NOVARTIS

Global Medical Affairs - General Medicine

QVA149 (Indacaterol maleate/Glycopyrronium bromide)

Clinical Trial Protocol CQVA149A2316 / NCT02603393

A 26-week, randomized, double blind, parallel-group multicenter study to assess the efficacy and safety of QVA149 (110/50 mcg o.d.) vs tiotropium (18 mcg o.d.) + salmeterol/fluticasone propionate FDC (50/500 mcg b.i.d.) in patients with moderate to severe COPD

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List of abbreviations

AE	Adverse Event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	Area under the curve
BDI	Baseline Dyspnea Index
b.i.d.	twice a day
CCV	Cardio- and Cerebro-Vascular events
CFR	US Code of Federal Regulations
COPD	Chronic Obstructive Pulmonary Disease
CPO	Country Pharma Organization
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CTC	Common Toxicity Criteria
ECG	Electrocardiogram
EDC	Electronic Data Capture
eDiary	electronic diary device
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
FDC	Fixed-dose combination
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
hCG	human Chorionic Gonadotropin
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS	Inhaled corticosteroid
IEC	Independent Ethics Committee
i.v.	intravenous
IRB	Institutional Review Board
IRT	Interactive Response Technology
LABA	Long acting beta2 agonist
LAMA	Long acting muscarinic antagonist

[redacted]

LFT	Liver function test
MDI	Metered Dose Inhaler
MedDRA	Medical dictionary for regulatory activities
mMRC	modified Medical Research Council
NYHA Class	New York Heart Association Classification
OC/RDC	Oracle Clinical/Remote Data Capture
o.d.	once a day
PLA	Placebo
p.o.	oral(ly)
PSW	Premature Study Withdrawal
SABA	Short acting beta2 agonist
SAE	Serious Adverse Event
SAMA	Short acting muscarinic antagonist
SDDPI	Single Dose Dry Powder Inhaler
SmPC	Summary of Product Characteristics
SMQ	Standardized Medical Queries
SUSAR	Suspected Unexpected Serious Adverse Reactions
TD	Study treatment discontinuation
TDI	Transitional Dyspnea Index
WHO	World Health Organization

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Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time
Control drug	Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the drug being tested in the trial
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch	A portion of the study which serves a specific purpose. Typical Epochs are: screening/recruitment, wash-out, treatment, and follow-up
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug" or "investigational medicinal product."
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This *includes* any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally *does not include* protocol-specified concomitant background therapies when these are standard treatments in that indication
Medication number	A unique identifier on the label of each investigational/study treatment package in studies that dispense medication using an IRT system
Protocol	A written account of all the procedures to be followed in a trial, which describes all the administrative, documentation, analytical and clinical processes used in the trial.
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease
Period	A subdivision of a study
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Study treatment/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), active drug run-ins or background therapy
Study/investigational treatment discontinuation	Point/time when patient permanently stops taking study/investigational treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Patient Number	A unique number assigned to each patient who enrolls into the study
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study

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Amendment 01

Amendment rationale

This protocol amendment was made to provide the correct number of patients on which the 24-hour weighted mean urine cortisol was determined.

Changes to the protocol

The number of patients on which the 24-hour weighted mean urine cortisol was determined was changed from approximately 300 to approximately 380.

This change is shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

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Protocol summary

Protocol number	CQVA149A2316
Title	A 26-week, randomized, double blind, parallel-group multicenter study to assess the efficacy and safety of QVA149 (110/50 µg o.d.) vs tiotropium (18 µg o.d.) + salmeterol/fluticasone propionate FDC (50/500 µg b.i.d.) in patients with moderate to severe COPD
Brief title	Evaluation of the efficacy and safety of QVA149 (110/50 µg o.d.) vs tiotropium (18 µg o.d.) + salmeterol/fluticasone propionate FDC (50/500 µg b.i.d.) in patients with moderate to severe COPD
Sponsor and Clinical Phase	Novartis, phase IV
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to determine whether the efficacy and safety of QVA149 (110/50 µg o.d.) and triple treatment with tiotropium (18 µg o.d.) + salmeterol/fluticasone propionate FDC (50/500 µg b.i.d.) are comparable in patients with moderate to severe COPD without a history of frequent exacerbations.
Primary Objective(s)	To demonstrate the non-inferiority of QVA149 (110/50 µg o.d.) on trough FEV1 vs. tiotropium (18 µg o.d.) + salmeterol/fluticasone propionate FDC (50/500 µg b.i.d.) after 26 weeks of treatment in moderate-to-severe COPD patients.
Secondary Objectives	• To evaluate the effect of QVA149 (110/50 µg o.d.) compared with tiotropium (18 µg o.d.) + salmeterol/fluticasone propionate FDC (50/500 µg b.i.d.) over 26 weeks of treatment in terms of: • Rate of moderate or severe COPD exacerbations. • Rate of moderate or severe COPD exacerbations requiring • Systemic glucocorticosteroids and antibiotics during the treatment period (moderate exacerbations only). • Hospitalizations during the treatment period and rehospitalization within 30 days during the treatment period (severe exacerbations only). • To evaluate the effect of QVA149 (110/50 µg o.d.) compared with tiotropium (18 µg o.d.) + salmeterol/fluticasone propionate FDC (50/500 µg b.i.d.) on: • Trough FEV_1 and FVC over 26 weeks of treatment. • Total score of the St. George's Respiratory Questionnaire (SGRQ-C) after 12 and 26 weeks of treatment • Total score of the Transitional Dyspnea Index (TDI) after 12 and 26 weeks of treatment • Mean use of rescue therapy (number of puffs/day) and the percentage of days without rescue therapy over the 26 week treatment period. • To assess the safety (particularly with regard to ECG, laboratory tests, vital signs and adverse events) and tolerability (discontinuation due to adverse events) of QVA149 (110/50 µg

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	o.d.) vs. tiotropium (18 µg o.d.) + salmeterol/fluticasone propionate FDC (50/500 µg b.i.d.) over the 26 weeks of treatment. • To assess the safety of QVA149 (110/50 µg o.d.) vs. tiotropium (18 µg o.d.) + salmeterol/fluticasone propionate FDC (50/500 µg b.i.d.) in terms of HPA axis function, as determined by 24-hour weighted mean urine cortisol, in a subset of patients.
Study design	The study is a multicenter, randomized, parallel-group, double-blind, triple-dummy study to assess the efficacy of the two active treatment arms of QVA149 (110/50 µg o.d.) and tiotropium (18 µg o.d) + salmeterol/fluticasone propionate FDC (50/500 b.i.d) in patients with moderate-to-severe COPD.
Population	The study population will consist of approximately 1000 male and female adults (age 40 years and greater) with a clinical diagnosis of stable COPD who have moderate to severe airflow obstruction (GOLD 2014) and a smoking history of at least 10 pack years. Eligible patients will be those that have been maintained on triple therapy (a LAMA plus a FDC of LABA/ICS) for a minimum of six months, and are clinically stable (defined as not having >1 moderate-severe exacerbation within the last 12 months).
Inclusion criteria	• Patients who have signed Informed Consent Form prior to initiation of any study-related procedure. • Male and female adults aged ≥ 40 years. • Patients with moderate to severe airflow obstruction with stable COPD according to the 2014 GOLD Guidelines. • Patients with a **post**-bronchodilator FEV_1 ≥40 and < 80% of the predicted normal value, and **post**-bronchodilator FEV_1/FVC < 0.70 at run-in Visit 101. (**Post** refers to 15 min after inhalation of 400 µg of salbutamol). • Current or ex-smokers who have a smoking history of at least 10 pack years (e.g. 10 pack years = 1 pack /day x 10 years, or ½ pack/day x 20 years). An ex-smoker is defined as a patient who has not smoked for ≥ 6 months at screening. • Patients who are on triple treatment at least for the last 6 months (LAMA +LABA/ICS).
Exclusion criteria	• Key exclusion criteria. Full criteria are within the protocol: • Patients contraindicated for treatment with, or having a history of reactions/ hypersensitivity to any of the following inhaled drugs, drugs of a similar class or any component thereof: • long and short acting anticholinergic agents • long and short acting beta-2 agonists • sympathomimetic amines • lactose or any of the other excipients of trial medication • History or current diagnosis of ECG abnormalities indicating significant risk of safety for patients participating in the study such as: • Concomitant clinically significant cardiac arrhythmias, e.g., sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker • History of familial long QT syndrome or known family history of

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	Torsades de Pointes • Resting QTc (Fridericia method) ≥450 msec for males and females at Visit 101. • Concomitant use of agents known to significantly prolong the QT interval unless they can be permanently discontinued for the duration of study. • Patients who have clinically significant renal, cardiovascular (such as but not limited to unstable ischemic heart disease, NYHA Class III/IV left ventricular failure, myocardial infarction), arrhythmia (see below for patients with atrial fibrillation), neurological, endocrine, immunological, psychiatric, gastrointestinal, hepatic, or hematological abnormalities which could interfere with the assessment of the efficacy and safety of the study treatment. • Patients who have had more than one COPD exacerbation that required treatment with antibiotics and/or oral corticosteroids and/or hospitalization in the 12 months prior to Visit 1. • Patients who developed a COPD exacerbation of any severity either 6 weeks before the screening (Visit 1) or between screening (Visit 1) and treatment (Visit 201) will not be eligible but will be permitted to be re-screened after a minimum of 6 weeks after the resolution of the COPD exacerbation. • Patients with any history of asthma. • Patients with a blood eosinophil count > 600/mm^3 during screening (Visit 101). • Patients unable to use an electronic patient diary. • Patients unable to use a dry powder inhaler device or a pressurized MDI (rescue medication) or unable to comply with the study regimen. Spacer devices are not permitted. • History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
Investigational and reference therapy	QVA149 110/50 µg capsules o.d. for inhalation, supplied in blisters delivered via Novartis single dose dry powder inhaler Novartis single dose dry powder inhalerNovartis single dose dry powder inhaler. Salmeterol/fluticasone propionate FDC 50/500 µg dry inhalation powder delivered via Accuhaler™. Tiotropium 18 µg capsules o.d. for inhalation, supplied as commercially available blisters, delivered via HandiHaler®.
Efficacy assessments	• Pulmonary Function (Spirometry) • COPD exacerbations • Rescue medication usage • Modified Medical Research Council (mMRC) Dyspnea Scale • COPD Assessment Test (CAT) • St. George Respiratory Questionnaire C (SGRQ-C) • BDI/TDI • eDiary

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Safety assessments	• Adverse events • Physical examination • Urine pregnancy test (females of childbearing potential) • ECG • Vital signs • Pneumonia • 24 hr urinary cortisol (in a sub-set of patients) • Oropharyngeal sample culture for candidiasis • Laboratory: standard biochemistry and hematology; urinalysis
Other assessments	• Resource utilization • Biomarkers
Data analysis	The primary objective is to demonstrate the non-inferiority of QVA149 (110/50 µg q.d.) compared to tiotropium (18 µg q.d.)+salmeterol/fluticasone FDC (50/500 µg b.i.d) in terms of trough FEV_1 after 26 weeks of treatment in patients with moderate to severe COPD. The primary variable is the mean change from baseline in post-dose trough FEV_1 after 26 weeks of treatment. Trough FEV_1 at Day 182 is defined as the mean of the two FEV_1 values measured at 23h15min and 23h45min after the morning dose taken at site on Day 181. The primary efficacy endpoint will be analyzed using a Mixed-Effect Model Repeated Measures (MMRM) model. The model will include fixed, categorical effects of treatment and visit, country/region, and treatment-by-visit interaction as well as the continuous, fixed covariates of baseline and baseline-by-visit interaction. If additional covariates are considered to be required these will be predefined and included in the analysis plan finalized prior to database lock. The within-patient correlation will be modeled using an unstructured covariance matrix. The between-treatment comparison will be carried out using the adjusted mean difference between treatments at Day 182 and 95% confidence interval of the adjusted mean difference will be displayed. All timed trough FEV_1 data i.e. day 29, day 85, day 181 and day 182, recorded post-baseline will be included in the primary MMRM model and no imputation will be applied to missing data. Non-inferiority of QVA149 (110/50 µg o.d.) from tiotropium (18 µg o.d.) + salmeterol/fluticasone propionate FDC (50/500 µg b.i.d.) will be demonstrated if the confidence interval for the mean Day 182 FEV_1 difference of QVA149 (110/50 µg o.d.) minus tiotropium (18 µg o.d.) + salmeterol/fluticasone propionate FDC (50/500 µg b.i.d.) lies entirely to the right of (higher than) –50 mL.
Key words	COPD, QVA149, Triple-Therapy, Dual Broncho dilation

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1 Introduction

1.1 Background

Chronic Obstructive Pulmonary Disease (COPD), a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Current treatment guidelines for COPD recommend the use of bronchodilators for all severities, either on an as-required basis, or regular basis (GOLD 2014). Inhaled long-acting bronchodilator therapy such as β2 agonists (LABAs, such as formoterol, salmeterol and indacaterol) and muscarinic antagonists (LAMAs, such as tiotropium and glycopyrronium bromide) are established and widely used treatment options for COPD (GOLD 2014).

Published studies (Mak et al 1990; Carstairs et al 1985; Ikeda et al 2012) have shown that the mechanisms of action of long-acting bronchodilator therapy such as LABAs and LAMAs are complementary due to the differential density of β2-adrenoceptors and M3-receptors in central versus smaller airways. Thus, LABAs should be more effective in relaxing small airways and LAMAs in large airways. There is also clinical evidence that suggests that combining bronchodilators from these two pharmacological classes results in significantly greater improvements in lung function (FEV1) compared with the individual components alone (Cazzola and Molimard 2010, Wang et al 2011). Studies to date have also shown other meaningful outcomes such as improvement in inspiratory capacity, reduction in dyspnea, improved symptom scores, and less rescue medication use, as compared with individual drugs used alone (Van der Molen and Cazzola 2012).

QVA149 is a fixed combination of a long acting β2-agonist (Indacaterol maleate – QAB149) and a long acting muscarinic antagonist (Glycopyrronium bromide – NVA237). This combination product will be delivered by the Novartis Single Dose Dry Powder Inhaler (SDDPI).

QVA149 was investigated in a comprehensive phase III program development comprising more than 11,000 COPD patients across more than 40 countries. Data from this QVA149 Phase III Development Program have demonstrated improvement in lung function, quality of life, decrease in COPD symptoms and decrease in short-acting β2 agonist (SABA) use with a safety profile similar to placebo (Vogelmeier et al 2013, Bateman et al 2013).

When compared to current standard of care treatments like fluticasone/salmeterol or OL tiotropium, QVA149 phase III studies demonstrated significant improvements in terms of lung function, dyspnea, symptoms, quality of life and short-acting β2 agonist)- free days (Vogelmeier et al 2013, Bateman et al 2013). Additional information can be found in the QVA149 Investigator's Brochure.

These comparative studies have been performed in COPD populations with comparable stage and clinical characteristics between the treatments arms.

