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QVA149

CQVA149A2325

A randomized, double-blind, placebo-controlled, two-period crossover study to assess the effect of inhaled QVA149 on global and regional lung function and gas exchange in patients with moderate to severe COPD

Authors: Personal Data

Document type:	Amended Protocol Version
EUDRACT number:	2013-004461-13
Version number:	v02 (Clean)
Development phase:	IV
Release date:	17-Feb-2017

Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study conduct.

Notification of serious adverse events

Refer to Section 9.2 of the protocol for definitions and reporting requirements for Serious Adverse Events (within 24 hours after awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department and notify the Clinical Trial Leader.).

Contact information is listed in the Site Operations Manual.

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List of abbreviations

AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AUC	area under the concentration time curve
AST	aspartate aminotransferase
BMI	Body Mass Index
BUN	blood urea nitrogen
CD-ROM	compact disc – read only memory
CFR	Code of Federal Regulation
CK	creatinine kinase
CO_2	carbon dioxide
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CV	coefficient of variation
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
FEF	Forced expiratory flow
FEV1	Forced expiratory volume in one second
GCP	Good Clinical Practice
h	hour
HRCT	High Resolution Computed Tomography
HIV	human immunodeficiency virus
i.v.	intravenous
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee

IRB	Institutional Review Board
IRT	Interactive Response Technology
LDH	lactate dehydrogenase
LLN	lower limit of normal
LLQ	lower limit of quantification
MRI	Magnetic Resonance Imaging
mg	milligram(s)
ml	milliliter(s)
o.d.	once a day
p.o.	oral
PA	posteroanterior
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
RBC	red blood cell(s)
REB	Research Ethics Board
s.c.	subcutaneous
SAE	serious adverse event
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
TBL	total bilirubin
ULN	upper limit of normal
ULQ	upper limit of quantification
WBC	white blood cell(s)

Protocol synopsis

Protocol number	QVA149A2325
Title	A randomized, double-blind, placebo-controlled, two-period crossover study to assess the effect of inhaled QVA149 on global and regional lung function and gas exchange in patients with moderate to severe COPD
Brief title	Imaging study of inhaled QVA149 on lung function and gas exchange in patients with moderate to severe COPD
Sponsor and Clinical Phase	Novartis Phase IV
Intervention type	Drug
Study type	Interventional
Purpose and rationale	This study will investigate the effect of QVA149 on global and regional lung ventilation using MRI hyperpolarized gas lung imaging to enhance the understanding of QVA pharmacology in COPD patients. The assessment of regional ventilation measures can be combined with a MRI perfusion evaluation of the lung to visualize ventilation-perfusion mismatches which will also be evaluated in response to QVA149 treatment compared to placebo. Current physiological measures of small airway dysfunction are limited, subject to a high degree of variability and do not allow a quantitative assessment of global and regional ventilation defects. The MRI approach represents an opportunity to better understand the impact of a potent dual bronchodilator on the small and central airways and thereby increasing ventilated lung volume, gas exchange, and ventilation-perfusion deficits.
Primary Objective(s)	To assess global ventilated lung volume in moderate to severe COPD patients using hyperpolarized gas lung imaging after 7 days of treatment with QVA149 compared to placebo.
Secondary Objectives	To assess regional lung ventilated volume in moderate to severe COPD patients using hyperpolarized gas lung imaging after 7 days of treatment with QVA149 compared to placebo.
Study design	A double-blind, randomized, placebo-controlled, two-period, cross-over study in patients with moderate to severe COPD. The study will consist of a 2-week screening period, a 7-9 day run-in, baseline, a double-blind 8-day (up to 10 day) treatment Period 1 followed by a washout period before crossing over to a double-blind 8-day (up to 10 day) treatment Period 2, and an end-of-study visit up to one week after the last MRI assessments.
Population	The study population consists of approximately 34 male and female moderate to severe COPD patients aged 40 years and above.

Inclusion criteria	• Written informed consent must be obtained before any assessment is performed. • Male and female with COPD aged 40 years and above. • Smokers and ex-smokers who have a smoking history of at least 10 pack years. Smokers will be defined as any patient who reports tobacco use within the last month. • Patients with a diagnosis of moderate to severe COPD according to GOLD 2015 criteria. Patients with airflow limitation indicated by a post-bronchodilator FEV1/FVC < 0.70 and by a post-bronchodilator FEV1 ≥ 30 % and <80 %. ○ Post-bronchodilator refers to 1 hr (+/- 5 minutes) after sequential inhalation of 84 µg ipratropium bromide (or equivalent dose) and 400 µg salbutamol/360 µg albuterol (or equivalent dose) Spacer devices are not permitted during reversibility testing. • Patients must weigh ≥45 kg and ≤100 kg to participate in the study. • Able to communicate well with the investigator, to understand and comply with the requirements of the study.
Exclusion criteria	• History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes. • Any significant medical condition that in the opinion of the Investigator may compromise patient safety, patient compliance, interfere with evaluations, or preclude completion of the trial. For example, COPD exacerbations within the 6 weeks prior to screening requiring oral steroids and/or antibiotics Corporate Confidential Information • Patients with concomitant pulmonary disease, e.g., pulmonary tuberculosis (unless confirmed by chest x-ray to be no longer active) or clinically significant bronchiectasis. • Patients with a history of asthma • Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant. • Patients unable to successfully use a dry powder inhaler device or perform spirometry, MBNW/Lung Volumes, and DLCO measurements • Subjects with contraindications to MRI.
Investigational and reference therapy	QVA149 110/50 µg o.d. capsules for inhalation, supplied in blisters via Novartis single dose dry powder inhaler (SDDPI).
Efficacy/PD assessments	• MRI lung imaging • Spirometry • MBNW

Safety assessments	• Adverse events and serious adverse events • Vital signs • ECG
Other assessments	Not applicable
Data analysis	The number and percentage of subjects with adverse events will be tabulated by body system and preferred term with a breakdown by treatment. A patient with multiple adverse events within a body system and treatment period is only counted once towards the total of this body system and treatment. The percent of global ventilated volume on Day 7 of each treatment period at the study site will be analyzed using mixed effects model. The model will include fixed effects for sequence, treatment and period. Patient factor will be included as a random effect. An unstructured covariance matrix will be applied. Confidence intervals together with standard error (SE) and P-value will be calculated for the contrast QVA149 vs Placebo.
Key words	Chronic Obstructive Pulmonary Disease, COPD, Glycopyrronium bromide, Indacaterol maleate, small airways, Helium-3 MRI,

1 Introduction

1.1 Background

Chronic obstructive pulmonary disease (COPD) is a disease of progressive airflow obstruction involving airways of all sizes, ultimately leading to alveolar destruction and loss of gas-exchange capacity resulting in disability and death. Worldwide, COPD is projected to rank fifth in burden of disease and third with respect to mortality by 2020 (Buist et al 2007). It affects approximately 20% of chronic cigarette smokers. There is a high level of unmet medical need in the management of COPD patients, including effective symptomatic relief or treatment of dyspnoea, limited exercise tolerance, mucus hyper-secretion, cough and poor quality of life (GOLD 2015).

Current treatment guidelines for COPD recommend the use of bronchodilators for all severities, either on an as-required (pro re nata: prn) basis, or on a regular basis (GOLD 2015). Inhaled long-acting bronchodilators such as β2-adrenergic agonists (LABAs) and muscarinic antagonists (LAMAs) are recommended as a monotherapy or in combination (LABA+LAMA) (in GOLD B, C and D patients) for treatment of COPD patients.

Though COPD is considered to be a progressive disease of airways of all sizes, there is emerging evidence that the small airways (i.e. bronchioles < 2mm in diameter) are the site of early and the major site of obstructive pathology in COPD and that the disease may be reversible (McDonough et al 2011). However, as the disease progresses, there is incremental large airway involvement though there is considerable phenotypic, physiologic and anatomic heterogeneity. This study focuses primarily on a panel of endpoints that investigate small airway function. The assessment and potential improvement of both the ventilation and perfusion deficit resulting from smaller airway dysfunction could be important in preventing further deterioration or clinical improvement in longer studies manifested by fewer exacerbations.

