the inhaler to see if any powder is left in the capsule. If there is powder left in the capsule, close the inhaler and repeat steps 6 to 8. Most people are able to empty the capsule in one or two inhalations.
9 	Remove capsule: After use, open the inhaler, remove the empty capsule by tipping it out, and discard it. Close the inhaler and replace the cap. Never leave a capsule in the inhaler.

Additional information

Occasionally, very small pieces of the capsule can get past the screen and enter your mouth. If this happens, you may be able to feel these pieces on your tongue. It is not harmful if these pieces are swallowed or inhaled. The chances of the capsule shattering will be increased if the capsule is pierced more than once (Step 5). Therefore it is recommended that you follow the storage directions, remove the capsule from the blister **immediately** before use and pierce each capsule only **once**.

How to clean your inhaler

Clean your inhaler every week. Wipe the mouthpiece inside and outside with a clean, **dry** lint-free cloth to remove any powder residue. Alternatively, use a clean, dry, soft brush.

19 Appendix 8: List of MRI parameters captured in the eCRF

Heart function			
Heart frequency (SA cine):			

Blood Pressure during MRI	systolic	diastolic	
Prior to heart sequence:		/	mmHg
Prior to oxygen:		/	mmHg
During to oxygen:		/	mmHg
End of MRI:		/	mmHg

Left ventricle	Value	Index	
LV-EDV:		ml	ml/m²
LV-ESV:		ml	ml/m²
LV-SV:		ml	ml/m²
LV-EF:		%	
LV-mass:		g	g/m²
E/Ea:			

LV significant focal wall motion abnormalities:

Right ventricle	Value	Index	
RV-EDV:		ml	ml/m²
RV-ESV:		ml	ml/m²
RV-SV:		ml	ml/m²
RV-EF:		%	
RV-mass:		g	g/m²

RV significant focal wall motion abnormalities:

Pulmonary arterial blood flow (room air):	
Forward volume:	ml/beat
Regurgitant volume :	ml/beat
Maximal flow velocity:	cm/s
Mean systolic flow velocity:	cm/s
Mean flow velocity (total cardiac cycle):	cm/s
Acceleration volume:	ml
Acceleration time:	ms
Duration of systole:	ms
Heart frequency:	/min
Diameter of pulmonary artery:	cm
Area of pulmonary artery (syst):	mm^2
Area of pulmonary artery (diast):	mm^2

Pulmonary arterial blood flow (100% oxygen):	
Forward volume:	ml/beat
Regurgitant volume :	ml/beat
Maximal flow velocity:	cm/s
Mean systolic flow velocity:	cm/s
Mean flow velocity (total cardiac cycle):	cm/s
Acceleration volume:	ml
Acceleration time:	ms
Duration of systole:	ms
Heart frequency:	/min
Diameter of pulmonary artery:	cm
Area of pulmonary artery (syst):	mm^2
Area of pulmonary artery (diast):	mm^2

Lung perfusion	
PBF mean total:	ml/min/100 ml lung volume
Variation coefficient PBF total:	ml/min/100 ml lung volume
Coronary flow (trachea):	ml/min/100 ml lung volume
Right lung PBF (mean)	
total:	ml/min/100 ml lung volume
upper lobe:	ml/min/100 ml lung volume
middle lobe:	ml/min/100 ml lung volume
lower lobe:	ml/min/100 ml lung volume
Left lung PBF (mean)	
total:	ml/min/100 ml lung volume
upper lobe:	ml/min/100 ml lung volume
lower lobe:	ml/min/100 ml lung volume
anterior/posterior PBF fraction :	
PTT:	s

Oxygen MRI:	
O_2 wash-out time:	s
room air	
T1	ms
variation coefficient	
100% oxygen	
T1	ms
variation coefficient	
OTF:	10^{-4} s^{-1} $\%O_2^{-1}$

Ventilation MRI:
Fractional ventilation total (coronal)
Fractional ventilation :
Fractional ventilation total normalized:
variation coefficient:
% area under cutoff:
Fractional ventilation saggital right
Fractional ventilation :
Fractional ventilation total normalized:
variation coefficient:
% area under cutoff:
Fractional ventilation saggital left:
Fractional ventilation :
Fractional ventilation total normalized:
variation coefficient:
% area under cutoff:

19 F washout time	
Mean:	s
Variation coefficient of washout time:	
Mean number of breaths:	
Variation coefficient of number of breaths:	

20 Appendix 9: List of echocardiography parameters captured in the eCRF

1. Left atrium and left ventricle

LA-Vol. (bipl):	__ __ __ , __	ml			
E:	__ __ __ , __	cm/s	A:	__ __ __ , __	cm/s
E (Valsalva):	__ __ __ , __	cm/s	A (Valsalva):	__ __ __ , __	cm/s
E-DT:	__ __ __	ms	A-Dur:	__ __ __	ms
IVRT:	__ __ __	ms	IVCT:	__ __ __	ms
ET:	__ __ __	ms			
TDI					
S'-lat:	__ __ , __	cm/s	S'-sept:	__ __ , __	cm/s
E'-lat:	__ __ , __	cm/s	E'-sept:	__ __ , __	cm/s
A'-lat:	__ __ , __	cm/s	A'-sept:	__ __ , __	cm/s
Strain					
4CV LS:	__ __	%	2CV LS:	__ __	%
3CV LS:	__ __	%	GLS (LV):	__ __	%
Pulmonary veins					
S:	__ __ , __	cm/s	D:	__ __ , __	cm/s
AR-Dur:	__ __ __	ms			

2. Right atrium und right ventricle

RA area	__ __ , __	cm^2	TAPSE:	__ __	mm
RV-E:	__ __ __ , __	cm/s	RV-A:	__ __ __ , __	cm/s
RV-E-DT:	__ __ __	ms	RVOT-VTI:	__ __ __	cm
TDI					
RV-S':	__ __ , __	cm/s	IVA:	__ , __ __	m/s^2
RV-E':	__ __ , __	cm/s	RV-IVRT:	__ __ __	ms
RV-A':	__ __ , __	cm/s			
RV-TCO:	__ __ __	ms	RV-ET	__ __ __	ms
Strain					
LS (free wall):	__ __	%	LS (septum):	__ __	%
GLS(RV):	__ __	%			

3. Pulmonary pressure

TR-dPmax	__ __ __	mmHg			
PR-dPmax:	__ __	mmHg	PR-dPend:	__ __	mmHg
VCI:	__ __	mm			

- ○ inspiratory collapse (>50%)
- ○ reduced respiratory variation (<50%)
- ○ no respiratory variation