Building on the strength and value of combination therapies, the clinical practice of using 'triple therapy' for COPD treatment has become popular in recent years. This approach

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generally consists of combining a LABA and an ICS fixed-dose combination such as salmeterol/fluticasone propionate (SFC) with an anticholinergic/muscarinic antagonist (i.e., long-acting tiotropium bromide or short-acting ipratropium bromide). The rationale for using these compounds together lies in the fact that they have different molecular mechanisms of action and, consequently, their combined use could maximize their clinical benefits for patients suffering from this debilitating disease (Salama et al 2011).

According to GOLD 2014 COPD guidelines long term treatment with inhaled corticosteroids is recommended for patients with severe and very severe COPD and frequent exacerbations that are not adequately controlled by long-acting bronchodilators (Evidence A). These guidelines also emphasize that long-term treatment containing inhaled corticosteroids should not be prescribed outside their indications, due to the risk of pneumonia and the possibility of an increased risk of fractures following long-term exposure. QVA149 once daily provided clinically relevant improvements in lung function compared with SFC twice daily with significant symptomatic benefits in patients with moderate-to-severe COPD and no history of exacerbation in the last year. (Vogelmeier et al 2013). This study confirmed the superiority of dual bronchodilator treatment to a Fixed Dose Combination (FDC) of ICS/LABA in this population.

Current GOLD guidelines (GOLD 2014) recommend the use of triple therapy as an alternative first-line choice for the maintenance treatment of only group D patients. While current guidelines suggest using LABAs and/or muscarinic antagonists and ICSs in only a small number of patients, the use of this triple therapy (in which a combination inhaler is prescribed in combination with another single drug inhaler) is more widely used in clinical practice than recommended (Jones 2009, Salama et al 2011). In research conducted at US primary care sites, it has been found that 20% of Stage 1 and 39% of Stage 2 COPD patients are currently using ICS (Small et al 2012) In fact, there is evidence of widespread use of triple therapy for COPD even in primary care where patients have predominantly mild disease and occasional bronchitis (Gaebel et al 2011).

There is insufficient evidence to determine if triple therapy is superior to dual bronchodilator therapy in patients without a history of frequent exacerbations (Gaebel et al 2011). It is also unclear whether these patients could be managed just as effectively with dual bronchodilator therapy as triple, with less cost and improved patient convenience.

The effect of QVA149 vs. triple treatment with LABA/ICS FDC+LAMA has not been studied.

1.2 Purpose

The purpose of this study is to determine whether the efficacy and safety of QVA149 (110/50 µg o.d.) and triple therapy with tiotropium (18 µg o.d.) + salmeterol/fluticasone propionate FDC (50/500 µg b.i.d.) are comparable in patients with moderate to severe COPD without a history of frequent exacerbations (primarily GOLD category B). Data from this study will provide additional efficacy and safety data on QVA149 use in a patient population in which the use of inhaled corticosteroids and hence triple therapy may be unnecessary according to current GOLD guidelines.

[redacted]

2 Study objectives

2.1 Primary objective

To demonstrate the non-inferiority of QVA149 (110/50 µg o.d.) on post-dose trough FEV_1 vs. tiotropium (18 µg o.d.) + salmeterol/fluticasone propionate FDC (50/500 µg b.i.d.) after 26 weeks of treatment in moderate-to-severe COPD patients.

2.2 Secondary objectives

- To evaluate the effect of QVA149 (110/50 µg o.d.) compared with tiotropium (18 µg o.d.) + salmeterol/fluticasone propionate FDC (50/500 µg b.i.d.) over 26 weeks of treatment in terms of:
  - Rate of moderate or severe COPD exacerbations requiring
    - Systemic glucocorticosteroids and/or antibiotics during the treatment period (moderate exacerbations only).
    - Hospitalizations during the treatment period and rehospitalization within 30 days during the treatment period (severe exacerbations only).
- To evaluate the effect of QVA149 (110/50 µg o.d.) compared with tiotropium (18 µg o.d.) + salmeterol/fluticasone propionate FDC (50/500 µg b.i.d.) in terms of:
  - Trough FEV_1 and FVC over 26 weeks of treatment.
  - Total score of the St. George's Respiratory Questionnaire (SGRQ-C) after 12 and 26 weeks of treatment
  - Total score of the Transitional Dyspnea Index (TDI) after 12 and 26 weeks of treatment
  - Mean use of rescue therapy (number of puffs/day) and the percentage of days without rescue therapy over the 26 weeks treatment period.
- To assess the safety (particularly with regard to ECG, laboratory tests, vital signs and adverse events) and tolerability (discontinuation due to adverse events) of QVA149 (110/50 µg o.d.) vs. tiotropium (18 µg o.d.) + salmeterol/fluticasone propionate FDC (50/500 µg b.i.d.) over the 26 weeks of treatment.
- To assess the safety of QVA149 (110/50 µg o.d.) vs. tiotropium (18 µg o.d.) + salmeterol/fluticasone propionate FDC (50/500 µg b.i.d.) in terms of HPA axis function, as determined by 24-hour weighted mean urine cortisol, in a sub-set of patients.

2.3 Exploratory objectives

To explore:

- The score changes from baseline in CAT over the 26 week treatment period and mMRC at week 26
- Rate of all protocol defined exacerbations
- Symptoms reported over 26 weeks treatment using e-diary
- Oropharyngeal candidiasis evaluation by positive oropharyngeal swab sample culture

[redacted]

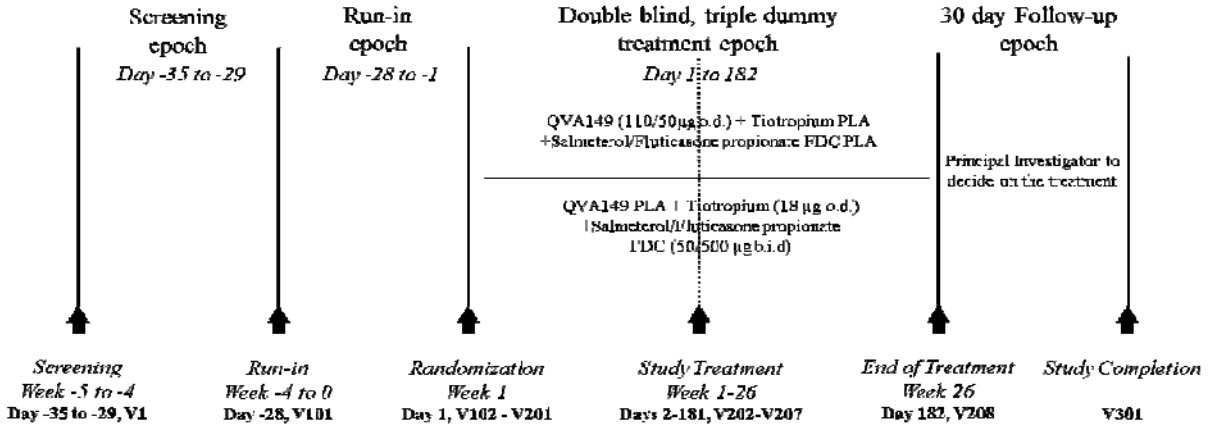
3 Investigational plan

3.1 Study design

The study is a multicenter, randomized, parallel-group, double-blind, triple-dummy study to assess the efficacy of the two active treatment arms of QVA149 (110/50 µg o.d.) and tiotropium (18 µg o.d) + salmeterol/fluticasone propionate FDC (50/500 b.i.d) in patients with moderate-to-severe COPD.

The study consists of four epochs: screening (1 week), run-in (4 weeks), blinded treatment (26 weeks) and follow-up (4 weeks). See Figure 3-1.

Figure 3-1 Study Design



Screening epoch

At Visit 1 (Screening) informed consent will be obtained before any study related assessments or procedures are performed. All patients signing informed consent must be registered in the Interactive Response Technology (IRT) system. COPD medications and eligibility criteria will be assessed (as outlined in Assessment Table 6-1) and if necessary, arrangements made to adjust prohibited therapy (see Table 5-1, Table 5-2 and Table 5-3).

The patients will also be provided with a short acting β2-agonist (salbutamol or albuterol) for use as a rescue inhaler on an "as needed" basis throughout the study; for more details on rescue medication please refer to Section 5.5.6.

In order to assess lung function for inclusion criteria, the patients must be informed at Screening visit (after having signed the informed consent) to withhold use of COPD medication at home ≥24 hours for tiotropium and ≥12 hours for salmeterol/fluticasone propionate FDC before coming to the clinic on the day of the Run-in visit (Visit 101). COPD medication will be dispensed in the clinic after spirometry testing.

Run-in Epoch

At Visit 101 (week -4) inclusion and exclusion criteria will be checked again and other assessments as outlined in Assessment Table 6-1 will be performed. In women of childbearing potential a pregnancy test will be done.

Spirometry testing should only be performed if no COPD medication was taken in the morning. If not, this visit should be rescheduled.

During the run-in epoch all patients will be given tiotropium (18 µg o.d.) + salmeterol/fluticasone propionate FDC (50/500 µg b.i.d.) treatment regardless of their previous triple combination before study entry (Instructions will be given to the patient on the correct use of the inhalation devices). If they are already taking this triple combination they will continue to take the same treatment during the run-in epoch.

The patients will be supplied with an electronic diary device (eDiary, Appendix 3) to collect rescue medication usage and symptom information between Visit 101 (baseline run-in, Day -28) and Visit 201 (Randomization, Day 1) in order to receive baseline information. The eDiary will also be used to collect symptom information and rescue medication (salbutamol or albuterol) usage throughout the course of the study treatment epoch. For details on the eDiary please refer to Section 6.6.4.

At the time of randomization patients will be randomized to QVA149 or continue to take triple treatment in a 1:1 ratio. In this way possible deterioration during this period will be prevented.

End of Run-in Epoch /Start of Treatment Epoch (Randomization)

Visit 102 (Run-in) and Visit 201 (Randomization) will occur on the same day.

At Visit 102 (Day 1), the patients will come to the clinic in the morning to complete the questionnaires (except for mMRC questionnaire which is completed at Visit 101) as well as have eligibility criteria reviewed. This visit should occur approximately 28 days after Visit 101. After the questionnaires are completed, the eDiary symptom data will be reviewed and all other assessments (see Table 6-1) including spirometry will be performed.

At Visit 201 (Randomization Visit, Day 1, taking place right after Visit 102), all patients who meet the eligibility criteria and already maintained on triple treatment (LABA/ICS+LAMA combination) will be randomized in a 1:1 ratio to one of the two treatment arms for the 26 week treatment epoch. The study treatment will be dispensed (see Section 5.5.2) and instructions will be given to the patient on the correct use of the inhalation device and study treatment.

Patients must be informed not to take study treatment prior to ALL future clinic visits, as this will be administered in clinic after all pre-dose procedures and assessments have been performed.

In other words, patients must withhold salmeterol/ fluticasone propionate FDC ≥12 hours prior to visits; tiotropium and QVA149 ≥24 hours prior to visits.

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Treatment Epoch

Patients will attend 7 study visits (up to Visit 208) during the treatment epoch. Patients should be seen for all visits on the designated day or as close as possible for all Visits from 202 to 208.

The investigator should instruct the patient to notify the study site about any new medications he/she takes after the start of the study. All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient has started study treatment must be listed on the concomitant medications page of the eCRF.

All randomized patients will be contacted by telephone between the visits if the interval between the visits is 4 weeks or longer to check if patient's COPD symptoms have worsened, any treatment required and e-diary completed accordingly (see Assessment Table 6-1). Patients, who discontinue study treatment early, will be asked to continue with study visit through Visit 207 while off study treatment. See Section 5.5.9 for treatment discontinuation. In case of study withdrawal, please refer to Section 5.5.10.

Patients will then enter a 30 day follow-up epoch to collect patient safety data.

Follow-up Epoch

All randomized patients, regardless of whether they completed study treatment through Week 26 or discontinued study treatment prior to Week 26, will be contacted (by telephone) 4 weeks after last study visit/treatment for a Safety Follow-up Visit 301.

Patients should also be aware that they may be contacted in the future if any additional follow-up information is required, following the appropriate approvals and informed consents as required.

If a patient refuses to return for any assessments or is unable/unwilling to do so, every effort (preferable at least three documented efforts) should be made to contact the patient or a knowledgeable informant to ensure the safety of the patient. Attempts to contact the patient should be documented in the source records.

Investigators will be required to follow all procedures during the conduct of the study.

No interim analysis is planned.

3.2 Rationale of study design

A double-blind, triple-dummy, two-arm design was selected to provide scientifically robust comparison data between treatment arms. The potential change in lung function seen in those patients treated with QVA149 (110/50 µg o.d.) will be compared to baseline and to the change in lung function in those receiving tiotropium (18 µg o.d.) + salmeterol/fluticasone propionate FDC (50/500 µg b.i.d.) treatment. The duration of 26 weeks is considered appropriate in order to demonstrate the improvements in lung function as well as assess the effect on a variety of patient reported outcomes.

We chose this blinded and parallel design to minimize the bias due to different Dry Powder Inhaler (DPI) devices. All patients will be using all three devices throughout the study either with placebo or with an active product.

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

The selection of QVA149 dose in this study (110/50 µg o.d.) was based on data from the QAB149 and NVA237 mono-component programs. Those programs identified the doses as 150 µg once daily for QAB149 and 50 µg once daily for NVA237. However, in formulating the QVA149 combination product, an increase in fine particle (respirable) fraction was observed for the QAB149 component (compared with the monocomponent). As a consequence, to ensure that the fine particle dose of QAB149 delivered to the lung from the combination matches that delivered from the monocomponent, the dose for the QAB149 component of QVA149 has been adjusted to 110 µg. The selection of doses for tiotropium (18 µg o.d.) and salmeterol/fluticasone propionate FDC (50/500 µg b.i.d.) are based on their respective development programs in COPD treatment, and are approved doses.

COPD guidelines issued by Committee for Medicinal Products for Human Use (CHMP) and other health authorities suggest that an evaluation of the lung function as expressed by FEV_1 measures should normally be made over a period of at least twelve weeks. Hence, patients will be assessed at week 12 and up to week 26 in order to demonstrate that QVA149 is at least non-inferior to therapy with tiotropium (18µg o.d.) + salmeterol/fluticasone propionate FDC (50/500 µg b.i.d.) in terms of change from baseline in trough FEV_1.

3.4 Rationale for choice of comparator

Tiotropium (18 µg o.d.) and salmeterol/fluticasone propionate FDC (50/500 µg b.i.d.) are the most widely used maintenance treatments in COPD. These products have well established scientific data showing their efficacy and safety both individually and in combination with each other (triple treatment) (Salama et al 2011).

3.5 Purpose and timing of interim analyses/design adaptations

Not applicable.

3.6 Risks and benefits

The risk to patients in this trial will be minimized by compliance with all of the eligibility criteria and by close clinical monitoring. Altering the current COPD medication regimen during the run-in period and switching from one triple treatment to another one (if the current triple combination is different than study triple combination) or randomizing the patients during the study treatment either to the same triple treatment as in run-in or QVA149 is not likely to pose any risk of "under-treatment". Although ICS is withdrawn in the QVA149 arm ICS is not recommended in these patients according to the current GOLD COPD strategy document (GOLD 2014). Therefore all patients are receiving sufficient COPD treatment in both arms, along with appropriate rescue medication.