Due to the heterogeneity of the COPD patient population, this study will apply non-invasive imaging technology to assess both the structural and functional responses of the small airways to treatment with QVA. Hyperpolarized gas imaging is a methodology that utilizes helium-3 (He-3) gas that is polarized outside of the MRI scanner and then delivered to the patient (via inhalation) while in the scanner. The resulting MR images generated from the hyperpolarized helium gas within the lung produce high resolution volumetric images of the ventilatory (both static and dynamic) distribution of the inhaled gas. The extent of the ventilation defects observed in COPD by He-3 MRI has been established to correlate with both age and disease severity (Kirby et al 2010).

The intent of this study is to evaluate the impact of a dual, potent bronchodilator treatment on ventilation defects assessed by hyperpolarized helium MRI. By combining the ventilation imaging with standard dynamic gadolinium contrast-enhanced 1H MR imaging that reflects the lung perfusion, an estimate of the ventilation/perfusion mismatch can be determined. An additional opportunity with the He-3 MRI method is to assess the apparent diffusion coefficient of the helium that has very high sensitivity to emphysematous destruction and airspace size thus providing additional validation of the traditional high resolution

CT imaging that will be applied at screening to optimize patient selection regarding extent of emphysema. Thus, the goals of the non-invasive imaging modalities in this study are for the purposes of assessment of small airway responses by determining global and regional ventilation defect scores, changes in subsequent lung tissue perfusion, and functional improvements in gas trapping.

QVA149 is a fixed combination of a long-acting β2-agonist (Indacaterol maleate – QAB149) and a long-acting muscarinic antagonist (Glycopyrronium bromide – NVA237) that has been recently approved in Europe, Japan and several other countries worldwide for the maintenance treatment of COPD. QVA149 has been evaluated in a comprehensive Phase III development program comprising more than 11,000 COPD patients across 47 countries. Available data has demonstrated improvement in lung function, health-related quality of life, decrease in COPD symptoms and decrease in use of short-acting β2-adrenergic agonist (SABA) with a safety profile similar to the individual monotherapy components (Dahl et al 2013; Bateman et al 2013; Mahler et al 2014).

1.1.1 Relevant data summary

Detailed background information on the chemistry, pharmacology, toxicology and pharmacokinetics of QVA149 are given in the Investigator's Brochure and in the package insert of marketed QVA149 (Ultibro Breezhaler® Package Insert 2013), respectively.

The most relevant data for the present study are summarized in the sections below.

1.1.1.1 Preclinical data

QVA149 is a combination of QAB149 and NVA237 ligands which bind to β2 and muscarinic receptors, respectively. The in vitro activity cellular activity and selectivity profile for the combination drug QVA149 is an additive profile of the individual components.

1.1.1.2 Toxicology data including teratogenicity and reproductive toxicity data

The non-clinical safety program for QVA149 is based upon the complete toxicology programs conducted for both individual active drugs which included chronic, reproductive, genotoxicity and carcinogenicity studies.

A bridging toxicology program was performed for QVA149 that included in vitro and in vivo safety pharmacology assessments, 2-week inhalation toxicity studies in rats and dogs, a 13-week inhalation toxicity study in dogs as the most sensitive species and an inhalation embryo-fetal development study in rats. No new toxicological findings were observed. The effects seen in the QVA149 inhalation toxicity studies and the safety pharmacology studies are consistent with the known effects of indacaterol (tachycardia, shortened ECG intervals, ischemic heart damage) and glycopyrronium (tachycardia, shortened ECG intervals) and relate to the exaggerated pharmacological effects of high-dose β2-adrenergic receptor agonists and muscarinic receptor antagonists, respectively. In the 14-day and 13-week inhalation dog studies, the QVA149 mid- and high-dose groups and also the dose groups in the cardiovascular inhalation safety pharmacology study in telemetered dogs showed potentiation of the effects on heart rate in comparison with either of the components alone.

In addition, investigations with the components of QVA149, indacaterol maleate and glycopyrronium bromide have shown that the conducted preclinical experiments do not provide any evidence that the drugs have the potential to influence (induce or inhibit) each other's pharmacokinetics (PK) via pathways of metabolism. Toxicokinetic data for the co-administration of indacaterol and glycopyrronium in inhalation toxicology studies in rats and dogs showed no apparent PK interaction.

1.1.1.3 Human safety and tolerability data

QVA149 was studied in clinical trials with the approved 110/50µg o.d. and was found safe and well tolerated based on a safety profile that is comparable to its monotherapy components and is consistent with other products in the class. The safety database includes patients treated with QVA149 up to 64 weeks. The safety profile for QVA149 in COPD patients is characterized by typical β_2-adrenergic agonist and anticholinergic symptoms related to the individual monotherapy components.

The totality of the safety data in the QVA149 programs, show that adverse events were consistent with those expected for the LAMA and LABA classes of drugs in COPD patients; there was no clinically meaningful difference in frequencies of AEs by preferred term, severity, relatedness, or SAEs between QVA149 and placebo or the monotherapy components QAB149 and NVA237.

The most common events (>5%) occurred in the respiratory, thoracic and mediastinal disorders and infections and infestations system organ classes. Most common adverse drug reactions related to the combination (reported >3% and higher than placebo) were COPD and nasopharyngitis.

The overall incidence of death was comparable to placebo and the active comparators. Causes of death were consistent with those expected in the studied patient population.

The incidence of adverse events of interest including CCV events (including MACE and atrial fibrillation events), and events due to anti-cholinergic and β-adrenergic effects were all comparable to placebo and the monotherapy components.

QVA149 showed clinically insignificant systemic effects of β-adrenergic stimulation at therapeutic doses. Mean heart rate changes were less than one beat per min, and tachycardia was infrequent and reported at a lower rate than with placebo. Relevant prolongations of QTcF were not detectable compared to placebo. The frequency of notable QTcF intervals (>450 ms) and reports of hypokalemia were similar to placebo.

The frequencies of clinically notable laboratory abnormalities were comparable for QVA149, placebo and the monotherapy components with the exception of a slight imbalance in glucose abnormalities that were higher for QVA149 compared to placebo, but comparable to the active comparators.

Subgroup analyses on all safety topics did not reveal conclusive evidence for a particular sub population who was at risk of adverse outcomes, or revealed a relevant difference in AE profile.

Other safety parameters did not show clinically meaningful changes from baseline and were balanced across treatment groups.

The safety data shows that QVA149 has an acceptable safety profile comparable to its monotherapy components and to placebo.

1.1.1.4 Human pharmacokinetic data

The steady-state exposure to indacaterol after QVA149 110/50 µg o.d. was either similar or slightly lower than systemic exposure after QAB149 150 µg (monotherapy product inhalation). Based on the in vitro performance data, the dose of indacaterol delivered to the lung is expected to be similar for QVA149 110/50 µg and QAB149 150 µg. The steady-state exposure to glycopyrronium after QVA149 110/50 µg o.d. was similar to systemic exposure after NVA237 50 µg o.d. (monotherapy product inhalation).

There was no pharmacokinetic drug-drug interaction resulting from the concomitant administration of glycopyrronium and indacaterol based on steady state exposure data. Following inhalation of QVA149 110/50 µg o.d. the median time to reach peak plasma concentrations of indacaterol and glycopyrronium was approximately 15 minutes and 5 minutes, respectively.

There were no relevant differences in systemic exposure to indacaterol or glycopyrronium following QVA149 administration between healthy subjects and patients with COPD. There was no clinically relevant covariate effect of body weight, age, gender, or baseline FEV1 on the pharmacokinetics of indacaterol or glycopyrronium following QVA149 administration. There was no relevant ethnic/race effect (across Caucasian, Chinese, and Japanese subjects) on systemic exposure to indacaterol and glycopyrronium. QVA149 can be used at the recommended dose in patients with mild and moderate hepatic or renal impairment. In patients with severe renal impairment or end-stage renal disease requiring dialysis, QVA149 should only be used if the expected benefit outweighs the potential risk.

1.1.1.5 Human pharmacodynamic data

The totality of the human pharmacodynamic and efficacy data from the clinical studies (spirometry, exacerbations and patient-reported outcomes, use of rescue medication) reflect a clinically relevant benefit in COPD patients for treatment with QVA149 110/50 µg administered. A summary of the results for the QVA149 programs are:

QVA149 110/50 µg administered once daily demonstrated clinically meaningful efficacy:

- Improvements in lung function (an increase in the primary endpoint, trough FEV1) which was statistically significantly superior to placebo (above the MCID), the monotherapy components QAB149 and NVA237, and the active comparator, tiotropium.
- Improvement in lung function, standardized FEV1 AUC (0-12h), which was statistically significantly superior to the active comparator fluticasone/salmeterol.
- Rapid onset of action and significantly improved peak FEV1 versus all comparators studied.
- Sustained bronchodilation (pre-dose FEV1) over 64 weeks of treatment.
- Clinically meaningful and statistically significant versus NVA237 in reducing the rate of moderate or severe COPD exacerbations in severe to very severe patients over 64 weeks of treatment.

- Provided consistent symptomatic benefit to patients with improvements in TDI, SGRQ and symptoms over time compared to placebo.
- Reduced use of rescue medication compared to placebo, individual monotherapy components (QAB149 and NVA237), tiotropium and fluticasone/salmeterol.
- Showed a statistically significant increase in exercise endurance in patients treated with QVA149 compared to placebo.
- Clinically meaningful and statistically significant bronchodilator response in terms of lung function and physiological markers of hyperinflation compared to placebo.
- QVA149 was safe and well tolerated, providing effective bronchodilation and improvement in disease-specific QOL in Japanese patients with moderate to severe COPD for 52 weeks of treatment.
- QVA149 provided clinically meaningful improvements in lung function after six weeks of treatment, with corresponding significant improvements in patient-reported dyspnea, compared with blinded tiotropium and placebo.

1.2 Study purpose

This study will investigate the effect of QVA149 on global and regional lung ventilation using MRI hyperpolarized gas imaging to enhance the understanding of QVA149 pharmacology in COPD patients.

The assessment of regional ventilation measures can then be combined with a MRI perfusion evaluation of the lung to visualize ventilation-perfusion mismatches. The reduction of ventilation-perfusion mismatch will also be evaluated in response to QVA149 treatment compared to placebo. Current physiological measures of small airway dysfunction are limited, subject to a high degree of variability and do not allow a quantitative assessment of global and regional ventilation defects. The MRI approach represents an opportunity to better understand the impact of a potent dual bronchodilator on the small and central airways and thereby measure the increases in ventilated lung volume, gas exchange, and reduction of ventilation-perfusion deficits.

2 Study objectives

2.1 Primary objective(s)

Primary objective(s)	*Endpoints related to primary objective(s)*
• To assess global ventilated lung volume after treatment with QVA149 compared to placebo	• Global lung ventilation volume as expressed in percentage (%VV) of total lung volume using hyperpolarized helium (^{3}He) lung MRI

2.2 Secondary objective(s)

Secondary objective(s)	*Endpoints related to secondary objective(s)*
• To assess regional lung ventilated volume after treatment with QVA149 compared to placebo	• MRI using hyperpolarized helium (^{3}He) to assess regional ventilation defects as expressed in percentage (% VDV) of total lung volume for each lobar region • Standard ^{1}H MRI with gadolinium enhancement to measure pulmonary perfusion(ml/g/min)
• To evaluate physiologic measures of lung function after treatment with QVA149 compared to placebo to provide a measure of assay sensitivity for this study	• Spirometry to assess FEV1, FVC, FEV1/FVC ratio
• To assess small airway function after treatment with QVA149 compared to placebo	• Lung Clearance Index by Multiple Breath Nitrogen Washout (MBNW)

3 Investigational plan

3.1 Study design

This is a double-blind, randomized, placebo-controlled, two-period, cross-over study in patients with moderate to severe COPD.

The study will consist of a 2-week screening period, a 7-9 day run-in, a baseline visit, a double-blind up to 10 day treatment Period 1 followed by a washout period before crossing over to a double-blind up to 10-day treatment Period 2, and an end-of-study visit. At the Run-In visit study subjects will be taken off medications specified in Table 5-2 and will receive rescue medication. The investigator will need to assess whether subjects can tolerate being off long-acting bronchodilators prior to baseline assessments.

To minimize patient burden, MRI and lung function assessments (spirometry, MBNW/lung volumes, DLCO) will not be scheduled for the same day. Subjects will have two MRI sessions – approximately 20 mins for He^3 MRI and 10 mins for proton MRI for a total of 30-45 mins per session that includes the setup and completion of 4-5 sequences. Actual MRI assessments will commence 2 hours after subject dosing at the site. Assessments for evaluation of MRI endpoints will be done on Day 7 and all other assessments, in particular spirometry, MBNW/lung volumes, and DLCO will be done on the day following MRI assessments i.e. Day 8 of treatment during Period 1 and Period 2.

If for important operational reasons MRI assessments cannot be performed on Day 7 of the respective treatment period, treatment in this period may be extended by up to 3 days. If MRI assessments cannot be performed on Day 7, then Day 7 and Day 8 assessments can be flexibly scheduled in any order (i.e. Day 7 assessments can be performed before or after Day 8 assessments and vice-versa) between Day 7 and Day 10, with all efforts made to minimize total days of treatment.

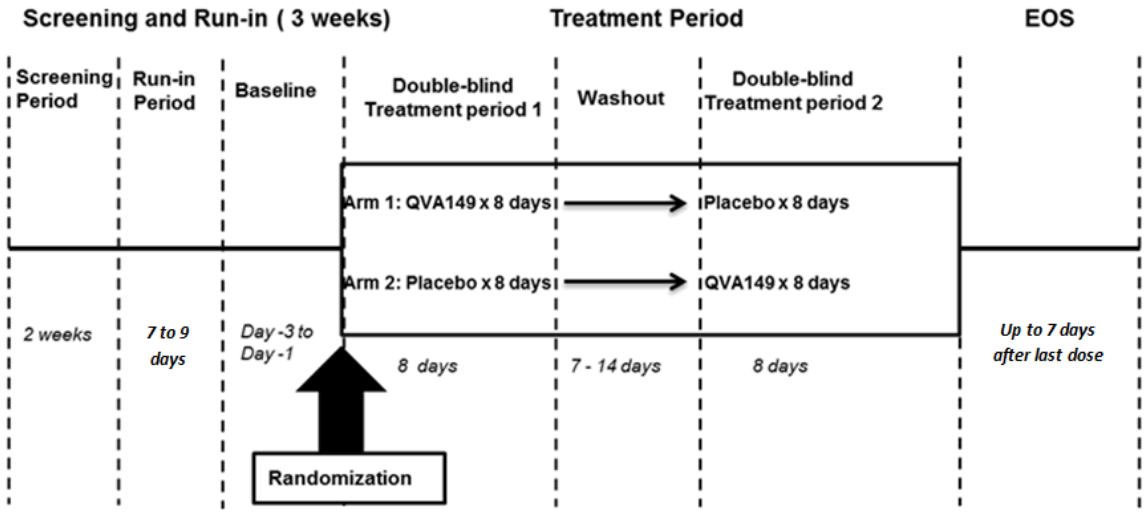
If the Day 7 or Day 8 assessments are scheduled on Day 8, 9 or 10 the subject will continue dosing until the day of the last assessment with a maximum 10 day dosing period. Sites will be requested to maintain the same sequence of MRI and lung function assessments for both treatment periods.