Providing the patients with rescue medication (short acting beta agonist; SABA) and active treatment during the screening, run-in period and throughout the study mitigates any deterioration risk. 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

[redacted]

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

The risk of side effects from the study medication are known for compounds QVA149, QAB149 and NVA237. The most frequently reported side effects seen for QVA149 to date are; nasopharyngitis, upper respiratory tract infection, cough, and headache. See QVA149 Investigator's Brochure and for QAB149 and NVA237 see QAB149 and NVA237 sections of the QVA149 Investigator's Brochure.

The risk of side effects for the active comparator salmeterol/fluticasone 50/500 µg b.i.d) are those known for salmeterol and fluticasone, such as tremor, headache, palpitations, pneumonia, bronchitis, hypokalemia, nasopharyngitis, throat irritation, sinusitis, muscle cramps, traumatic fractures, hoarseness and candidiasis in the mouth and throat. (Seretide Accuhaler® 50/500 µg SmPC).

The most common adverse reactions for the other active comparator, Tiotropium (>5% incidence in the 1-year placebo-controlled trials) are upper respiratory tract infection, dry mouth, sinusitis, pharyngitis, non-specific chest pain, urinary tract infection, dyspepsia, and rhinitis (Spiriva Handihaler™ 18 µg SmPC).

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. This increased risk has not been demonstrated in patients with COPD.

4 Population

The study population will consist of approximately 1000 male and female adults (age 40 years and greater) with a clinical diagnosis of stable COPD who have moderate to severe airflow obstruction (GOLD 2014) and a smoking history of at least 10 pack years. Eligible patients will be those that have been maintained on triple therapy (a LAMA plus a FDC of LABA/ICS) for a minimum of six months prior to Visit 1, and are clinically stable (defined as not having >1 moderate-severe exacerbation (see Section 6.6.2) within the last 12 months prior to Visit 1). Therefore patients who are currently being maintained on triple therapy (LABA/ICS+LAMA) for at least 6 months prior to Visit 1 and with clear documentation of no more than one moderate or severe exacerbation in the last 12 months prior to Visit 1 will be recruited.

It is anticipated that at least 1400 patients will need to be screened in order to randomize 1000 patients into 2 treatment arms of the study with a randomization ratio of 1:1.

Patients will be randomized into the study with the intention that 750 patients will complete the study. Dropouts will not be replaced. The study will be multi-national.

Patients will be stratified by smoking status (current/ex-smoker) and severity of airflow limitation (using GOLD 2014 classification).

[redacted]

4.1 Inclusion criteria

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

1. Patients who have signed Informed Consent Form prior to initiation of any study-related procedure.
2. Male and female adults aged ≥ 40 years.
3. Patients with moderate to severe airflow obstruction with stable COPD (Stage 2 or Stage 3) according to the 2014 GOLD Guidelines.
4. Patients with a **post**-bronchodilator FEV_1 ≥40 and < 80% of the predicted normal value, and **post**-bronchodilator $FEV_1/FVC < 0.70$ at run-in Visit 101.
   (**Post** refers to 15 min after inhalation of 400 µg of salbutamol) (Readings assessed by site and checked centrally).
5. Current or ex-smokers who have a smoking history of at least 10 pack years (e.g. 10 pack years = 1 pack /day x 10 years, or ½ pack/day x 20 years). An ex-smoker is defined as a patient who has not smoked for ≥ 6 months at screening.
6. Patients who are on triple treatment at least for the last 6 months (LAMA +LABA/ICS).

4.2 Exclusion criteria

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

1. Use of other investigational drugs/devices (approved or unapproved) at the time of enrollment, or within 30 days or 5 half-lives of Visit 1, whichever is longer.
2. Patients contraindicated for treatment with, or having a history of reactions/ hypersensitivity to any of the following inhaled drugs, drugs of a similar class or any component thereof:
   - long and short anticholinergic agents
   - long and short acting beta-2 agonists
   - sympathomimetic amines
   - lactose or any of the other excipients of trial medication
3. History or current diagnosis of ECG abnormalities indicating significant risk of safety for patients participating in the study such as:
   - Concomitant clinically significant cardiac arrhythmias, e.g., sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker
   - History of familial long QT syndrome or known family history of Torsades de Pointes
4. Resting QTc (Fridericia method) ≥450 msec for males and females at Visit 101.
5. Concomitant use of agents known to significantly prolong the QT interval unless it can be permanently discontinued for the duration of study.
6. Patients who have a clinically significant laboratory abnormality at Visit 101 and would be at potential risk if enrolled into the study.
7. Patients who have clinically significant renal, cardiovascular (such as but not limited to unstable ischemic heart disease, NYHA Class III/IV left ventricular failure, myocardial

[redacted]

infarction), arrhythmia (see below for patients with atrial fibrillation), neurological, endocrine, immunological, psychiatric, gastrointestinal, hepatic, or hematological abnormalities which could interfere with the assessment of the efficacy and safety of the study treatment.

8. Patients with paroxysmal (e.g. intermittent) atrial fibrillation are excluded. Patients with persistent atrial fibrillation as defined by continuous atrial fibrillation for at least 6 months and controlled with a rate control strategy (i.e., beta blocker, calcium channel blocker, pacemaker placement, digoxin or ablation therapy) for at least 6 months may be considered for inclusion. In such patients, atrial fibrillation must be present at Visit 101 and Visit 102) visits, with a resting ventricular rate < 100/min. At visit 101, atrial fibrillation must be confirmed by central reading.
9. Patients with narrow-angle glaucoma, symptomatic benign prostatic hyperplasia or bladder-neck obstruction or moderate to severe renal impairment or urinary retention (BPH patients who are stable on treatment can be considered).
10. Patients who have not achieved acceptable spirometry results at Visit 101 in accordance with ATS (American Thoracic Society)/ERS (European Respiratory Society) criteria for acceptability (one retest may be performed for patients that don't meet the acceptability criteria).
11. Patients who have had more than one COPD exacerbation that required treatment with antibiotics and/or oral corticosteroids and/or hospitalization in the last year prior to Visit 1.
12. Patients who developed a COPD exacerbation of any severity either 6 weeks before the screening (Visit 1) or between screening (Visit 1) and treatment (Visit 201) will not be eligible but will be permitted to be re-screened after a minimum of 6 weeks after the resolution of the COPD exacerbation.
13. Patients who have had a respiratory tract infection within 4 weeks prior to screening Visit 1.
14. Patients who develop a respiratory tract infection between screening and treatment will not be eligible, but will be permitted to be re-screened 4 weeks after the resolution of the respiratory tract infection.
15. Patients requiring long term oxygen therapy prescribed for >12 hours per day.
16. Patients with any history of asthma.
17. Patients with a blood eosinophil count > 600/mm^3 during screening (Visit 101).
18. Patients with allergic rhinitis who use a H1 antagonist or intra-nasal corticosteroids intermittently (treatment with a stable dose or regimen is permitted).
19. Patients with concomitant pulmonary disease (e.g. lung fibrosis, sarcoidosis, interstitial lung disease, pulmonary hypertension, clinically significant bronchiectasis).
20. Patients with a diagnosis of α-1 anti-trypsin deficiency.
21. Patients with active pulmonary tuberculosis.
22. Patients with pulmonary lobectomy or lung volume reduction surgery or lung transplantation.
23. Patients participating in or planning to participate in the active phase of a supervised pulmonary rehabilitation program during the study (Maintenance program is permitted).
24. Patients receiving any medications in the classes listed in Table 5-1.

[redacted]

25. Patients receiving any COPD related medications in the classes specified in Table 5-2 must undergo the required washout period prior to Visit 101 and follow the adjustment to treatment program.
26. Patients receiving medications in the classes listed in Table 5-3 should be excluded unless the medication has been stable for the specified period and the stated conditions have been met.
27. Patients unable to use an electronic patient diary.
28. Patients unable to use a dry powder inhaler device or a pressurized MDI (rescue medication) or unable to comply with the study regimen. Spacer devices are not permitted.
29. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
30. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
31. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of study treatment. Effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 m prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient
    - Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository
    - Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception
    - Placement of an intrauterine device (IUD) or intrauterine system (IUS)

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

[redacted]

5 Treatment

5.1 Protocol requested treatment

Since this is a triple dummy study patients will receive medication kits consisting of either:

- Active QVA149 with Novartis single dose dry powder inhaler
- Placebo salmeterol/fluticasone propionate FDC with Accuhaler™
- Placebo tiotropium with HandiHaler®

OR

- Placebo QVA149 with Novartis single dose dry powder inhaler.
- Active salmeterol/fluticasone propionate FDC with Accuhaler™
- Active tiotropium with HandiHaler®

5.1.1 Investigational treatment

- QVA149 110/50 µg capsules o.d. for inhalation, supplied in blisters delivered via Novartis single dose dry powder inhaler
- Placebo to salmeterol/fluticasone propionate FDC 50/500 µg will be provided as dry inhalation powder via Accuhaler™
- Placebo to tiotropium 18 µg will be provided as inhalation capsules delivered via HandiHaler®

QVA149 110/50 µg o.d. will be provided as inhalation capsules. Placebo inhalation capsules will be equally matched in size, shape and color to QVA149 110/50 µg o.d. inhalation capsules.

5.1.2 Reference therapy

- Salmeterol/fluticasone propionate FDC 50/500 µg dry inhalation powder delivered via Accuhaler™.
- Tiotropium 18 µg capsules o.d. for inhalation, supplied as commercially available blisters, delivered via HandiHaler®.
- Placebo to QVA149 110/50 µg o.d. capsules for inhalation, supplied in blisters, delivered via Novartis single dose dry powder inhaler.

Under no circumstances is an alternative inhalation device to be used for the administration of any of the investigational or reference therapies during the treatment period.

5.2 Treatment arms

Patients will be assigned by randomization to one of the following two treatment arms in a ratio of 1:1 during the triple dummy period.

1. QVA149 110/50 µg o.d., delivered via Novartis single dose dry powder inhaler plus Tiotropium matching placebo o.d. delivered via the manufacturer's HandiHaler® device plus Fluticasone/salmeterol propionate FDC matching placebo, b.i.d., delivered via the manufacturer's Accuhaler® device.

[redacted]

2. QVA149 matching placebo o d, delivered via Novartis single dose dry powder inhaler plus Tiotropium 18 µg o.d., delivered via the manufacturer's HandiHaler® device plus Fluticasone/salmeterol propionate FDC 500/50 µg b.i.d. dry inhalation powder delivered via the manufacturer's Accuhaler® device.

5.3 Treatment assignment, randomization

At Visit 201 all eligible patients will be randomized via Interactive Response Technology (IRT) to one of the 2 treatment arms. The investigator or his/her delegate will contact the IRT after confirming at Visit 102 that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of investigational treatment to be dispensed to the patient. The randomization number will not be communicated to the caller.

The randomization numbers will be generated by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers.

A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

The randomization scheme for patients will be reviewed and approved by Novartis.

5.4 Treatment blinding

Patients, investigator staff, persons performing the assessments, and data analysts will remain blinded to the identity of the treatment from the time of randomization until database lock, using the following methods:

- Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone involved in the study;
- The identity of the treatments will be concealed by the use of investigational treatments that are identical in packaging, labeling and schedule of administration.

A triple -dummy design is used because the identity of the study treatments cannot be disguised due to their different forms.

Unblinding will only occur in the case of patient emergencies (see Section 5.5.12) and at the conclusion of the study.

5.5 Treating the patient

5.5.1 Patient numbering

Each patient is uniquely identified by a Patient Number which is composed of a 4-digit site number assigned by Novartis and a sequential 3-digit sequential patient number assigned by the investigator. Once assigned to a patient, the Patient Number will not be reused.

[redacted]

Upon signing the informed consent form, the patient is assigned the next sequential number by the investigator. The investigator or delegate will contact the IRT and provide the requested information for the patient to register them into the IRT. The site should select the CRF book with a matching Patient Number from the EDC system to enter data.

If the patient fails to be treated for any reason, the IRT must be notified within two days that the patient was not treated. The reason for not being treated will be entered on the Screening Epoch Study Disposition CRF.

5.5.2 Dispensing the investigational treatment

Each study site will be supplied by Novartis with investigational treatment. The investigational treatment packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the 2 treatment arms and a specific visit. Investigator staff will identify the investigational treatment package(s) to dispense to the patient by contacting the IRT and obtaining the medication number(s). Immediately before dispensing the package to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique patient number.

5.5.3 Handling of study treatment

This section defines how to handle the investigational medicinal product (IMP).

5.5.3.1 Handling of investigational treatment

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

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the investigational treatment but no information about the patient just the medication number.

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

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

5.5.3.2 Handling of other study treatment

Not applicable.

[redacted]

5.5.4 Instructions for prescribing and taking study treatment

Each study site will be supplied by Novartis with study treatment organized in uniquely numbered medication kits.

- QVA149 110/50 µg o.d., delivered via. Matching placebo o.d., delivered via Novartis single dose dry powder inhaler.
- Tiotropium 18 µg o.d., delivered via the manufacturer's proprietary inhalation device (HandiHaler®). Matching placebo o.d., delivered via HandiHaler®.
- Fluticasone/salmeterol propionate FDC 500/50 µg b.i.d. dry inhalation powder delivered via Accuhaler™ device. Matching placebo, b.i.d., delivered via Accuhaler™.

Each patient will receive three kits at each dispensing visit, one QVA149/placebo, one tiotropium/placebo and one fluticasone+salmeterol propionate/placebo FDC, except for Visits 205 and 206, where the patients will receive six kits (two each of QVA149/placebo, tiotropium/placebo and fluticasone+salmeterol propionate/placebo FDC).

At Visits 201 (Randomization, Day 1) through 207 (Day 141) study medication will be administered in the clinic by the investigator at a designated time between 08:00 AM and 11:00 AM (see Table 6-2).

Patients will be instructed to take at home one capsule in the morning between 08:00 AM and 11:00 AM from each of their medication kits and one capsule in the evening, in the following order;

- AM (approximately between 08:00-11:00): one inhalation from the QVA149 Novartis single dose dry powder inhaler) **followed by** one inhalation from tiotropium HandiHaler® and one from fluticasone/salmeterol propionate FDC Accuhaler™ device.
- PM (approximately 12 hours after their AM dose +/- 30 minutes): one inhalation from fluticasone/salmeterol Accuhaler™ device.

Patients should also be instructed to replace each blister and inhalation device back into the appropriate box immediately after they have taken their dose.

All used and unused study medication / packaging must be returned by the patient at each Visit.

Patients must be instructed to withhold use of their morning dose of study medication at home on morning of clinic visit days as study medication will be dispensed in the clinic. Patients must also be instructed to withhold the use of short acting β_2-agonists (rescue medication) for at least 6 hours prior to all clinic visits, unless the use is absolutely necessary, in which case the visit is to be rescheduled to the next possible day.

The date and time of the morning dose of study medication dose administration at each clinic visit (Visits 201-207) will be recorded on the Dosage Administration Record electronic Case Report Form (eCRF).

Patients will be instructed on how to use the study treatment inhalation devices. Additional inhalation devices and blisters with placebo capsules will be provided for training and demonstration purposes as needed (see Appendix 4 for the patient instructions on how to use the inhalers).