Study drug should be taken on each assessment day in the presence of and under the guidance of study site personnel. The assessment days are Day 1, Day 7 (MRI) and Day 8 (lung function tests) for each treatment period. Deviations within the time-frame given above are permissible. At all other times the subjects will take the drug at home and note date and time in the provided patient diary along with information about rescue medication use.

Randomization takes place on Day 1 of Treatment Period 1. Each treatment period consists of a once daily dose of QVA149 or placebo over 8 days (dosing is allowed for up to 10 days). The treatment will be administered by oral inhalation using the Concept 1 inhalation device.

A wash-out period of at least 7 days, but no more than 14 days, will separate the two treatment periods.

Safety assessments will include physical examinations, ECGs, vital signs, standard clinical laboratory evaluations (hematology, blood chemistry and urinalysis), adverse event and serious adverse event monitoring.



3.2 Rationale of study design

The study is a randomized, double-blind, placebo controlled, two arm cross over study. The crossover design is being used to evaluate the effect of the global endpoints of imaging following bronchodilation with QVA149 compared to placebo without any prior knowledge or data.

The 7-9 day run-in period will determine whether screened COPD patients can tolerate being off long-acting bronchodilators for the duration of the study. Withholding long-acting β2-agonists (LABAs)/long-acting muscarinic antagonists (LAMAs) and providing rescue medication only is common practice in short-term lung function trials in COPD patients. Patients who would find it hard to abstain from long-acting bronchodilators during the study will be identified during this run-in period and will not be randomized. Therefore, this is expected to reduce the number of patients dropping out of the study after randomization by excluding patients who can't tolerate the use of rescue medication only.

The washout period between the two treatment periods is of one to two weeks duration in order to ensure that there is no carry over pharmacodynamic effect of the study medications between treatment periods. The half-life of the bronchodilatory effect of QVA149, although not formally investigated, is, based on 24 hour spirometry data estimated to be < 1 day. Therefore no QVA149 PD effect is expected 13 days after last dosing when the next MRI assessment is scheduled to be conducted (1 week of washout plus 1 week of treatment in period 2). The helium gas does not stay in the lungs as it is washed out in a few breaths, within minutes of being administered.

The crossover design allows for a comparably small sample size since treatment effects are estimated per individual subject and intraindividual variability is inherently lower than inter-subject variability. In addition, the pharmacodynamic characteristics of QVA149, e.g. fast onset of bronchodilatory action, allow for a short study duration which also favors the use of a crossover study design.

3.3 Rationale of dose/regimen, duration of treatment

QVA149 is a marketed product (Ultibro Breezhaler (R)) and the current recommended dose is 110 mcg indacaterol / 50 mcg glycopyrronium once daily.

Based on data from previous lung function trials, the treatment duration of 7 days is expected to achieve clinically significant bronchodilation with QVA149. In addition, the duration of treatment is sufficiently short limiting the risk of patients dropping out during the study.

The use of a double-blind placebo arm as a comparator is to provide a comparison group to evaluate the direct effect of treatment in the investigated endpoints. This will require the subject to be without long-acting bronchodilators for a maximum of 33 days (i.e. 7-9 days of run-in, a maximum of 10 days during Period 1 (if randomized to placebo during Period 1) plus a maximum of 14 days of wash-out. To minimize any potential negative impact of this study on the participants, subjects will remain on their background inhaled corticosteroid (ICS) therapy throughout the study if they were on ICS when entering the study. In addition, SABA rescue medication will be provided to be used as needed if required by subject symptoms. For subjects with moderate to severe COPD (very severe not included) this is considered an acceptable procedure.

3.4 Rationale for choice of comparator

The use of a double-blind placebo arm as a comparator is to provide a comparison group for an unbiased collection of lung function assessment data to allow for evaluation of the direct effect of QVA149 treatment in the primary and secondary endpoints.

3.5 Purpose and timing of interim analyses/design adaptations

Interim analyses may be conducted to support decision making concerning the current clinical study, the sponsor’s clinical development projects in general or in case of any safety concerns.

3.6 Risks and benefits

Altering the current COPD medication regimen of enrolled COPD patients carries a potential risk of de-stabilizing the patient. Patients who cannot tolerate the change in medication regimen are expected to be identified during the run-in period and if deemed intolerable of the change in medication not randomized. In randomized patients the short duration of the trial and the provision of rescue medication (SABA) for both treatment arms provides sufficient risk mitigation for changing the treatment of a patient and having an effective drug-free placebo and washout period.

During the study, patients will be allowed to use inhaled corticosteroids if they were treated with them during screening and use their provided rescue medication (short-acting beta2-agonists provided at the end of Visit 2) until a window of 6 hours before lung function/MRI assessments.

Risk to subjects (COPD exacerbations, increase on symptoms or decrease in the lung function) will be minimized by compliance with the eligibility criteria, study procedures, close clinical monitoring and use of rescue medication for the relief of acute respiratory symptoms.

Similarly, 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 part of the regular medical assessments of this patient population.

The risks of side effects from the study medication are those known for QVA149 which is a licensed medication, marketed as Ultibro® Breezhaler®. The most frequently reported side effects with QVA149 aside COPD to date are nasopharyngitis, upper respiratory tract infection, cough, and headache. Further information can be obtained from the QVA149 Investigator's Brochure and the Summary of Product Characteristics for Ultibro Breezhaler.

The United States Food and Drug Administration (FDA) issued a warning concerning long acting beta-2 agonists (LABA). The warning states that LABAs may increase the chance of severe asthma episodes and asthma related death in patients with asthma. The warning was based on a study that evaluated the safety of salmeterol, which showed an increase in asthma related deaths in patients with asthma receiving salmeterol and their usual asthma medication (Vogelmeier et al 2013).

Indacaterol, which is one part of the study medication QVA149, is a LABA. However, indacaterol and QVA149 are not indicated to treat asthma and studies have not been done that show whether or not indacaterol has the same risks as salmeterol when given to patients with asthma. There is also currently no data that show whether or not there is the same risk when given to patients with COPD. Per the eligibility criteria in Section 4, patients with a prior or current asthma diagnosis are excluded.

There may be unknown risks of QVA149 which may be serious and unforeseen.

A 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.

Potential risks associated with Hyperpolarized Helium-3 MRI and GD enhanced MRI

There have been no ill effects reported from exposure to the magnetism or radio waves used in MRI. A known risk of MRI is that the magnet could attract certain types of metal. Therefore, metal within the patient's body will be evaluated (this includes pacemakers, defibrillators, vascular clips, prosthetic heart valves, metallic particles in the eye, non-fixed metallic particles, certain dyes found in tattoos, etc.) If there is any question about potentially hazardous metal within the patient's body, they will be excluded from participation in this

study. There is a possibility of discomfort from lying still for protracted periods (45 mins) during examination inside the scanner.

The RF coil detector, which is necessary to obtain the MR images of the lungs with the hyperpolarized gas, transmits and receives radio waves at much lower power than used with most standard MRI techniques. The coil is considered by the manufacturer a non-significant risk device, but it has not been approved by the FDA.

Hyperpolarized Helium-3

Helium-3 is considered to be safe and well-tolerated as an inhaled MR contrast agent for lung imaging. The most common respiratory related symptoms include sore, dry or scratchy throat; tickle in throat; and cough. Additional non-respiratory related symptoms have also occurred and include headache and lightheadedness. Other respiratory related symptoms include wheezing, chest tightness or chest pain and a decrease >10% in %PO2. Patients with lung disease have not been shown to be at greater risk for experiencing an adverse event compared to those without lung disease. This also holds true for subjects with severely compromised lung function (FEV1 < 40% of predicted). Helium does not stay in the lungs. Helium is washed out in a few breaths, within minutes of being administered.

Gadolinium

The pulmonary imaging exam includes the use of an exogenous contrast agent gadolinium diethyltriaminepentaacetic acid (GdDTPA) to assess lung perfusion. As with the use of an intravenous contrast agent, as with any injected agent, there is a small risk of a serious allergic reaction. This dye may cause an allergic reaction with symptoms that include rash, itchiness, or hives. Serious reactions are rare, and there have been fewer than 10 cases of serious allergic reactions (called anaphylaxis) in over a million injections. Nephrogenic Systemic Fibrosis (NSF) is a serious malady that has been reported only in certain people who have renal insufficiency and which can also occur in patients with renal transplants or liver transplant.

To avoid the very low NSF risk, the calculated glomerular filtration rate (GFR) will be required to be greater than 30. This is the value below which NSF has not been reported.

High resolution CT

This use of HRCT involves minimal risk and is necessary to obtain the research information desired. The total amount of radiation for the HRCT scans will not exceed about 10.0 mSv or 1000 mrem on most current HRCT scanner platforms, which is well within both US and EU guidelines for annual exposure limits for whole body radiation. Some people may have a ‘closed in’ feeling while inside the CT machine.

Blood Sampling

A maximum of 15 mL of blood is planned to be collected over a period of approximately 43 days, from each subject as part of the study. Additional samples for monitoring of any safety findings would be in addition to this. This is not considered to be a risk for this population.

4 Population

The study population will be comprised of male and female moderate to severe COPD patients aged 40 years and above.

A total of approximately 34 subjects will be enrolled to participate in the study and randomized. At least 28 subjects are expected to complete the study.

4.1 Inclusion criteria

1. Written informed consent must be obtained before any assessment is performed.
2. Male and female with COPD aged 40 years and above.
3. Smokers and ex-smokers who have a smoking history of at least 10 pack years. Smokers will be defined as any patient who reports tobacco use within the last month.
4. Patients with a diagnosis of moderate to severe COPD according to GOLD 2015 criteria. Patients with airflow limitation indicated by a post-bronchodilator $FEV_1/FVC < 0.70$ and by a post-bronchodilator $FEV_1 \geq 30$ % and <80 %.
   - Post-bronchodilator refers to 1 hr (+/- 5 minutes) after sequential inhalation of 84 µg ipratropium bromide (or equivalent dose) and 400 µg salbutamol/360 µg albuterol (or equivalent dose). Spacer devices are not permitted during reversibility testing.
5. Patients must weigh ≥45 kg and ≤100 kg to participate in the study.
6. Able to communicate well with the investigator, to understand and comply with the requirements of the study.

4.2 Exclusion criteria

1. Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, or within 30 days, whichever is longer; or longer if required by local regulations
2. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes.
3. Any significant medical condition that in the opinion of the Investigator may compromise patient safety, patient compliance, interfere with evaluations, or preclude completion of the trial. For example, COPD exacerbations within the 6 weeks prior to screening requiring oral steroids and/or antibiotics.

10. Patients who have had a lower respiratory tract infection within 6 weeks prior to screening, or significant illness which has not resolved within two (2) weeks prior to initial dosing.
11. Patients with concomitant pulmonary disease, e.g., pulmonary tuberculosis (unless confirmed by chest x-ray to be no longer active) or clinically significant bronchiectasis.
12. Patients with a history of asthma, indicated by (but not limited to):

15. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant.

19. Patients unable to successfully use a dry powder inhaler device or perform spirometry, MBNW/lung volumes and DLCO measurements

22. For a subject to be enrolled in the study the following exclusion criteria relating to MRI will apply.

5 Restrictions for Study Subjects

During recruitment, screening/informed consent review, and baseline visit, the subjects must be informed and reminded of the following restrictions:

5.1 Contraception requirements

Not applicable. Women of childbearing potential are excluded from the study.

6 Treatment

6.1 Study treatment

Details on the storage and management of study medication, randomization and instructions for prescribing and taking study treatment are outlined in Section 3 of the Site Operations Manual.

6.1.1 Investigational treatment

QVA149 110/50 µg o.d. capsules for inhalation, supplied in blisters via the Concept 1 inhalation device, a single dose dry powder inhaler (SDDPI).

The investigational drug, QVA149 and matching placebo will be prepared by Novartis and supplied to the Unblinded Pharmacist/Unblinded Personnel at Investigator site as single blind patient kits.

The inhaler is supplied by the Novartis Drug Supply Management. The handling and administration instruction will be provided and training on how to use the inhaler will be provided by Novartis or its designee as appropriate at the study initiation visit.

6.1.2 Additional study treatment

Please refer to Section 6.9 for more details regarding rescue medication.

6.2 Treatment arms

Subjects will be assigned to one of the following two treatment arms in a ratio of 1:1 (active: placebo). Study treatments are defined as:

- **A**: single daily dose of 110/50 µg QVA149 for 8-10 days.
- **B**: single daily dose of matching placebo for 8-10 days.

Table 6-1 Definition of treatment sequences

Sequence	Period 1	Period 2
1	A	B
2	B	A

6.3 Permitted dose adjustments and interruptions of study treatment

Study drug dose adjustments and/or interruptions are not permitted.

6.4 Treatment assignment

Randomization numbers will be assigned in ascending, scrambled order to eligible subjects (see Site Operations Manual for details). The investigator will enter the randomization number on the CRF.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A Randomization list/ Treatment Allocation Card will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of treatment arms to randomization numbers in the specified ratio. The randomization scheme for subjects will be reviewed and approved by a member of the Novartis IIS Randomization Group.

Patients must meet the inclusion/exclusion criteria to be randomized. If a randomization number is allocated to a patient who subsequently does not meet the study eligibility criteria, then the patient is a screen failure. The allocated randomization number will be reused in the study. The unblinded pharmacist should document that the treatment allocation card, if used, was opened and dose was prepared, but no drug administration occurred. The allocation card will be re-used for the next available patient in the study.

6.5 Treatment blinding

This is a double blind study: subjects, investigator staff, persons performing the assessments, and data analysts will remain blind to the identity of study treatments according to the specifications provided in the Site Operations Manual.

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, and odor.

Randomization data are kept strictly confidential, and are accessible only to authorized personnel, until unblinding of the trial as described in the table in the Blinding levels table in the Site Operations Manual.

Unblinding will only occur in the case of patient emergencies (see Section 6.6) and at the conclusion of the study.

Further information regarding blinding (and unblinding) is presented in the Site Operations Manual.

6.6 Emergency breaking of assigned treatment code

Emergency unblinding should only be undertaken when it is essential to treat the subject safely and efficaciously. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. A complete set of emergency code break cards will be provided to the investigator site(s) and a complete set will be available at Novartis. All code break cards must be retained until the end of the study and returned to Novartis. They must be stored in a secure place but be accessible in case of emergency. The investigator will receive a blinded code break card for each subject, with the details of drug treatment covered by a removable, scratch-off cover. In an emergency, the scratch-off cover can be removed to determine the treatment. The scratch-off covers are not to be removed for any reason other than an

emergency. When the investigator removes the scratch-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 CRF.** The investigator must also immediately inform the Novartis local 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 code break cards in case of emergency. If appropriate, the investigator will inform the subject how to contact his/her backup in cases of emergency when he/she is unavailable.

6.7 Treatment exposure and compliance

As dose administration will occur in study site and at home, compliance will be confirmed as fully as possible by site staff checking medication as it is returned by the subject. Study treatment compliance is assessed by the investigator at all visits. The Investigator or designee collects, from the patient, the used/unused investigational medication and packaging (capsules/blister strips and SDDPIs) at all dispensing visits. Any doses administered in the clinic will be checked by site staff.

Study drug compliance is assessed from the capsule count and from information provided by the patient and/or caregiver.

The correct allocation of the study medications will be entered into the eCRF to ensure a complete record of dosing for each subject.