[redacted]

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

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

If any technical complaints or faults are identified with either the device and/or the blisters, these should be returned to Novartis with the completed Device Return Form. The forms will be supplied to each investigator site by the Field Monitor.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Study treatment dose adjustments and/or interruptions are not permitted unless the investigator considers an interruption is necessary for the treatment of an adverse event or exacerbation (see Section 6.6.2).

Patients who experience a moderate to severe COPD exacerbation may continue in the study (see Section 6.6.2 for definition and more information).

Any interruption of study medication should be for the shortest time period possible and any interruption of study medication for more than 5 consecutive days during the treatment epoch should be discussed with the Novartis Medical Monitor to review the patient's eligibility to continue in the trial.

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

5.5.6 Rescue medication

At Visit 1 (Screening), all patients will be provided with a short acting β2-agonist (salbutamol or albuterol) which they will be instructed to use throughout the study as rescue medication.

Nebulized salbutamol or albuterol is not permitted as rescue medication. No other rescue treatment is permitted during the run-in and treatment epochs.

Salbutamol or albuterol is not to be administered within 6 hours of Visit 101 (Baseline run-in, Day -28) and Visit 201 (Randomization, Day 1), unless absolutely necessary, in which case the visit is to be rescheduled.

During the treatment epoch salbutamol or albuterol should be taken as rescue medication (when required) only. In order to standardize measurements, following randomization patients should be instructed to abstain from taking rescue medication (salbutamol or albuterol) within 6 hours of the start of each visit where spirometry is being performed unless absolutely necessary.

Following randomization, if rescue medication is taken within 6 hours prior to a spirometry visit, the visit should be rescheduled to the next day, if possible. The investigator must use their judgment when deciding how many times a visit for an individual patient should be rescheduled.

[redacted]

In the event that a patient uses a dose of rescue medication after taking study medication at any visit, the visit should continue as planned. In this case the approximate time of rescue medication intake will be captured through the central spirometer.

Use of rescue medication (number of puffs taken in the previous 12 hours) will be recorded (once in the morning and once in the evening) by the patient, in the electronic patient diary.

5.5.7 Concomitant treatment

The investigator should instruct the patient to notify the study site about any new medications taken 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.

5.5.8 Prohibited Treatment

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

Table 5-1 Prohibited treatment

Class of Medication[1]	Minimum cessation period prior to Visit 101 (Baseline run-in)
Non-potassium sparing diuretics (unless administered as a fixed-dose combination with a potassium conserving drug	7 days
Non-selective systemic beta-blocking agents[2]	7 days
Cardiac anti-arrhythmics Class Ia	7 days
Cardiac anti-arrhythmics Class III	7 days, amiodarone 3 months
Other drugs with potential to significantly prolong the QT interval	14 days or 5 half-lives, whichever is longer
Tricyclic antidepressants (Please note that tetracyclics, which are similar in class with regards to drug interaction are also to be excluded)	14 days
All antipsychotic agents (first, second and third generation, inclusive of atypical antipsychotics) Combinations of antipsychiotic agents with antidepressants are prohibited	14 days
Serotonin Noradrenaline Reuptake Inhibitors (SNRIs)	14 days
Other noradrenaline reuptake inhibitors	14 days
Monoamine-oxidase inhibitors	14 days
Live attenuated vaccine	30 days
Antibiotics (long term maintenance)[3]	30 days
Systemic Mast cell stabilizers (e.g., cromoglycate, nedocromil, ketotifen)	7 days
Systemic anticholinergics	7 days

[redacted]

Class of Medication[1]	Minimum cessation period prior to Visit 101 (Baseline run-in)
IgE inhibitors (e.g., Xolair)	6 months
Leukotriene antagonists and leukotriene synthesis inhibitors	7 days

[1]This table is not considered all-inclusive. Medications should be assessed for adherence to the indication and other inclusion/exclusion criteria.

[2] Selective β1 blocking agents are permitted.

[3] Short courses of antibiotics are permitted during the study.

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

Table 5-2 Prohibited COPD-related medications during the trial

Class of Medication[1, 2]	Minimum washout period prior to Visit 101 (Baseline run-in)
Short acting muscarinic antagonist (SAMA)[2]	8 hours
Fixed combinations of short-acting β_2 agonists and short-acting muscarinic antagonist (SABA/SAMA)	8 hours
Short-acting β_2 agonists (SABA) [3]	6 hours
Oral Phosphodiesterase-IV inhibitor	7 days
Xanthines (any formulation)	7 days
Parenteral or oral corticosteroids	30 days
Intra-muscular depot corticosteroids	3 months

[1]This table is not considered all-inclusive. Medications should be assessed for adherence to the indication and other inclusion/exclusion criteria. These medications are also prohibited if administered for other indications.

[2]All of these medications are permitted for the treatment of a COPD exacerbation during the study except depot corticosteroids. If depot corticosteroid treatment is required, the patient should be withdrawn from the study treatment.

[3]SABA and SAMA prohibited with exception of study rescue medication (see Section 5.5.6).

[redacted]

Table 5-3 Medication allowed under certain conditions if taken as follows

Class of Medication[1]	Condition under which medication is permitted
Selective Serotonin Reuptake Inhibitors	Stable dose for at least 30 days prior to Visit 1 (Screening) and during the trial.
Intra-nasal corticosteroids	Stable dose for at least 30 days prior to Visit 1 (Screening).
H_1-antagonists	Stable dose/regimen for at least 5 days prior to Visit 1 (Screening) (Except mizolastin or terfenadine)
Inactivated influenza, pneumococcal or any other inactivated vaccine	Not administered within 48 hours prior to a trial visit

[1]This table is not considered all-inclusive. Medications should be assessed for adherence to the indication and other inclusion/exclusion criteria.

5.5.9 Discontinuation of study treatment

Investigational treatment must be discontinued under the following circumstances:

- In case of adverse events for which continued inhalation of the study treatment would be detrimental and/or abnormal test procedure results indicating risk for the patient on continued inhalation of the study treatment (patient should continue with TD visit).
- Emergence of the following adverse event:
  Absolute QTcF > 500 msec, confirmed by repeat ECG measurements
- Pregnancy
- Use of prohibited treatment as per Table 5-1 and Table 5-2

If premature discontinuation of study treatment occurs, the patient should return to the clinic as soon as possible for a study treatment discontinuation **(TD)** visit. At this study treatment discontinuation visit assessments should be completed and recorded in the eCRF as per Table 6-1.The investigator must determine the primary reason for the patient's premature discontinuation of study treatment and record this information on the Dosage Administration eCRF.

The investigator and study staff must discuss with the patient, the patient's continued participation in the study and request patients to continue attending study visits according to the study visit schedule with all assessments completed up to Visit 207. If the patient cannot or is unwilling to attend any visit(s), the site staff should maintain regular phone contact with the patient, or with a person pre-designated by the patient. This phone contact should preferably be done according to the study visit schedule. Data will continue to be collected concerning the patient's health status, including information regarding new / concomitant treatments, adverse events, and vital status. The Week 26 spirometry assessments conducted at Visit 207 and safety assessments at Visit 207 are the priority assessments for patients that prematurely discontinue study treatment. At a minimum, the investigator should make every effort to obtain information regarding serious adverse events.

[redacted]

The appropriate personnel from the site and Novartis will assess whether investigational treatment should be discontinued for any patient whose treatment code has been broken inadvertently for any reason.

The investigator must also contact the IRT to register the patient's discontinuation from investigational treatment.

At a minimum, patients will be contacted for safety evaluations during the 30 days following the last study visit or following the last administration of investigational treatment if there are post-treatment follow-up visits (whichever is later), including a final contact at the 30-day point. Documentation of attempts to contact the patient should be recorded in the source documentation.

5.5.10 Withdrawal of consent

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

Withdrawal of consent occurs only when a patient 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 contacts and does not allow analysis of already obtained biologic material.

If a patient withdraws consent, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information in the source documentation. Study treatment must be discontinued and no further assessments conducted. Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

5.5.11 Loss to follow-up

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

5.5.12 Emergency breaking of assigned treatment code

Emergency treatment code breaks should only be undertaken when it is essential to treat the patient safely and efficaciously. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the monitor for the site and the Trial Lead (TL) that the code has been broken. The patient will automatically be entered as discontinued from study treatment within the IRT system after codebreaking.

[redacted]

The investigator (and designated site staff) will have 24hr/7day access to IRT during the study, and will be able to unblind patients in cases of emergency.

Study treatment must be discontinued after emergency unblinding. Study treatment must also be discontinued for any patient whose treatment code has been inadvertently broken or for any non-emergency reason.

5.5.13 Study completion and post-study treatment

Study completion for an individual patient will occur after he/she has completed through to the final evaluation (Visit 301). Completion of the study will be when all randomized patients have completed through to the final evaluation (Visit 301) or have withdrawn from the study.

When the patient has completed all scheduled study assessments or prematurely withdrawn from the study, the investigator must contact the IRT to record the patient completion / discontinuation and complete applicable eCRFs.

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

5.5.14 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, ongoing patients should be seen as soon as possible and treated for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

6 Visit schedule and assessments

6.1 Assessment schedule

The study will consist of a screening epoch, a run-in epoch, a 26 week blinded treatment epoch and a follow-up epoch of 30 days after the last treatment.

Table 6-1 lists all of the assessments and indicates with an "X" or "S" when the assessment(s) are performed at that visit. Patients should be seen for all visits on the designated day or as close to it as possible. The number of days between Visit 1 and Visit 101 will depend on the baseline epoch time for prohibited concomitant medication, as described in Section 5.5.7 the minimum interval between Visit 1 and Visit101 is at least one day (Patients need to sign informed consent first before they will be asked not to take their morning dose of COPD medications on the day of the next visit, when the reversibility assessment will be done; see Section 3.1).All data obtained from these assessments must be reported in the patient's source documentation.

Patients who discontinue study treatment should return for the TD (Treatment Discontinuation) Visit as soon as possible as noted in Table 6-1.

For all visits in which they occur, the assessments listed below are to be performed in the following order:

[redacted]

- St George's Respiratory Questionnaire (SGRQ-C)
- Modified Medical Research Council (mMRC) Dyspnea Scale
- COPD Assessment Test (CAT)
- Baseline Dyspnoea Index/Transition Dyspnoea Index (BDI/TDI)
- ECG
- Vital signs: pulse rate, blood pressure
- Blood sample/urine samples
- Spirometry measurements must always occur at the scheduled time point (see Table 6-2 for Timed Assessments)

Whenever other assessments are scheduled at the same time-point, spirometry must take precedence such that it occurs at the scheduled time point or as near as possible. If necessary other assessments (excluding SGRQ-C, mMRC, CAT, BDI/TDI) can be performed after spirometry.

Bloods must always be drawn after ECG measurement.

[redacted]

Table 6-1 Assessment schedule

Epoch	Screening	Run-in		Treatment										Follow-up (by phone)
Visit number	**1**	**101**	**102**	**201**	**202**	**203**	**204**	**205**	**206**	**207**	**208**	**299**	**-**	**301**
Visit	**Screening**	**Baseline run-in**	**Run-in**	**Randomization**							**End of treatment**	**PSW**	**Treatment discontinuation (TD)**	**Study completion**
Week	**-5 to -4**	**-4**	**1**	**1**	**2**	**4**	**8**	**12**	**20**	**26**	**26**			**30**
Day	**-35 to-29**	**-28**	**1**	**1**	**15**	**29**	**57**	**85**	**141**	**181**	**182**			**212**
Obtain informed consent	x													
Demographics	x													
Inclusion/exclusion criteria	x	x	x											
Relevant medical history	x													
Disposition: Screening	x													
Run-in		x	x*											
Treatment											x	x		
Follow-up														x
COPD exacerbation history	x													
History of CV risk factors	x													
History of pulmonary diseases	x													
Smoking history	x													
Smoking status				x						x		x	x	

[redacted]

Epoch	Screening	Run-in		Treatment										Follow-up (by phone)
Visit number	**1**	**101**	**102**	**201**	**202**	**203**	**204**	**205**	**206**	**207**	**208**	**299**	**-**	**301**
Visit	**Screening**	**Baseline run-in**	**Run-in**	**Randomization**							**End of treatment**	**PSW**	**Treatment discontinuation (TD)**	**Study completion**
Week	**-5 to -4**	**-4**	**1**	**1**	**2**	**4**	**8**	**12**	**20**	**26**	**26**			**30**
Day	**-35 to-29**	**-28**	**1**	**1**	**15**	**29**	**57**	**85**	**141**	**181**	**182**			**212**
Pregnancy test (urine)		s								s			s	
Record medical resource use	x	x		x	x	x	x	x	x	x			x	
Physical examination		s						s		s			s	
ECG[1,2]		x	x	x				x		x			x	
Vital signs (Systolic and diastolic BP and radial pulse)[2]		x	x	x		x		x		x			x	
Record height (visit 101 only) and weight		x								x			x	
Prior and current concomitant medication review/adjustment	x	x	x	x	x	x	x	x	x	x	x		x	
Tiotropium (18 µg o.d.) + salmeterol/fluticasone propionate FDC (50/500 µg b.i.d.) run-in		x												
Review surgery and procedures	x	x	x	x	x	x	x	x	x	x	x		x	
Spirometry (centralized)[2] (Reversibility)		x		x		x		x		x	x		x	

[redacted]

Epoch	Screening	Run-in		Treatment										Follow-up (by phone)
Visit number	**1**	**101**	**102**	**201**	**202**	**203**	**204**	**205**	**206**	**207**	**208**	**299**	**-**	**301**
Visit	**Screening**	**Baseline run-in**	**Run-in**	**Randomization**							**End of treatment**	**PSW**	**Treatment discontinuation (TD)**	**Study completion**
Week	**-5 to -4**	**-4**	**1**	**1**	**2**	**4**	**8**	**12**	**20**	**26**	**26**			**30**
Day	**-35 to-29**	**-28**	**1**	**1**	**15**	**29**	**57**	**85**	**141**	**181**	**182**			**212**
Contact IRT (IWRS)	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Urinalysis (dipstick)[2]		x	x					x		x			x	
Hematology[2]/ Biochemistry[2]		x		x		x		x		x			x	
Oropharyngeal examination[3]		s		s	s	s	s	s	s	s			s	
24 h urine collection (cortisol measurement)[4]				x				x		x			x	
mMRC[5]		x								x				
CAT[5]			x			x		x		x		x	x	
SGRQ-C[5]			x					x		x			x	
BDI/TDI[5]			x					x		x			x	
Inhalation device training		S		S										
AE recording[6]	x	x	x	x	x	x	x	x	x	x	x	x	x	x
SAE recording[6]	x	x	x	x	x	x	x	x	x	x	x	x	x	x

[redacted]