6.8 Recommended treatment of adverse events

In the event of paradoxical bronchospasm the subject should be treated with a rapidly-acting inhaled bronchodilator, with repeated doses as required and carefully monitored until recovery has been documented. Subjects will be withdrawn from the study and should be carefully advised on future exposure to inhaled medications.

Medication used to treat AEs must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

6.9 Rescue medication

At the Run-In visit all subjects will be provided with a short acting β2-agonist (salbutamol/albuterol) inhaler which they will be instructed to use throughout the trial as rescue medication. Patients randomized will be provided with rescue medication for the entire duration of the trial.

No other rescue medication is permitted.

Subjects need to be instructed to abstain from rescue medication (salbutamol/albuterol) for at least 6 hours prior to Spirometry, DLCO, MBNW/Lung Volumes and MRI imaging assessments. Rescue medication can be taken within the 6 hours prior to testing if warranted by subject's symptoms if absolutely necessary. If subject takes rescue medication within the 6 hours prior to spirometry, PFT, MBNW, or imaging assessments, all attempts should be made to reschedule the visit, if possible. If rescheduling the visit is not possible, the subjects

with rescue medication use within 6 hours prior to said assessments should continue with their planned visit, but will be excluded from the PD analysis set.

Patients are required to record information about rescue medication use in the patient diary provided.

Use of rescue medication must be recorded by site staff on the Concomitant medications/Significant non-drug therapies CRF after start of study drug.

6.10 Concomitant treatment

The investigator should instruct the patient to notify the study site about any new medications s/he 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.

Any medication not listed in the prohibited medication table that is required by the patient for a medical condition and does not affect the study endpoints is allowed.

7 Discontinuation and study completion

7.1 Discontinuation of study treatment

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

In addition, study treatment must be discontinued and the subject withdrawn from the trial under the following circumstances:

- subject withdraws consent
- adverse events for which continued inhalation of the study drug would be detrimental to the subject e.g. paradoxical bronchospasm
- abnormal test procedure results indicating risk for the patient on continued inhalation of the study drug.
- pregnancy.
- deterioration in the patient’s health that requires alternative intervention not permitted per protocol.
- deviations from the prescribed dose regimen for the study drug: more than 2 consecutive missed doses between days 2 and 10 of each treatment period.
- use of prohibited treatment as per protocol.
- any other protocol deviation that results in a significant risk to the subject’s safety.

7.2 Study completion and post-study treatment

Each subject will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them. Study completion is defined as when the last subject completes their End of Study visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision.

7.2.1 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

7.3 Withdrawal of consent

Subjects may withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent occurs only when a subject does not want to participate in the study anymore and does not want any further visits or assessments and does not want any further study related contact and does not allow analysis of already obtained biologic material.

If a subject withdraws consent, the investigator must make every effort to determine the primary reason for this decision and record this information. Study treatment must be discontinued and no further assessments conducted. All biological material that has not been analyzed at the time of withdrawal must not be used. Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

7.4 Study Stopping rules

Stopping rules for safety are listed below:

The Study may be put on hold and no further dosing or enrollment will take place pending a full safety review in case of any of the following:

- Two SAEs of a similar nature in two different subjects that are suspected of being related to study drug
- Two AEs of a similar nature in two different subjects which are severe in intensity and suspected of being related to study drug

Following the review a decision will be made to resume or stop the study.

7.5 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, subjects should be seen as soon as possible and treated as a prematurely withdrawn subject. 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 subject's interests.

The investigator will be responsible for informing IRBs/IECs of the early termination of the trial.

8 Procedures and assessments

Table 8-1 Assessment Schedule

EPOCH	SCREENING			TREATMENT PERIOD 1					TREATMENT PERIOD 2			
STUDY PHASE	SCREENING[2]	RUN-IN [3]	BASELINE	TREATMENT PERIOD 1			PHASE/SC	WASHOUT [4]	TREATMENT PERIOD 2			PHASE/SC
Visit Number [1]	Visit 1	Visit 2	Visit 3	Visit 101	Visit 102	Visit 103	Visit 199 [5]		Visit 201	Visit 202	Visit 203	Visit 299 [6]
Study Day(s)	Day -30 to Day -8	Day -7	Day -1	Day 1	Day 7	Day 8			Day 1	Day 7	Day 8	
Visit Window		-2 +0	-2 +0		-0 +3	-1 +2				-0 +3	-1 +2	
Informed consent	X											
Inclusion / Exclusion criteria	X			X[PR]								
Physical examination	X						X[7]					X[7]
Medical history/current medical conditions	X			X[PR]								
Body Height	X											
Body Weight	X						X[7]					X[7]
Pulse Rate	X			X[PR]			X[7]		X[PD]			X[7]
Body Temperature	X			X[PR]			X[7]		X[PD]			X[7]
Blood Pressure	X			X[PR]			X[7]		X[PD]			X[7]
ECG Evaluation	X						X[7]					X[7]
Serum Pregnancy test (Females only)	X											
Urine Pregnancy test (Females only)	X			X[PR]	X	X	X[7]		X	X	X	X[7]
Hematology	X											
Blood Chemistry	X											
Urinalysis	X											
Hepatitis/HIV Screen	X											
HbA1c	X											
Alcohol Test and Drug Screen	X											
High Resolution CT[8]	X[9]											
Spirometry	X[10]			X[11]		X[11]			X[11]		X[11]	
DLCO	X[12]					X[13]					X[13]	
Multiple Breath Nitrogen Washout/Lung Volumes	X[12]					X[13]					X[13]	
MRI[14]			X		X[15]					X[15]		

RANDOMIZATION				X								
Rescue Medication dispensed		X										
Study Drug administration in clinic[16]				X	X	X			X	X	X	
Phase/Study Completion Information			X				X[7]					X[7]
Adverse Events	X	X	X	X	X	X	X[7]		X	X	X	X[7]
Concomitant Therapies	X	X	X	X	X	X	X[7]		X	X	X	X[7]
Patient Diary[17]		X	X	X	X	X	X[7]	X	X	X	X	X[7]

8.1 Informed consent procedures

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

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 subject source documents.

The date of signing of informed consent (and withdrawal, if later withdrawn) should be documented in the CRF.

Novartis will provide to investigators a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC.

A copy of the approved version of all consent forms must be provided to the Novartis monitor after IRB/IEC approval.

8.2 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data will be collected on all subjects.

Relevant medical history/current medical conditions data includes data until signature of informed consent. Where possible, diagnoses and not symptoms will be recorded.

Investigators have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

Hepatitis screen, HIV screen

All subjects will be screened for Hepatitis B surface antigen (HBsAg). Screening for Hepatitis C will be based on HCV antibodies. Evaluation for HIV seropositivity will be performed, and, if positive, confirmation by a second technique available at the laboratory site, e.g., Western blot. Results will be available as source data and will not be recorded within the CRF.

Alcohol test, Drug screen

Subjects will be tested for substances of abuse (e.g. alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates).

Results will be available as Source data and will not be recorded within the eCRF.

HbA1c diabetes

All patients will be tested for poorly controlled Type I and Type II diabetes. Patients HbA1c levels should not be >8%.

Results will be available as Source data and will not be recorded in the eCRF

8.3 Efficacy / Pharmacodynamics

Pharmacodynamic assessments are specified below, with the methods for assessment and recording specified in the Site Operations Manual. Assessments will be performed/samples collected at the time point(s) defined in the Assessment Schedule.

8.3.1 MRI

Hyperpolarized Helium Lung Imaging: Using an inhaled gaseous contrast agent, hyperpolarized helium-3 (He-3), the regional distribution of inhaled gas within the lung can be assessed using MRI a method that does not involve the use of ionizing radiation. In young healthy subjects, inhaled helium-3 gas distributes evenly throughout the airspaces producing uniformly high signal throughout the lung on the MR images (Parraga et al 2008, Altes et al 2001). When there is focal reduction in airflow such as that present in COPD, the airspaces distal to the area of obstruction do not fill with the gas and appear dark on the images, depicted as a so-called "ventilation defect". Multiple different factors such as mucus plugging, and airway narrowing and airway narrowing or closure from a variety of etiologies can cause ventilation defects on hyperpolarized gas MRI.