Epoch	Screening	Run-in		Treatment										Follow-up (by phone)
Visit number	**1**	**101**	**102**	**201**	**202**	**203**	**204**	**205**	**206**	**207**	**208**	**299**	**-**	**301**
Visit	**Screening**	**Baseline run-in**	**Run-in**	**Randomization**							**End of treatment**	**PSW**	**Treatment discontinuation (TD)**	**Study completion**
Week	**-5 to -4**	**-4**	**1**	**1**	**2**	**4**	**8**	**12**	**20**	**26**	**26**			**30**
Day	**-35 to-29**	**-28**	**1**	**1**	**15**	**29**	**57**	**85**	**141**	**181**	**182**			**212**
Hospitalization due to COPD occurrence recording	x	x	x	x	x	x	x	x	x	x	x	x	x	
COPD exacerbation recording		x	x	x	x	x	x	x	x	x	x	x	x	
Dispense rescue medication/review use	x	x	x	x	x	x	x	x	x	x			X[7]	
Issue/train on eDiary		S		S										
Review/upload eDiary			x		x	x	x	x	x	x	x	x	x	
Administer study treatment at visit				x	x	x	x	x	x	x				
Dispense study treatment (IRT)				S		S	S	S	S					
Record study treatment compliance					x	x	x	x	x	x			x	
Telephone contact with patient[8,9]		x[8]	x[8]				x[9]	x[9]	x[9]	x[9]				
Survival follow-up[10]														x

TD = Study treatment discontinuation (unscheduled visit) PSW = Premature study withdrawal
S = these assessments are source documentation only and will not be entered into the eCRF

[redacted]

*for patients not eligible to continue run-in after Visit 101

[1]. ECG measurements: At Visit 101, a single ECG will be performed 5 to15 min prior to spirometry

[2]. See Table 6-2 for details of timed assessments from Visit 201. Reversibility will be performed at Visit 101 only

[3]. Oropharyngeal examinations will be conducted at Visit 101 and all subsequent visits until the end of the study. If a fungal infection of the mouth or throat is suspected by either symptoms or direct examination, a culture should be taken and sent to the central lab for testing to confirm diagnosis. The patient should be followed and treated appropriately until resolution. The patient may continue in the study at the discretion of the investigator and the sponsor

[4]. Urine cortisol and urine creatinine will be performed in sub-set of patients only

[5]. mMRC, CAT, SGRQ-C, and BDI/TDI should be done before any other assessments, BDI only at Baseline

[6]. Any reported cases of pneumonia should be confirmed with chest X-ray. AE reporting starts from signing of informed consent. If a COPD exacerbation occurs during the pre-screening/ screening period, the patient will not be eligible but will be permitted to be re-screened after a minimum of 6 weeks after the resolution of the COPD exacerbation

[7]. Dispensation of rescue medication at visit TD is optional

[8]. Site to call patient prior to V101 and V102 to remind them to stop taking rescue medication 6h (SABA) and 8h (SAMA) prior to visits

[9]. Patients will be contacted by telephone approximately 2 weeks prior to Visit 204, 205, and approximately 3 weeks prior to Visit 206 and 207 to check if patient's COPD symptoms have worsened, any treatment required and e-diary completed accordingly

In case of a COPD exacerbation, the patient should be encouraged by the site to contact it for an advice. If necessary an unscheduled visit to the site may be organized.

[10]. Information about a patient's survival will be obtained by a telephone call 30 days after the patient's last dose of study treatment or last visit/observation for patients who discontinue.

[11]. [redacted]

6.2 Timed assessments

From Visit 201 (Randomization, Day 1) onward, patients will be assessed both pre- and post-dose at the times specified in Table 6-2.

For visits that include mMRC, CAT, SGRQ-C and BDI/TDI, the patient must arrive early enough to ensure there is adequate time to complete these questionnaires before other assessments and adhere to scheduled times.

The questionnaires have to be completed in the following order: SGRQ-C, mMRC, CAT, and BDI/TDI. Spirometry measurements must always occur at the scheduled time point (see Table 6-2 for Timed Assessments).

Whenever other assessments are scheduled at the same time-point, spirometry must take precedence such that it occurs at the scheduled time point or as near as possible. If necessary other assessments (excluding SGRQ-C, mMRC, CAT, BDI/TDI) can be performed after spirometry. Bloods must always be drawn after ECG measurement.

[redacted]

Table 6-2 Timed assessments

	Time point[1]	Urinalysis	ECG	Vital signs[2]	Hematology/Blood chemistry/ Biomarker	Spirometry[3]
	Ensure SGRQ-C, mMRC, CAT and BDI/TDI are completed before other assessments start					
Visit 201	>-45 min	X*	X*	X*		
	-45 min					X
	-45 to -20 min				X	
	-15 min					X
	0 min	Study treatment administered in clinic				
	30 min					X
	1 h		X	X		X
Visit 203	-45 min			X		X
	-45 to -20 min				X	
	-15 min					X
	0	Study treatment administered in clinic				
	30 min					X
	1 h			X		X
Visit 205	>-45 min	X	X	X		
	-45 min					X
	-45 to -20 min				X	
	-15 min					X
	0 min	Study treatment administered in clinic				
	30 min					X
	1 h		X	X		X
Visit 207(or TD)	>-45 min	X	X	X		
	-45 min					X
	-45 to -20 min				X	
	-15 min					X
	0 min	Study treatment administered in clinic				
	30 min					X
	1h		X	X		X
Visit 208	23h 15 min					X
	23 h 45 min					X

* Assessments are completed as part of Visit 102 (End of run-in, Day 1).

[1] Time relates to the dose given from device at visit unless otherwise specified

[2] Systolic and diastolic blood pressure and heart rate

[3] A minimum 3 min rest period from the beginning of ECG assessments to the start of spirometry maneuvers must be observed at all times

[redacted]

6.3 Information to be collected on screening failures

All patients who have signed informed consent but not entered into the next epoch will have the study completion page for the screening epoch, demographics, inclusion/exclusion, and serious adverse event (SAE) data collected up until the point that the patient is considered to have failed screening. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

For all patients who have signed informed consent and are entered into the run-in epoch of the study will have all adverse events **occurring after informed consent is signed** recorded on the Adverse Event CRF.

Investigators will 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.

6.4 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all patients include:

- Date of birth
- Age (calculated)
- Sex
- Race and ethnicity
- Patient initials (where allowed by local legislation)
- Height
- Weight
- Date of diagnosis of COPD
- Relevant medical history / current medical condition present before signing informed consent
- Smoking history
- Smoking status
- Health Status
- Prior concomitant medications (both COPD related and non-COPD related). Prior concomitant medications are those prior to Visit 1
- Pre- and post-bronchodilator spirometry (baseline spirometry):
  - At Visit 101, FEV_1 and FVC pre and post bronchodilator inhalation (see Spirometry guidance in Appendix 2)
  - At Visit 201 FEV_1 and FVC pre and post inhalation of investigational drugs
- Physical examination (not databased other than in the context of relevant medical history)
- Laboratory results
- Vital signs
- ECG

[redacted]

6.5 Treatment exposure and compliance

The time of study treatment administration at each in-office dosing visit will be collected on the eCRF as well as any dosing interruptions. For assessments where spirometry is performed, the time of dosing is to be taken from the spirometer.

Study treatment compliance should be assessed by the investigator and/or designee at all visits. The Investigator or designee will collect, from the patient, the used / unused investigational medication and packaging (morning and evening capsules / blister strips and inhalation devices) at all dispensing visits. Study treatment compliance will be assessed from the capsule count (unused medication) and empty blister strips (used medication) and from information provided by the patient and/or caregiver. This information will be captured in the source documentation. The total number of doses of investigational treatment administered since the last dispensing visit will be captured in the source documentation, and the start and end date of study treatment and any missed doses will be recorded on the eCRF.

The number of puffs of rescue medication inhaled will be recorded twice daily by the patient in the eDiary. The patient will be instructed accordingly at Visit 101 when he/she is provided with the eDiary and the use of rescue medication is discussed. The use of rescue medication will be reviewed at each visit and data from the eDiary downloaded at each visit. Where necessary, the Investigator will discuss compliance/document issues regarding rescue medication use with the patient.

6.6 Efficacy

- Pulmonary function (Spirometry)
- COPD exacerbations
- Rescue medication usage
- Modified Medical Research Council (mMRC) Dyspnea Scale
- COPD Assessment Test (CAT)
- St. George Respiratory Questionnaire C (SGRQ-C)
- BDI/TDI
- eDiary

6.6.1 Spirometry

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

6.6.2 COPD exacerbations

COPD exacerbation is defined as:

A worsening of the following two or more major symptoms for at least 2 consecutive days:

- dyspnea
- sputum volume
- sputum purulence

OR

[redacted]

A worsening of any of the above symptoms together with an increase in any one of the following minor symptoms for at least 2 consecutive days:

- sore throat
- colds (nasal discharge and/or nasal congestion)
- fever without other cause
- cough
- wheeze

All COPD exacerbations should be recorded on the COPD exacerbation eCRF page only.

For the purposes of this study, the type of treatment provided for a COPD exacerbation will determine the severity of the exacerbation and how that severity should be recorded on the COPD exacerbation eCRF page:

- A worsening of symptoms that meets the above symptom definition that is not treated with systemic corticosteroids and/or antibiotics will be considered a **mild** COPD exacerbation
- A COPD exacerbation is considered of **moderate** severity if treatment with systemic corticosteroids or antibiotics or both was required
- A **severe** COPD exacerbation requires hospitalization in addition to treatment with systemic corticosteroids and/or antibiotics. An emergency room (ER) visit of longer than 24 hours will be considered a hospitalization. A COPD exacerbation that required an emergency room visit for less than 24 hours will be considered to be of moderate severity, providing the exacerbation was treated with systemic corticosteroids or antibiotics or both

The criteria for a protocol defined exacerbation are based on a worsening of symptoms occurring after randomization as compared to the baseline threshold established during the run-in period. The baseline threshold is determined by patient recording of daily symptom using an electronic diary device supplied at the start of the study.

In the event of a COPD exacerbation matching the above definition occurring at any time after signing of informed consent, patients should be treated for the exacerbation as deemed necessary by the investigator.

A worsening of symptoms that either do not meet the above symptom definition but is treated by the investigator with systemic corticosteroids or antibiotics, or that meets the symptom definition but does not receive antibiotics and/or systemic corticosteroids, is not considered a moderate or severe COPD exacerbation for the study. However, these events should be captured on the COPD exacerbation eCRF as mild exacerbations.

The start date for a COPD exacerbation recorded in the eCRF should be the first day of symptom worsening of two or more major symptoms or of one major and one minor symptom, as defined above. The end of a COPD exacerbation episode is marked by the return to pre-exacerbation symptom status. At the end of an exacerbation the patient must attend the clinic, where possible, for assessment of the episode. Mild COPD exacerbations can be followed-up via a telephone call with the patient.

[redacted]

Patients who develop a COPD exacerbation between screening and prior to treatment will be discontinued but will be permitted to be re-enrolled after a minimum of 6 weeks and after the resolution of the COPD exacerbation (see exclusion criteria).

If systemic corticosteroids are taken for a COPD exacerbation within 7 days prior to any study visit, the visit must be rescheduled to allow a washout of 7 days (Patient should be discontinued if treated with Depo-Medrone® as discussed in Section 5.5.7). Scheduled spirometry should not be performed during an exacerbation until it has completely resolved. Following treatment for the exacerbation, the patient will be expected to continue in the study provided the investigator considers that the patient can safely return to their pre-exacerbation medications. No spirometry assessments should be taken until after the exacerbation has resolved.

6.6.3 Rescue medication usage

Use of rescue medication (number of puffs taken in the previous 12 hours) will be recorded morning and evening, by the patient, in the eDiary. The number of puffs taken in between and during the clinic visit will be captured in the eDiary. For more information please refer to Section 5.5.6.

6.6.4 Modified Medical Research Council (mMRC) Dyspnea Scale

The modified Medical Research Council (mMRC) Dyspnea Scale (Fletcher et.al. 1959), is a five-item instrument (part of the Borg scale) to assess a patient's degree of breathlessness in relation to physical activity (Mahler and Wells 1988). Participants will be required to read a brief description of an activity and then select a statement that best describes their experience with dyspnea at Visit 101.

The mMRC will be used to compare the severity of dyspnea throughout the study. Please see Appendix 8 for the scale.

6.6.5 COPD Assessment Test (CAT)

The COPD assessment test (CAT) is a short instrument used to quantify the symptom burden of COPD and will be used to assess the health status of patients in this study (Jones et al 2009). It is completed by the patient at the beginning of the study visit just after the SGRQ-C and mMRC but before any other assessment to avoid influencing the responses.

The CAT is completed by the patient at the investigator's site at Visits as per assessment Table 6-1 or at the time of discontinuation for patients who prematurely withdraw from the study.

The CAT consists of eight items. Each item is presented as a semantic 6-point differential scale, providing a total score out of 40. A higher score indicates a worse health status. The result is immediately available without the need for any calculation, apart from summing the scores on individual items.

Scores of 0 - 10, 11 - 20, 21 - 30 and 31 - 40 represent a mild, moderate, severe or very severe clinical impact of COPD upon the patient.

An example of the COPD Assessment Test (CAT) is provided in Appendix 7.

[redacted]

6.6.6 St. George Respiratory Questionnaire C (SGRQ-C)

The St. George Respiratory Questionnaire C (SGRQ-C) will be used to provide the health status measurements in this study (Jones et al 1992). The SGRQ-C (refer to Appendix 6) will be self-administered by the patient at the investigator's site at Visits as per assessment Table 6-1 or at the time of discontinuation for patients who prematurely discontinue from study treatment (TD Unscheduled Visit).

The SGRQ-C questionnaire should always be completed before any other assessments are made to avoid influencing the responses. A detailed guide relating to the administrative procedures of the questionnaires are given in Appendix 5.

The appropriate language version of the questionnaires will be used in each participating country. The same language should be used by a particular patient throughout the study. The study person administering the questionnaire should be familiar with the measures and the associated user guides and training materials provided.

The patient should complete the questionnaires in a quiet area and be allowed to ask questions; however site staff should take care not to influence the patient's responses. The patient will be instructed to provide the truest and best response for them. Patients should date but not initial the questionnaire. The questionnaire will be checked for completeness and collected before the patient leaves the site.

Missing data should be avoided; therefore the study coordinator will check the questionnaires for completeness before the patient leaves the site, and if necessary, encourage the patient to complete any missing responses. At later visits patients are not allowed to review their previous responses. The original questionnaire will be kept with the patient's file as the source document.

Instrument scoring and handling of missing item data will be conducted in accordance with the user guide for the SGRQ-C (Appendix 5). Responses will be collected on digital paper to allow the use of a digital pen (Only the original digital paper provided can be used for the digital pens (i.e., these pages must not be photocopied). The collection of this data will be centralized and additional information will be supplied.

The SGRQ-C contains 40 items divided into two parts covering three aspects of health related to COPD:

- Part I covers "Symptoms" and is concerned with respiratory symptoms, their frequency and severity;
- Part II covers "Activity" and is concerned with activities that cause or are limited by breathlessness;
- Part II is also concerned with "Impacts", which covers a range of aspects concerned with social functioning and psychological disturbances resulting from airways disease.

A score will be calculated for each of these three subscales and a "Total" score will also be calculated. In each case the lowest possible value is zero and the highest 100. Higher values correspond to greater impairment of health status.

Completed questionnaires will be reviewed and examined by the investigator, before the clinical examination, for responses which may indicate potential AEs or SAEs. The investigator should review not only the responses to the questions in the questionnaire but also

[redacted]

for any unsolicited comments written by the patient. Investigators should not encourage the patients to change the responses reported in the questionnaire.

If AEs or SAEs are confirmed then the physician must record the events as per instructions given in Section 7.1 and Section 7.2 of the protocol.

6.6.7 BDI/TDI

Patients must be interviewed by a trained assessor who will grade the degree of impairment due to dyspnea at Visit 102 (Baseline Dyspnea Index, BDI). The Transitional Dyspnea Index (TDI) will be assessed at Visits as per Assessment Table 6-1 and at the time of discontinuation for patients who prematurely discontinue from study treatment (TD Unscheduled Visit). These assessments must be undertaken after completing the SGRQ and prior to the spirometry and study treatment administration.

Preferably, the same assessor should complete all the BDI/TDI assessments for an individual patient and they should be blinded to other study assessments for this patient.

Details of the BDI and TDI (Mahler and Wells 1988) are provided in Appendix 9.

6.6.8 eDiary

At Visit 101 all eligible patients will be provided with a patient electronic diary (referred to as an eDiary). The patients will be instructed to routinely complete the patient Diary twice daily at the same time morning and evening (approximately 12 hours later).

The eDiary will facilitate the identification of symptoms that meet the definition of a COPD exacerbation, as described in Section 6.6.2, so it's very important that it's completed twice daily.

Each morning and evening, before taking study treatment, the patient records

- Daily clinical symptoms: cough, wheezing, shortness of breath, sputum volume and sputum color, night time awakening, fever, sore throat and cold
- Number of puffs of rescue medication (number of puffs taken in the previous 12 hours, see Section 5.5.6)

Morning and evening time of dose for study medication taken in between clinic visits (Time of dose at the clinic will not be captured in the diary as this is recorded on the eCRF.

Details of the information to be collected in the Patient eDiary are provided in Appendix 3.

Sites and patients will receive appropriate training and guidance on the use of the electronic diary device.

At each visit from Visit 102 onwards, site personnel must review the patient diary data with the patient.

Please see Section 6.6.2 for the COPD exacerbation definition.

6.6.9 Appropriateness of efficacy assessments

The efficacy assessments (COPD exacerbations, FEV_1, FVC, rescue medication usage, health related quality of life as assessed by SGRQ-C, patient symptoms as assessed by mMRC, CAT

[redacted]

and BDI/TDI,) planned for this study are the standard efficacy assessments in COPD clinical trials.

6.7 Safety

- Adverse events
- Physical examination
- Urine pregnancy test (females of childbearing potential)
- ECG
- Vital signs
- Pneumonia
- 24 hr urinary cortisol (in a sub-set of patients)
- Oropharyngeal sample culture for candidiasis .
- Laboratory: standard biochemistry, hematology and urinalysis

6.7.1 Physical examination

A complete physical examination will be performed as per Assessment Table 6-1or at study treatment discontinuation visit (TD). 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 will be 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.

6.7.2 Vital signs

Type Vital signs will include radial pulse rate (measured for 60 seconds) and systolic and diastolic blood pressure. Pulse rate and blood pressure will be assessed after the patient has rested in the sitting or supine position for at least 5 minutes. If an automated Blood Pressure device is used, it will need to be calibrated according to the manufacturer's guidelines.

The Investigator needs to monitor the pulse rate for any irregular beats and investigate further using ECG. Vital signs will be obtained at the Visits as per Assessment Table 6-1.

6.7.3 Pneumonia

Pneumonia will be defined as an event characterized by increased respiratory symptoms (e.g. increased cough, dyspnea, wheezing, purulent sputum and fever) (i.e. body temperature greater than 38 °C) or pleuritic chest pain or leukocytosis or other clinical signs consistent with pneumonia considered relevant in the opinion of the investigator. Radiographic imaging (chest x-ray or CT scan), will be required to confirm the diagnosis. The diagnosis of COPD exacerbation will not preclude a diagnosis of pneumonia. The investigator will use clinical judgment to determine if the events are occurring simultaneously.

[redacted]

6.7.4 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 at Visit 101. Weight will be recorded again as per Assessment Table 6-1 or at time of study treatment discontinuation.

6.7.5 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

Please refer to Table 6-1, for assessment schedule of laboratory evaluations and Table 6-2 for timing of those assessments. All patients with laboratory tests containing clinically significant abnormalities should be followed regularly until the values return to within the normal ranges or until a valid reason other than drug-related adverse experiences is identified, even after the medication has discontinued.

Clinically notable laboratory findings are defined in Appendix 1.

6.7.5.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count will be measured per Assessment Table 6-1 and Timed assessments Table 6-2.

6.7.5.2 Clinical chemistry

Albumin, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphate, total bilirubin, blood urea nitrogen (BUN), C-reactive protein (CRP), total cholesterol, LDL-C, HDL-C, lactate dehydrogenase (LDH), calcium, fibrinogen, magnesium, phosphate, sodium, potassium, creatinine, γ-GT, blood glucose, HbA1C, total protein will be measured per Assessment Table 6-1 and Timed assessments Table 6-2. If the total bilirubin concentration is increased above 1.5 times the upper limit of normal range, total bilirubin should be differentiated into the direct and indirect reacting bilirubin.

6.7.5.3 Urinalysis

Urine samples will be taken as per Assessment Schedule Table 6-1.Testing will include: specific gravity, pH, protein and blood (via urine dipstick test). Any abnormalities will require further analysis by the central lab, which will include microscopic examination including, leukocytes, hemoglobin (WBC/HPF, RBC/HPF,), and casts/HPF. If casts are noted, the type is to be specified. All patients with laboratory tests containing clinically significant abnormal values will be followed regularly until the values return to normal ranges or until a valid reason, other than drug-related adverse event, is identified. 24 hr Urine cortisol will be measured in a sub-set of approximately 380 patients. These patients will be randomly selected in a ratio of 1:1. The urine creatinine would also be measured to calculate cortisol/creatinine ratio. The Central Laboratory will supply procedures for the preparation and collection of these samples.

[redacted]

6.7.5.4 Oropharyngeal sample culture for candidiasis

Oropharyngeal swab sample culture for candidiasis will be performed per Assessment Schedule Table 6-1. Refer to Central Laboratory manual for further details.

6.7.6 Electrocardiogram (ECG)

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, blood sampling, urinalanysis, spirometry and symptom assessments. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

Clinically significant abnormalities should be recorded on the relevant section of the medical history/Current medical conditions/AE CRF / e(CRF) page as appropriate.
ECGs should be free of baseline wander and noise. Prior to an ECG being performed, the ECG operator should check the tracing to ensure that it is of high quality.

Centralized ECG Equipment

At Visit 101 a run-in baseline ECG will be measured to test for eligibility for trial inclusion. Patients whose ECG is abnormal at run-in baseline due to technical/mechanical faults may be rescreened.
Patients with persistent atrial fibrillation as defined by continuous atrial fibrillation for at least 6 months and controlled with a rate control strategy for at least 6 months may be considered for inclusion. In such patients, atrial fibrillation must be present at Visit 101 (confirmed by central reader) and Visit 102 (confirmed by local reader) with a resting ventricular rate < 100/min (if the interpretation of atrial fibrillation is not confirmed by central reader at Visit 102 the site must inform Novartis). ECGs will be performed pre and post dose per Assessment Schedule Table 6-1 and Timed assessments Table 6-2. All electrocardiograms should include 12 standard leads. An ECG tracing will also be taken for those patients who prematurely discontinue from the study.

For each ECG performed original traces and identical duplicate print-outs will be produced. The original trace will be sent electronically for central review directly from the ECG machine. Two ‘identical’ duplicate print-outs will be generated and kept at the investigator site as source documentation and as back-up for submission to the central reader in case of problems with the electronic transmission. The ‘identical’ duplicates kept at the investigator site will be dated and signed. The patient's number, the date, actual time of the tracing, and Study Code must appear on each page of the tracing.

ECGs must be performed only after patients have been resting in the supine position for at least 5 minutes. When the ECG recording time coincides with vital signs, spirometry, and blood draws, the ECG must be performed first, followed by vital signs and the blood draws but with enough time planned to ensure the spirometry is performed at the planned time point outlined in Table 6-2. Spirometry must be performed as close to the scheduled time point as possible.

Full details of all procedures relating to the ECG collection and reporting will be contained in an investigator manual to be provided to each investigator site.

[redacted]

In the event that the central cardiologist reports that an ECG is abnormal, then the investigator must comment as to whether the ECG abnormality is either clinically significant or clinically insignificant. A clinically significant abnormality should be reported as an AE. If necessary a cardiologist may be consulted.

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

6.7.7 Pregnancy and assessments of fertility

A urine pregnancy test will be performed in pre-menopausal women who are not surgically sterile (tests provided by the Central Laboratory) per Assessment Table 6-1. A positive pregnancy test at Visit 101 or at any time during the study requires the patient to be discontinued from the study treatment. Refer to Section 5.5.9 and Section 7.4 for more details.

6.7.8 Appropriateness of safety measurements

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

6.8 Other assessments

6.8.1 Resource utilization

At Visit 101 health care resource utilization including number of COPD-related hospitalizations, emergency room (ER) and outpatient visits in the previous year will be recorded as completely as possible.

At each subsequent scheduled visit the level of COPD-related health care resource utilization including number and length of hospitalization, numbers of ER and unscheduled doctor's office visits since the previous scheduled visit will be recorded. The frequency and duration of any inpatient hospitalization will be recorded along with the primary reason for the hospitalization.

For each hospitalization the duration spent in each of the following will be recorded: intensive care unit (ICU), general ward, Emergency Room (ER), other.

Hospitalizations will be defined as any visit to the hospital requiring an overnight stay. The frequency of outpatient visits will be recorded along with the type of physician the patient saw and the type of visit. An unscheduled doctor's office visit will be defined as any rescheduled visit to a medical practitioner not requiring an overnight stay. In addition any procedures conducted during the hospitalization or unscheduled doctor's office visit will be recorded in the eCRF. If adverse events or SAEs are confirmed then the physician must record the events as per instructions given in Section 7 of the protocol.

6.8.2 Health-related Quality of Life

See section 6.6.

6.8.3 Pharmacokinetics

Not applicable

[redacted]

6.8.4 Pharmacogenetics

Not applicable

6.8.5 Biomarkers

Several biomarkers have been identified in the literature (Agusti and Sin 2014) as being important in COPD to predict either risk of COPD exacerbations, disease progression or death. In this protocol serum WBC count, serum CRP, and fibrinogen will be measured as part of the standard laboratory measurements per Assessment Table 6.1.

7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation patient *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 patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments.

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

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

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

All protocol defined COPD exacerbations (as defined in section 6.6.2) should be recorded on the COPD exacerbation eCRF page only. All other COPD exacerbations that do not meet the definition in section 6.6.2 are to be recorded in the AE eCRF page only.

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

- the severity grade
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities

[redacted]

- its relationship to the study treatment (no/yes), or indistinguishable
- its duration (start and end dates) or if the event is ongoing; an outcome of not recovered/not resolved should be reported.
- whether it constitutes a serious adverse event (SAE - See Section 7.2 for definition of SAE)
- action taken regarding study treatment

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
- patient hospitalized/patient's hospitalization prolonged
- 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 treatment, the interventions required to treat it, and the outcome.

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

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

7.2 Serious adverse events

7.2.1 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:

[redacted]

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

- is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

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

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

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious events, 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.

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

All AEs (serious and non-serious) are captured on the CRF. SAEs also require individual reporting to DS&E as per section 7.2.2.

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient 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. Any SAEs experienced after the 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

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

Information about all SAEs (*either initial or follow up information)* is collected and recorded on the paper Serious Adverse Event Report Form. The investigator must assess the relationship to *each specific component of study treatment (if study treatment consists of several drugs)* complete the SAE Report Form in English, and send the completed, signed

[redacted]

form by fax within 24 hours after awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department. The telephone and fax number of the contact persons in the local department of Drug Safety and Epidemiology, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site. Follow-up information should be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE

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

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the investigational treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same investigational treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

7.3 Pneumonia

Pneumonia will be defined as an event characterized by increased respiratory symptoms (e.g. increased cough, dyspnea, wheezing, purulent sputum and fever) (i.e. body temperature greater than 38 °C) or pleuritic chest pain or leukocytosis or other clinical signs consistent with pneumonia considered relevant in the opinion of the investigator. Radiographic imaging (chest x-ray or CT scan), will be required to confirm the diagnosis. The diagnosis of COPD exacerbation will not preclude a diagnosis of pneumonia. The investigator will use clinical judgment to determine if the events are occurring simultaneously.

7.4 Liver safety monitoring

To ensure patient safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following two categories of abnormalities / adverse events have to be considered during the course of the study:

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and completion of the standard base liver CRF pages

Please refer to Table 13-1 in Appendix 1 for complete definitions of liver laboratory triggers and liver events.

[redacted]

Every liver laboratory trigger or liver event as defined in Table 13-1 of Appendix 1 should be followed up by the investigator or designated personal at the trial site as summarized below. Detailed information is outlined in Table 13-2 in Appendix 1.

For the liver laboratory trigger:

- Repeating the LFT within the next week to confirm elevation.

These LFT repeats should be performed using the central laboratory if possible. If this is not possible, then the repeats can be performed at a local laboratory to monitor the safety of the patient. Repeats laboratory should then be performed at central laboratory as soon as possible. If a liver event is subsequently reported, any local LFTs previously conducted that are associated with this event should be reported on the Liver CRF pages.

- If the elevation is confirmed, close observation of the patient will be initiated, including consideration of treatment interruption if deemed appropriate.

For the liver events:

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug if appropriate
- Hospitalization of the patient if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g., disease, co-medications)
- An investigation of the liver event which needs to be followed until resolution

These investigations can include serology tests, imaging and pathology assessments, hepatologist's consultancy, based on investigator's discretion. All follow-up information, and the procedures performed should be recorded on appropriate CRF pages, including the liver event overview CRF pages.

7.5 Renal safety monitoring

To ensure patient safety and enhance reliability in determining the nephrotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of renal events has to be followed.

The following two categories of renal adverse events have to be considered during the course of the study:

1. Serum event:
   - confirmed (after ≥ 24h) increase in serum creatinine of ≥ 25% compared to baseline during normal hydration status
2. Urine event New onset (≥1+) proteinuria, hematuria or glucosuria; or
   - Doubling in the urinary albumin-creatinine ratio (ACR) or urinary protein-creatinine ratio (PCR) (if applicable).

Every renal laboratory trigger or renal event as defined in Table 7-1 should be followed up by the investigator or designated personnel at the trial site as summarized below.