Lung Perfusion Imaging: MR perfusion imaging of the lung with gadolinium contrast agent will also be performed to determine whether vascular abnormalities producing perfusion deficits correspond to abnormalities in ventilation, so called hypoxic vasoconstriction.

The lung imaging methodology is limited to an expert imaging center with advanced pulmonary imaging experience and the dedicated MRI hardware necessary for hyperpolarized He-3. A detailed Imaging Acquisition Guidelines will be developed for the study. All imaging analysis procedures applied to produce the quantitative assessments of regional ventilation defects will be in a separate manual and all image analysis results will be transferred from a commercial imaging CRO.

8.3.2 Spirometry

Spirometry will be performed at study visits as outlined in the Assessment Schedule. A pre-dose assessment (-45 min and -15 min in relation to study drug administration) will be performed as well as post-dose assessments at 15 min, 1 hour and 2 hours following on-site administration of study medication.

Centralized spirometry will be provided by a vendor, and training and instructions will be provided. Spirometric parameters to be measured are:

- Forced Expiratory Volume in 1 second (FEV1)
- Forced Vital Capacity (FVC)
- FEV1/FVC ratio

Additional information for conduct of spirometric assessments will be provided in the Site Operations Manual.

8.3.3 Multiple Breath Nitrogen Washout

MBNW will be performed at visits as detailed in the Assessment Schedule using a multiple breath inert gas washout technique. The device provides the global index of ventilation inhomogeneity assessment (LCI = Cumulative Expired Volume/Functional Residual Capacity). Further information on this assessment can be found in the Site Operations Manual.

8.3.4 DLCO and Lung Volumes Assessment

Lung volumes and DLCO determinations will be performed at visits as outlined in the Assessment Schedule. Parameters measured will include DLCO, IC, FRC, TLC, RV and RV/TLC ratio. The parameters can be determined by the use of a conventional body plethysmograph or a device provided to the site. Additional information will be provided in the Site Operations Manual.

8.3.5 Patient diary

Subjects will be provided with individual diary cards to record each administration of study medication and information on use of rescue medication. This will be checked regularly by site staff.

8.4 Safety

Safety assessments are specified below; methods for assessment and recording are specified in the Site Operations Manual, with the Assessment Schedule detailing when each assessment is to be performed.

8.4.1 Physical examination

A physical examination will be performed at Screening and End of Study. It will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams are performed.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to the start of study must be included in the Relevant Medical History/Current Medical Conditions screen on the patient's eCRF. Significant findings made after the start of study which meet the definition of an Adverse Event must be recorded on the Adverse Event screen of the patient's eCRF.

8.4.2 Vital signs

Vital signs include temperature, pulse rate (measured for 60 seconds, if performed manually) and systolic and diastolic blood pressure. Pulse rate and blood pressure is assessed after the patient has rested in the sitting position for at least 3 minutes. If an automated blood pressure device is used, it should be calibrated according to the manufacturer's guidelines.

If vital signs are out-of-range in the opinion of the Investigator at screening or prior to initial dosing, the Investigator should obtain two additional readings, so that a total of up to three consecutive assessments are made, with the subject seated quietly for approximately five minutes preceding each repeat assessment. At least the last reading must be within an acceptable range in the opinion of the investigator in order for the subject to qualify.

8.4.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured. Body mass index (BMI) will be calculated using the following formula:

BMI = Body weight (kg) / [Height (m)]^2

8.4.4 Local Laboratory evaluations

Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported and discussed with Novartis personnel. The results should be evaluated for criteria defining an adverse event and reported as such if the criteria are met. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant. In case of doubt, Novartis personnel should again be contacted.

Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential and platelet count will be measured.

Clinical chemistry

Sodium, potassium, creatinine, urea, uric acid, chloride, albumin, calcium, alkaline phosphatase, total bilirubin, LDH, GGT, AST, ALT, aPTT, PT/INR, CK, HbA1c at screening, glucose, total cholesterol, triglycerides. If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated.

Urinalysis

Urine test by dipstick: leucocytes, nitrite, pH, protein, glucose, ketones, urobilinogen, bilirubin, blood/ hemoglobin

If the dipstick result is positive for protein, nitrite, leucocytes and/or blood, the sample will be sent for microscopic analysis of WBC, RBC and casts.

8.4.5 Electrocardiogram (ECG)

A standard single 12 lead ECG is collected at Visit 1 and End of Study. ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and spirometry. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

The original ECGs appropriately signed, should be collected and archived at the study site. Each ECG tracing should be labeled with study number, subject initials, subject number, date and time, and filed in the study site source documents.

QTcF, QT duration, heart rate, PR duration, and QRS complex duration will be recorded in the eCRF.

Clinically significant abnormalities are recorded on the relevant section of the medical history/Current medical conditions/AE eCRF page as appropriate.

8.4.6 Pregnancy and assessments of fertility

Women of child-bearing potential are excluded from this study.

Despite meeting the selection criterion of not being of child-bearing potential, all participating women will have regular urine pregnancy tests during the study. A positive urine pregnancy test requires immediate interruption of study drug until serum β-hCG is performed and found to be negative.

8.5 High Resolution CT

HRCT will be completed at screening for the purpose of fulfilling eligibility criteria. A historic HRCT performed within 6 months of the screening visit may be accepted as long as it is performed by a protocol approved by the Sponsor. The imaging acquisition guidelines for HRCT will include details of the protocol and machine settings and will be provided to all trial sites as part of the SOM.

9 Safety monitoring

9.1 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 providing written informed consent* for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The occurrence of adverse events should be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject 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 patients with underlying disease. Investigators have the responsibility for managing the safety of individual subject and identifying adverse events. Alert ranges for liver related events are included in Section 9.3.

Adverse events must be recorded on the Adverse Events CRF for subjects that pass screening and enter into the study. The adverse events should be reported according to the signs, symptoms or diagnosis associated with them, and accompanied by the following information:

1. 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
2. its relationship to the study treatment (no/yes),
3. its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported.
4. whether it constitutes a serious adverse event (SAE) See Section 9.2 for definition of SAE
5. action taken regarding [study/investigational] treatment(select as appropriate).

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 treatment permanently discontinued due to this adverse event
- concomitant medication given
- non-drug therapy given
- subject hospitalized/subject's hospitalization prolonged

6. its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

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 drug, 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 Brochure (IB) or Core Data Sheet (for marketed drugs) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the subject informed consent and should be discussed with the subject during the study as needed.

The investigator should also instruct each subject to report any new adverse event (beyond the protocol observation period) that the subject, or the subject'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.

9.2 Serious adverse event reporting

9.2.1 Definition of SAE

An SAE is defined as 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 e.g. scheduled lung function or progression of disease assessments elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
    - 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 subject or may require medical or surgical intervention.

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

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

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

All AEs (serious and non-serious) are captured on the CRF, SAEs also require individual reporting to DS&E as per Section 9.2.2.

9.2.2 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the last study visit must be reported to Novartis within 24 hours of learning of its occurrence, if the investigator becomes aware, as described below. Any SAEs experienced after this 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.

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 subject 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 EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

9.3 Liver safety monitoring

Not applicable in this COPD study.

9.4 Renal safety monitoring

Not applicable in this COPD study.

9.5 Pregnancy reporting

To ensure patient safety, each pregnancy in a subject on study drug 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. The study drug must be discontinued, though the subject may stay in the study, if she wishes to do so. All assessments that are considered as a risk during pregnancy must not be performed. The subject may continue all other protocol assessments. Pregnancy must be recorded on a Pharmacovigilance 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 Novartis study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on an SAE Report Form.

10 Data review and database management

10.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The monitor will visit the site to check the completeness of subject records, the accuracy of entries on the CRFs, 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 monitor during these visits.

The investigator must maintain source documents for each subject 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 CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the eligibility 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 CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

10.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to Novartis. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive a CD-ROM or paper copies of the subject data for archiving at the investigational site.

Data not requiring a separate written record will be defined in the Site Operations Manual and Assessment Schedule and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

10.3 Database management and quality control

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

Novartis staff review the data entered into the eCRFs 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 confirm or correct 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 who will make the correction to the database.

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.

HRCT and MRI readings as well as Spirometry, DLCO and MBNW/ Lung Volumes readings will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

At the conclusion of a non-IRT study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused drug supplies to Novartis.

11 Data analysis

Analysis of the data will be conducted under the direction of Novartis personnel in compliance with internal guidance documents and standards.

11.1 Analysis sets

For all analysis sets, subjects will be analyzed according to the study treatment(s) received.

The safety analysis set will include all subjects that received any study drug.

The primary population of interest is the PD population, all the patients with evaluable PD parameter data and no major protocol deviations impacting PD data will be included in the PD data analysis "PD population". Any PD data less than 6 hours after rescue medication use or within 7 days of systemic corticosteroid will be set to missing.

11.2 Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment sequence and subject. Summary statistics will be provided for all subjects, as well as for each treatment sequence.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment sequence and subject.

11.3 Treatments (study drug, rescue medication, other concomitant therapies, compliance)

Data for study drug administration (rescue medication) and concomitant therapies will be listed by treatment sequence and subject.

11.4 Analysis of the primary variable(s)

11.4.1 Variable(s)

The primary variable is to evaluate the pharmacodynamics response as reflected by percent of global lung ventilation volume on day 7 after the treatment with QVA149 compared to placebo in moderate to severe COPD patients.

11.4.2 Statistical model, hypothesis, and method of analysis

The percent of global ventilation volume on day 7 will be analyzed using a mixed effects model. The model will include sequence, period and treatment as fixed effects. Patient factor will be included as a random effect. An unstructured covariance matrix will be applied.

The final model estimates will include the LSmean for each treatment (QVA149 and placebo) together with standard error (SE), the adjusted mean difference between QVA149 and placebo, and corresponding 90% two-sided confidence intervals and P-value for the differences using placebo as the reference treatment.

Percent of global ventilation volume will be listed by treatment, subject and visit/time and descriptive summary statistics will be provided by treatment, and visit/time. Summary statistics will include arithmetic mean, SD, CV (arithmetic), median, minimum and maximum.

Graphical methods will be employed to show mean and individual figures for %global ventilation volume.

No adjustments for multiplicity will be applied for this exploratory study.

11.4.3 Handling of missing values/censoring/discontinuations

Subjects withdrawn for any reasons other than safety and tolerability may be replaced.

Where data has values below and above limits of quantification then the following rule will apply.

In the summary tables, the frequency (n, %) of values below the LLOQ and above the ULOQ, respectively, will be included.

In case of censored values (values below the LLOQ and/or values above the ULOQ), the summary statistics (arithmetic mean, standard deviation, geometric mean and CV% of geometric mean) will be calculated as the maximum likelihood estimates using a parametric model for data that can be right censored and left censored assuming the data being normally or log-normally distributed.

Values BLQ that are statistically analyzed will be analyzed at half the LLOQ.

11.4.4 Summary statistics of pharmacokinetics

Not Applicable

11.4.5 Supportive analyses

Not Applicable

11.5 Analysis of secondary and exploratory variables

11.5.1 Efficacy / Pharmacodynamics

Secondary pharmacodynamic variables are Forced Expiratory Volume in 1 second (FEV1), Forced Vital Capacity (FVC), FEV1/FVC ratio measured by spirometry, Lung Clearance Index measured by Multiple Breath Nitrogen Washout, Percent of regional ventilation defects volume measured by MRI using hyperpolarized helium (^{3}He), Pulmonary perfusion (ml/g/min) using Standard ^{1}H MRI with gadolinium enhancement, Collateral ventilation by hyperpolarized gas MRI lung imaging.

The primary model described for percent of global ventilation volume in Section 11.4.2 will be fit to all secondary and exploratory parameters of interest (separate model for each parameter). For spirometry parameters, the model may include fixed effects for time (15 min, 1 hour and 2 hours post dose) and treatment by time interaction term. Time will be repeated within each patient*period interaction and subject-average baseline and period-adjusted baseline as covariates in addition to the factors added to the primary analysis. An unstructured variance unstructured covariance matrix will be applied.

The subject average baseline will be derived as the average of their pre-dose assessments from each period. Period adjusted baseline will be calculated for each subject and for each period, as the difference between the period baseline and the subject average baseline, i.e. value of period baseline – value of average baseline (Kenward and Roger 1997).

Sensitivity analysis for LCI, Lung volumes and DLCO as described in Section 11.4.2 may be repeated with a mixed effects model by using screening visit as covariate.

Correlations between MR imaging parameters, spirometry, MBNW/ lung volumes and DLCO at baseline and end of each period for QVA149 and Placebo will be presented, and all end points will be summarized graphically and in tables.

All MR imaging, spirometry, MBNW/lung volumes and DLCO parameters will be listed by treatment, subject and visit/time and descriptive summary statistics will be provided by treatment, and visit/time. Summary statistics will include arithmetic mean, SD, CV (arithmetic), median, minimum and maximum.

Graphical methods will be employed to show mean and individual figures for all parameters.

11.5.2 Safety

Vital signs

All vital signs data will be listed by treatment, subject, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

ECG evaluations

All ECG data will be listed by treatment, subject and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

All laboratory data will be listed by treatment, subject, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Adverse events

All information obtained on adverse events will be displayed by treatment and subject.

The number and percentage of subjects with adverse events will be tabulated by body system and preferred term with a breakdown by treatment. An adverse event starting in one period and continuing into the next period is counted only in the onset period. A subject with multiple adverse events within a body system and treatment period is only counted once towards the total of this body system and treatment.

11.5.3 Pharmacokinetics

Not Applicable.

11.5.4 Pharmacokinetic / pharmacodynamic interactions

Not Applicable.

11.5.5 Other assessments

11.5.5.1 Exploratory biomarkers

Not Applicable.

11.6 Sample size calculation

Corporate Confidential Information

Allowing for a 20% dropout rate, a total sample size of 34 (17 per sequence) patients will be randomized to two treatment sequences.

Corporate Confidential Information

11.7 Power for analysis of key secondary variables

The sample size of 28 (14 per sequence) completers is also sufficient to confirm an assay sensitivity for trough FEV1 between QVA149 and Placebo. By examining several relevant crossover studies (QVA149A2303, NVA237A2205, NVA237A2208 and AC41113073 from Anoro PADAC Briefing Book), the within patient standard deviation for trough FEV1 is estimated as 175 mL. The estimate of the true drug effect on trough FEV1 is likely to be at least 170 mL. This was derived from the lower 90% CI boundary on trough FEV1 from QVA149A2303 study.

The study will also provide at least 80% power to detect a difference of 170 mL in trough FEV1 using a 2-sided test at a significance level of 10%.

11.8 Interim analyses

Interim analyses may be conducted to support decision making concerning the current clinical study, the sponsor's clinical development projects in general or in case of any safety concerns.

12 Ethical considerations

12.1 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.

12.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution should obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g. advertisements) and any other written information to be provided to subjects. 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 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.

For multi-center trials, a Coordinating Investigator will be selected by Novartis around the time of Last Patient Last Visit to be a reviewer and signatory for the clinical study report.

12.3 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.

13 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances should an investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

Investigators must apply due diligence to avoid protocol deviations. 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/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

13.1 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 prior to implementation.

Only amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented, provided the Health Authorities and the reviewing IRB/IEC are subsequently notified by protocol amendment.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, the CTL should be informed and (serious) adverse event reporting requirements (Section 9) followed as appropriate.

14 References

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