[redacted]

Table 7-1 Specific Renal Alert Criteria and Actions

Serum Event	
Serum creatinine increase 25 – 49% compared to baseline	Confirm 25% increase after 24-48h Follow up within 2-5 days
Acute Kidney Injury: Serum creatinine increase ≥ 50 % compared to baseline	Follow up within 24-48h if possible Consider drug interruption Consider patient hospitalization /specialized treatment
Urine Event	
New dipstick proteinuria ≥ 1+ Albumin- or Protein-creatinine ratio increase ≥ 2-fold Albumin-creatinine ratio (ACR) ≥ 30 mg/g or ≥ 3 mg/mmol; Protein-creatinine ratio (PCR)≥ 150 mg/g or >15 mg/mmol	Confirm value after 24-48h Perform urine microscopy Consider drug interruption / discontinuation
New dipstick glucosuria ≥ 1+ not due to diabetes	Blood glucose (fasting) Perform serum creatinine, ACR
New dipstick hematuria ≥ 1+ not due to trauma	Urine sediment microscopy Perform serum creatinine, ACR
For all renal events:	
Document contributing factors in the CRF: co-medication, other co-morbid conditions, and additional diagnostic procedures performed Monitor patient regularly (frequency at investigator's discretion) until either: Event resolution: sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline, or Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months	

7.6 Pregnancy reporting

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

Pregnancy should be recorded on the 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 study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

[redacted]

8 Data review and database management

8.1 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 field monitor will visit the site to check the completeness of patient records, the accuracy of entries on the (e)CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

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

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary 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 patients will be disclosed to the sponsor.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the OC/RDC system. Designated investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. 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 copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

Novartis staff *[and/or CRO working on behalf of Novartis]* review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to

[redacted]

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 that will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

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

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

Diary data will be entered into an electronic diary by the patient. The system will be supplied by a vendor(s), who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

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

Randomization codes and data about all study treatment(s) dispensed to the patient and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis.

8.4 Data Monitoring Committee

Not required.

8.5 Adjudication Committee

Two independent external adjudication committees will be established for this study. The committees will consist of experts outside of Novartis who are not involved in the study conduct.

A mortality adjudication committee will assess the cause of death occurring from first treatment until 30 days after completion of 26 week study treatment epoch. The Committee will consist of external experts (outside of Novartis) who are not involved in the study

[redacted]

conduct. It will include a panel of at least 3 experts, e.g. a pulmonologist, a cardiologist and an oncologist/internist. Committee members will be blinded with respect to the patient's study medication. At regular intervals the Committee will review narratives, discharge summaries and medical records as available to determine the most likely cause of death, in particular cardiovascular and respiratory related deaths.

A cardio- and cerebro-vascular (CCV) external adjudication committee will consist of external experts (outside of Novartis) who will review at regular intervals the program wide selected CCV events to ensure that the events are correctly classified. All the details of the adjudication process including the committee members will be included in the adjudication committee charter. Each adjudication committee will have its own charter and all details of the adjudication process will be included in the relevant committee charters.

9 Data analysis

9.1 Analysis sets

The following analysis sets are defined for data analysis.

The Randomized Set (RAN), will consist of all patients who were assigned a randomization number, regardless they actually received study medication. It will be used for summaries of patient disposition and analysis sets, and listings of major protocol deviations and premature discontinuations. Patients in RAN will be analyzed according to the treatment they were randomized to.

The Full Analysis Set (FAS) will consist of all patients in the RAN who received at least one dose of study medication. Following the intent-to-treat principle, patients in the FAS will be analyzed according to the treatment they were assigned to at randomization. The FAS will be used to analyze all efficacy endpoints, unless otherwise stated.

The Per-Protocol set (PPS) will include all patients in the FAS without any major protocol deviations. Major protocol deviations will be defined in the data handling plan prior to database lock and the un-blinding of the study. Patients in the PPS will be analyzed according to the treatment group they were randomized to. Patients who receive another than their randomized treatment because of a dispensing error will be excluded from the PPS. The PPS will be used for supportive analysis to assess robustness of the primary analysis.

The Safety set will include all patients who received at least one dose of study medication whether they were randomized or not. Patients will be analyzed according to the treatment they received. If patients receive more than one treatment during the study, they will be analyzed according to the treatment they were randomized to. The safety set will be used in the analysis of all safety endpoints and in the listings of certain notable safety data.

9.2 Patient demographics and other baseline characteristics

Demographic and baseline characteristics measured before randomization will be summarized by treatment group.

[redacted]

Continuous variables will be summarized using descriptive statistics (mean, median, standard deviation, minimum, and maximum) and categorical variables will be summarized in terms of the number and percentage of patients in each category.

Baseline is defined as the last measurement before first dose of study treatment.

No statistical analyses will be provided for baseline comparability among the treatment groups.

9.3 Treatments

Study treatment administration and concomitant medication data will be listed and summarized using Safety set.

The duration of exposure and the number of patients randomized who completed the study and who discontinued from study medication will be summarized.

Medications started and stopped prior to study treatment, and taken concomitantly will be summarized by treatment group in separate tables in the Safety Set.

Concomitant therapies will be recorded, listed and summarized separately for COPD related medications / non-drug therapies and other medications.

SABA (short acting β2-agonist) usage (number of puffs) during the screening period will be summarized.

Patients taking prohibited concomitant medications will be noted in the summary of protocol deviations.

Treatment compliance with study medication over the study period will be summarized.

9.4 Analysis of the primary variable(s)

The primary objective is to demonstrate the non-inferiority of QVA149 (110/50 µg q.d.) compared to tiotropium (18 µg q.d.)+salmeterol/fluticasone FDC (50/500 µg b.i.d) in terms of trough FEV_1 after 26 weeks of treatment in patients with moderate to severe COPD.

9.4.1 Variable(s)

The primary variable is the mean change from baseline in post-dose trough FEV_1 after 26 weeks of treatment. Trough FEV_1 is defined as the mean of the two FEV_1 values measured at 23h15min and 23h45min after the morning dose taken at site on Day 181. Baseline FEV1 is defined the average of the pre-dose FEV1 measured at -45 min and -15 min at Day 1.

9.4.2 Statistical model, hypothesis, and method of analysis

The comparison between QVA149 (110/50 µg o.d.) and tiotropium (18 µg o.d.)+salmeterol/fluticasone propionate FDC (50/500 µg b.i.d.) in terms of trough FEV_1 at Day 182 will be evaluated by testing the following null hypothesis (H_0) versus the alternative hypothesis (H_a) at one-sided 2.5% significance level:

- H_0: mean trough FEV_1 at Day 182 (QVA149 (110/50 µg o.d)) is inferior to the mean change from baseline in trough FEV_1 at Day 182 (tiotropium (18 µg o.d.) + salmeterol/fluticasone propionate FDC (50/500 µg b.i.d.)

[redacted]

- H_a: mean trough FEV_1 at Day 182 (QVA149 (110/50 µg o.d.)) is non-inferior to the mean change from baseline in trough FEV_1 at Day 182 (tiotropium (18 µg o.d.) + salmeterol/fluticasone propionate FDC (50/500 µg b.i.d.)

The primary efficacy endpoint will be analyzed using a Mixed-Effect Model Repeated Measures (MMRM) model.

The model will include fixed, categorical effects of treatment and visit, country/region, and treatment-by-visit interaction as well as the continuous, fixed covariates of baseline and baseline-by-visit interaction. If additional covariates are considered to be required these will be predefined and included in the analysis plan finalized prior to database lock. The within-patient correlation will be modeled using an unstructured covariance matrix. Restricted maximum likelihood method will be used. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

If the analysis fails to converge, spatial covariance, compound symmetry, or first order autoregressive model (AR1) structure will be used. The best model fit will be determined by the Akaike's Information Criterion.

The between-treatment comparison will be carried out using the adjusted mean difference between treatments at Day 182.

Non-inferiority of QVA149 (110/50 µg o.d.) from tiotropium (18 µg o.d.) + salmeterol/fluticasone propionate FDC (50/500 µg b.i.d.) will be demonstrated if the confidence interval for the mean FEV_1 difference of QVA149 (110/50 µg o.d.) minus tiotropium (18 µg o.d.) + salmeterol/fluticasone propionate FDC (50/500 µg b.i.d.) lies entirely to the right of (higher than) –50 mL.

9.4.3 Handling of missing values/censoring/discontinuations

If any of the -45 min and -15 min values contributing to the trough FEV_1 are collected within 7 days of systemic corticosteroid use, 6 hr of rescue medication, or actual measurement times are outside the 22 - 25 hour post-morning dose time window then the individual FEV_1 value will be set to missing.

If one of the two values is missing (or set to missing) then the remaining non-missing value will be taken as trough FEV_1. If both values are missing, or if the patient withdrew from the study, regardless of the reason for discontinuation, then trough FEV_1 will be regarded as missing in which case the missing value(s) of the patient at the particular visit(s) would not directly contribute to the primary analysis.

All timed trough FEV_1 data i.e. day 29, day 85, day 181 and day 182, recorded post-baseline will be included in the primary MMRM model and no imputation will be applied to missing data. Instead of imputation, in the model the profile of each patient is used to adjust the estimates of the parameters when data are not available (i.e. the post-withdrawal statistical behavior of a patient who discontinued is assumed to be the same as for a patient who remained in the study and who shared the same measurement history and the same covariates, including treatment group).

[redacted]

9.4.4 Supportive analyses

The following supportive analyses for trough FEV_1 will be performed:

1. The same MMRM model used in the primary analysis will be also performed on the PPS.
2. To assess the robustness of the primary results in the presence of missing data the following analyses are planned:

- An analysis of covariance (ANCOVA) model (including treatment, country/region, and baseline FEV_1) will be used to analyze complete datasets created using multiple imputations under varying assumptions. For example, missing FEV_1 values after discontinuation for patients on QVA who discontinued for any reason will be imputed based on information from tiotropium + salmeterol/fluticasone propionate FDC patients only. This analysis assumes that QVA patients after discontinuation have a similar response to patients on triple therapy. Additionally further analyses will be performed with the poorest outcome assigned to patients with missing responses and then in which the most favourable response is assigned to all such patients.
- Trough FEV_1 at Week 26 with missing data imputed with Last Observation Carried Forward (LOCF) from Day 29 will be analysed using the ANCOVA model as described above.

If these analyses provide inferences consistent with the primary analysis method then the conclusions will not be considered highly sensitive to how missing data are handled.

3. All available trough FEV_1 data at Week 26 (including retrieved data from patients who prematurely discontinue treatment but who attend subsequent scheduled visits) will be analyzed using the ANCOVA model described in point 2. To note this retrieved data may be affected by off-study medications.
4. Exploratory subgroup analyses for trough FEV1 using MMRM will be performed (using the appropriate interaction term in the model and an additional covariate as a fixed effect if necessary) for the FAS population. Subgroups will be defined in the analysis plan prior to database lock.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

9.5.1.1 COPD exacerbations

In patients with multiple exacerbations, if the start date of an exacerbation was less than 7 days after the end date of a previous episode, then this will be assumed to be one continuous exacerbation with the start date taken from the first episode and the end date from the second or last episode. The worst severity of these episodes will be taken as the severity of the collapsed exacerbation.

Number of moderate or severe COPD exacerbations during the treatment period will be summarized by treatment groups, as continuous variables and as categorical variables classified into 0, 1, 2, 3, >=4 events.

The rate of moderate or severe COPD exacerbations during the treatment period will be analyzed using a generalized linear model assuming a negative binomial distribution. The

[redacted]

time at risk for a patient is the length of time exposed to study treatment. The analysis model will include terms for treatment, country/region, and COPD exacerbation history (the number of moderate or severe COPD exacerbations in the year prior to screening). If additional covariates are considered to be required these will be predefined and included in the analysis plan finalized prior to database lock. An estimate of the ratio of moderate or severe COPD exacerbation rates between the treatment groups, together with the 95% confidence interval, will be presented.

The above summary and analysis will be repeated for the rate of moderate or severe COPD exacerbations requiring

- systemic glucocorticosteroids and antibiotics during the treatment period (moderate exacerbations only)
- hospitalizations during the treatment period and rehospitalization within 30 days during the treatment period (severe exacerbations only).

9.5.1.2 Trough FEV_1 and FVC, SGRQ-C, TDI, Rescue therapy

Trough FEV_1 change from baseline over 26 weeks of treatment will be analyzed using the same MMRM model described for the primary endpoint. FVC change from baseline, SGRQ-C total score change from baseline, and TDI total score over 26 weeks of treatment will be also analyzed using a similar MMRM model with baseline FEV1 replaced by the corresponding baseline for the endpoint. Baseline SGRQ-C is the last non-missing value prior to the first dose of double-blind treatment.

The mean daily number of puffs and percentage of days without rescue medication usage will be calculated for each patient over 26 weeks. Rescue use during the run-in epoch will be used to calculate the baseline. The mean daily number of puffs will be analyzed using a linear mixed model with fixed categorical effects of treatment and country/region, and a fixed continuous covariate of baseline. If additional covariates are considered to be required these will be predefined and included in the analysis plan finalized prior to database lock. Percentage of days without rescue medication usage will be analyzed using a similar model.

9.5.2 Safety variables

Baseline will be the last non-missing value prior to first dose of double-blind treatment.

9.5.2.1 Adverse events

Adverse events starting on or after the time of the first inhalation of double-blind treatment but not later than 7 days (30 days in the case of a SAE) after the last administration will be classified as a treatment emergent adverse event. Any adverse events that started during the study before the time of the first inhalation of double-blind treatment will be classified as a prior adverse event.

The following treatment emergent adverse event summaries will be produced: overall by system organ class and preferred term; overall by system organ class, preferred term and maximum severity; suspected treatment-related adverse events by system organ class and preferred term; SAEs by system organ class and preferred term; and adverse events leading to permanent discontinuation of study-treatment by system organ class and preferred term.

[redacted]

9.5.2.2 Laboratory data

All laboratory data will be listed with abnormal values flagged. The laboratory values and the change from baseline for continuous laboratory parameters will be summarized. A frequency table of results for categorical laboratory parameters will be produced. Shift tables relative to the normal reference ranges will summarize the change from baseline to post baseline for each laboratory parameter.

Laboratory data measured more than 7 days after last inhalation of double-blind treatment is regarded as post-treatment data and will not be summarized, only listed.

9.5.2.3 ECG and vital signs

ECG data and vital signs (blood pressure, radial pulse and weight) will be summarized by treatment at each time point for each visit separately. The maximum (QTc, systolic blood pressure, pulse rate) or minimum (diastolic blood pressure) value post baseline will also be summarized. Changes from baseline will be summarized by treatment.

Notable QTc values and changes from baseline will be summarized. A notable value is defined as a QTc interval of greater than 450 ms for both sexes. The categories used for the change from baseline in QTc are less than 30 ms, 30 to 60 ms, and greater than 60 ms. Change from baseline > 30 ms will be considered as a notable change. The number of patients with newly occurring or worsening notable QTc values for post baseline time points will be summarized.

Data measured more than 7 days after last inhalation of double-blind treatment is regarded as post-treatment data and will not be summarized, only listed.

9.5.3 Resource utilization

Data relating to resource utilization will be used for the purpose of economic evaluation which will be carried out and reported as a separate activity.

9.5.4 Pharmacokinetics

Not applicable

9.5.5 Pharmacogenetics/pharmacogenomics

Pharmacogenetics

Not applicable

9.5.6 Biomarkers

As described in Section 6.8.5 several biomarkers have been identified to be predictive of COPD exacerbation, disease progression and death. The analysis of biomarkers is exploratory. The summary statistics of the biomarkers at baseline and each visit will be displayed. More details will be included in analysis plan.

9.5.7 PK/PD

Not applicable.

[redacted]

9.6 Interim analyses

Not applicable.

9.7 Sample size calculation

The primary objective is to demonstrate non-inferiority of QVA149 (110/50 µg o.d.) versus tiotropium (18 µg o.d.)+salmeterol/fluticasone propionate FDC (50/500 µg b.i.d.) with respect to post-dose trough FEV_1 after 26 weeks of treatment.

For trough FEV_1 it is assumed that the estimated treatment difference between QVA149 and tiotropium (18 µg o.d.)+salmeterol/fluticasone propionate FDC (50/500 µg b.i.d.) is 0 mL and the non-inferiority margin is assumed to be -50mL. This non-inferiority margin is based on the treatment difference between ICS and placebo summarized in two Cochrane reviews (Nannini et al 2007 and Yang et al 2012) and the TIOSPIR spirometry sub-study (Wise et al. 2013). The selected trials were designed and conducted in COPD patients.

Based on the data pooled from two trials (Nannini et al 2007) investigating salmeterol/fluticasone versus placebo in terms of trough FEV_1, the estimated treatment difference between salmeterol/fluticasone and placebo is 160 mL with a 95% confidence interval of 120 to 200 mL. Yang et al. provided summary data from 6 trials investigating ICS doses of greater than 1000 g BDP equivalent/day versus placebo in terms of pre-dose FEV1, the estimated treatment difference between ICS and placebo is 80mL. A reasonable approach to establish the non-inferiority margin is to take one half of the lower bound of the confidence interval, which is -60 mL and -40mL respectively. The TIOSPIR spirometry sub-study in 1370 COPD patients used a non-inferiority margin of -50mL demonstrating the non-inferiority of the Respimat 5mcg device versus the HandiHaler 18mcg. Two formulations of tiotropium are similar in clinical efficacy and safety.

A sample size of 375 evaluable patients in each treatment group provides 92% power for the testing of non-inferiority assuming a non-inferiority margin of -50mL and a SD of 200mL (2.5% significance level, one-sided). The standard deviation of 200mL is based on a review of the results of phase III COPD studies run by the sponsor. Therefore assuming a dropout rate of 25% over 26 weeks a minimum sample size of 1000 patients (500 QVA149 (110/50 µg o.d.): 500 tiotropium (18 µg o.d.)+ salmeterol/fluticasone propionate FDC (50/500 µg b.i.d.) has been chosen.

nQuery (V7.0) has been used to calculate the sample sizes.

10 Ethical considerations

10.1 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 CFR 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

[redacted]

10.2 Informed consent procedures

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

Novartis will provide to investigators in a separate document 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, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

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

In the event that Novartis wants to perform testing on the samples that are not described in this protocol, additional Institutional Review Board and/or Ethics Committee approval will be obtained.

10.3 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, patient recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. 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.

10.4 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.

[redacted]

11 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 patients 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 ascertain they will apply due diligence to avoid protocol deviations. If an 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 and health authorities, where required, it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

11.1 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 patients may be implemented immediately provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in section 7 Safety Monitoring should be followed.

[redacted]

12 References

References are available upon request.

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[redacted]

13 Appendix 1: Clinically notable laboratory values

Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 13-1 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
Liver Laboratory Triggers	3 x ULN < ALT / AST □ 5 x ULN 1.5 x ULN < TBL □ 2 x ULN
Liver Events	ALT or AST > 5 × ULN
	ALP > 2 × ULN (in the absence of known bone pathology)
	TBL > 2 × ULN (in the absence of known Gilbert syndrome)
	ALT or AST > 3 × ULN and INR > 1.5
	Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN)
	Any clinical event of jaundice (or equivalent term)
	ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
	Any adverse event potentially indicative of a liver toxicity *

Table 13-2 Follow Up Requirements for Liver Events and Laboratory Triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 × ULN	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for *more than 2 weeks*, discontinue the study treatment	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)

[redacted]

Criteria	Actions required	Follow-up monitoring
	• Establish causality • Complete liver CRF	
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 48 hours • If elevation persists, establish causality • Complete liver CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	• Repeat LFT within 48 hours • If elevation persists, discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	• Discontinue the study treatment immediately • Hospitalize the patient • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Complete liver CRF	Investigator discretion

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN

[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia

[c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

[redacted]

14 Appendix 2: Spirometry Guidance

Equipment

Spirometers must meet the specifications and performance criteria recommended in the American Thoracic Society (ATS)/European Respiratory Society (ERS) Standardization of Spirometry (Miller et al.2005). Spirometers must have the capacity to print FVC tracings. All spirometry values should be reported at BTPS by the method established by the manufacturer.

Calibration

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

Preparing the test patient

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

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

Every effort should be made to assure consistent testing conditions throughout the study. A seated position with nose clips is recommended to reduce risks related to dizziness or syncope. When possible, spirometry should be conducted by the same technician using the same spirometer. To minimize the effects of diurnal variation on lung function, spirometry visits should start at approximately the same time of day at each visit.

Performing Spirometry

The patient's age, height and gender will be entered into the spirometer. It is important that the height is measured accurately at the study site. Spirometry, an effort-dependent test, requires careful instruction and cooperation of the patient. The technician should ensure a good seal around the mouthpiece, and confirm that the patient's posture is correct. The patient should be instructed to perform a maximal inspiration, followed by maximum forced expiration until no more air can be exhaled or for at least 6 seconds. Expiration must be rapid with exertion of maximal effort. The results of spirometry should meet the ATS/ERS criteria for acceptability (one retest may be performed for patients that don't meet the acceptability criteria).

Number of trials

A minimum of 3 acceptable forced vital capacity (FVC) maneuvers should be performed. If a patient is unable to perform a single acceptable maneuver after 8 attempts, testing should be discontinued.

[redacted]

Acceptability

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

Recording of data

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

Predicted normal

For patients greater than 18 years of age, this study will utilize the spirometric predication equation standards for the European Community for Coal and Steel (Quanjer et al 1993) or Nhanes.

Reversibility

All reversibility evaluations should follow the recommendations of the ATS/ERS Task force: Standardization of Lung Function Testing (Miller et al.2005). A pre-bronchodilator spirometry assessment should be performed after a washout period of at least:

- 6 h for short-acting β_2-agonists
- 8 h short-acting anticholinergics
- 24 hours after the last (morning) dose of their LAMA
- 12 hours after the last (evening) dose of their LABA/ICS

Post-bronchodilator spirometry assessment is performed 15 minutes after administration of 400µg salbutamol.

Reversibility is calculated as:

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

During reversibility testing for post-bronchodilator FEV_1, if lung function deteriorates (i.e. there is a decrease in post bronchodilator FEV_1 compared to pre-bronchodilator FEV_1 as opposed to an increase) after administration of salbutamol, then patient needs to be screen failed.

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

[redacted]

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[redacted]

15 Appendix 3: Patient Diary

The following information will be captured twice daily before taking study medication:

In the MORNING (pre-medication)	In the EVENING (pre-medication)
Number of puffs of rescue medication during the past 12 hours	Number of puffs of rescue medication during the past 12 hours
How would you rate your respiratory symptoms last night? No waking due to symptoms Woke up once due to symptoms Woke up more than once due to symptoms Woke up frequently or could not sleep due to symptoms	Did your respiratory symptoms stop you performing your usual daily activities today? Not at all A little Quite a lot Completely
How was your cough during the past 12 hours? None Mild Moderate Severe	How was your cough during the past 12 hours? None Mild Moderate Severe
How was your wheeze during the past 12 hours? None Mild Moderate Severe	How was your wheeze during the past 12 hours? None Mild Moderate Severe
How much sputum did you produce during the past 12 hours? None Less than 5 mL (1 teaspoon) Between 5 and 25 mL (1-5 teaspoons) More than 25 mL (5 teaspoons)	How much sputum did you produce during the past 12 hours? None Less than 5 mL (1 teaspoon) Between 5 and 25 mL (1-5 teaspoons) More than 25 mL (5 teaspoons)
What color was the sputum you produced during the past 12 hours? None White-grey Yellow Green	What color was the sputum you produced during the past 12 hours? None White-grey Yellow Green
During what activities did you first feel breathless in the last 12 hours? Never or only when running When walking uphill or up stairs When walking on flat ground At rest	During what activities did you first feel breathless in the last 12 hours? Never or only when running When walking uphill or up stairs When walking on flat ground At rest

[redacted]

Patient Diary (continued)

The following information will be captured:

Did you have a sore throat? 0) No 1) Yes, mild 2) Yes, moderate 3) Yes, severe	Did you have a sore throat? 0) No 1) Yes, mild 2) Yes, moderate 3) Yes, severe
Did you have a cold (nasal discharge and/or nasal congestion)? 0) No 1) Yes, mild 2) Yes, moderate 3) Yes, severe	Did you have a cold (nasal discharge and/or nasal congestion)? 0) No 1) Yes, mild 2) Yes, moderate 3) Yes, severe
Did you have a fever? 0) No 1) Yes, mild 2) Yes, moderate 3) Yes, severe	Did you have a fever? 0) No 1) Yes, mild 2) Yes, moderate 3) Yes, severe
Time of study treatment administration will be captured in the patient eDiary and transferred to Novartis.	

[redacted]

16 Appendix 4: Instructions for use of Novartis single dose dry powder inhaler Concept 1, Accuhaler and HandiHaler

Instructions for use of Concept 1 (inhaler for QVA149)

- **Purpose and scope**

This document provides instruction for use of Concept 1 device in home use setting. It applies to the blue button version of the device.

This document version is intended for use in clinical trials only. This document only describes the inhaler handling and no drug product related instructions such as contraindications, drug storage, administration etc.

The intended use of the Concept 1 device is to generate a dry powder aerosol (from the formulation contained with the capsule) for delivery of the dry powder formulation to the lung.

- **Instructions for use**

Instructions for using inhaler and capsules.

Do not swallow capsules.

Follow the instructions below for using your inhaler. You will take the study treatment contained within the capsules by inhalation using the inhaler. If you have any questions, please ask the doctor or nurse at the study center.

Your Inhaler and capsules

The study treatment package consists of both the inhaler and one or more blister-packaged capsules.

Capsules are supplied in blister cards.

Inhaler consists of a cap, mouthpiece and a base.

Your inhaler is designed to deliver the medicine contained within the capsules.

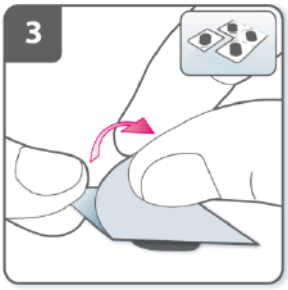
Do not use the study medication capsules with any other capsule inhaler, and do not use the inhaler to take any other capsule medicine.

How to use your inhaler

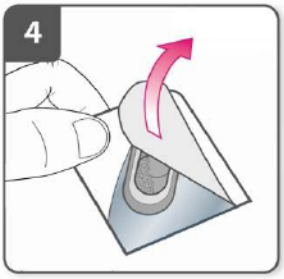
Pull off cap.

[redacted]

Open inhaler:
Hold the base of the inhaler firmly and tilt back the mouthpiece. This opens the inhaler.

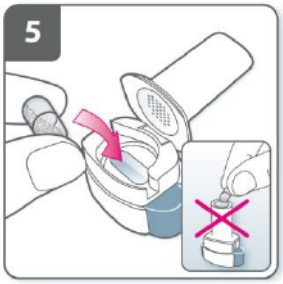


Prepare capsule:
Immediately before use, with dry hands, separate one of the blisters from the blister card by tearing along the perforations and lift the corner of the foil.



Remove a capsule:
Peel away the foil and remove the capsule from the blister.

Do not push the capsules through the foil.

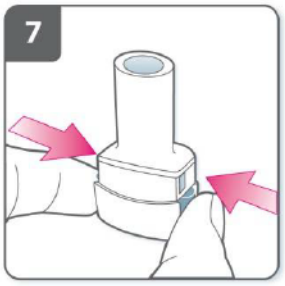


Insert capsule:
Place the capsule into the capsule chamber.

Never place a capsule directly into the mouthpiece.

Close the inhaler:
You should hear a “click” as the mouthpiece closes onto the inhaler base.

[redacted]

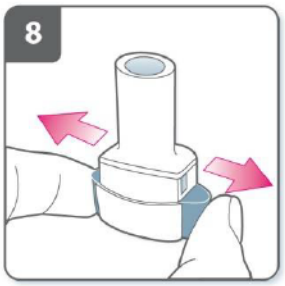


Pierce the capsule:

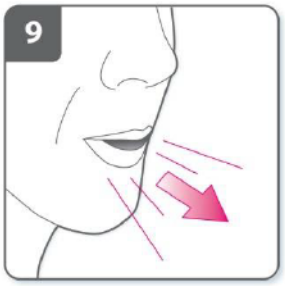
Hold the inhaler upright with the mouthpiece pointing up.

Pierce the capsule by firmly pressing together both side buttons at the same time. **Do this only once.**

You should hear a “click” as the capsule is being pierced.



Release the side buttons fully.



Breathe out:

Before placing the mouthpiece in your mouth, breathe out fully.

Do not blow into the mouthpiece.

Inhale the medicine

To breathe the medicine deeply into your airways:

Hold the inhaler as shown in the picture. The side buttons should be facing left and right. Do not press the side buttons.

Place the mouthpiece in your mouth and close your lips firmly around it.

Breathe in rapidly but steadily and as deeply as you can.

Note:

As you breathe in through the inhaler, the capsule spins around in the chamber and you should hear a whirring noise. You will experience a sweet flavour as the medicine goes into your lungs.

Additional information

Occasionally, very small pieces of the capsule can get past the screen and enter your mouth. If this happens, you may be able to feel these pieces on your tongue. It is not harmful if these pieces are swallowed. The chances of the capsule breakage will be increased if the capsule is accidentally pierced more than once (step 7).

[redacted]

Therefore it is recommended that you follow the storage directions, remove the capsule from the blister immediately before use and pierce each capsule only once.

If you do not hear a whirring noise:

The capsule may be stuck in the capsule chamber. If this happens:

Open the inhaler and carefully loosen the capsule by tapping the base of the inhaler. Do not press the side buttons.

Inhale the medicine again by repeating steps 9 to 11.

Hold breath:

After you have inhaled the medicine:

Hold your breath for at least 5-10 seconds or as long as you comfortably can while taking the inhaler out of your mouth.

Then breathe out.

Open the inhaler to see if any powder is left in the capsule.

If there is powder left in the capsule:

Close the inhaler.

Repeat steps 9, 10, 11 and 12.

Most people are able to empty the capsule with one or two inhalations.

Additional information

Some people may occasionally cough briefly soon after inhaling the medicine. If you do, don't worry. As long as the capsule is empty, you have received your medicine.

After you have finished taking your medicine:

Open the mouthpiece again, and remove the empty capsule by tipping it out of the capsule chamber. Put the empty capsule in your household waste.

Close the inhaler and replace the cap.

Do not store the capsules in the inhaler.

REMEMBER:

Do not swallow capsules.

Only use the inhaler contained in this pack.

Capsules must always be stored in the blister, and only removed immediately before use.

Never place a capsule directly into the mouthpiece of the inhaler.

Do not press the side buttons more than once.

Never blow into the mouthpiece of the inhaler.

[redacted]

Always release the push buttons before inhalation.
Never wash the inhaler with water. Keep it dry. See “How to clean your inhaler”.
Never take the inhaler apart.
Always use the new inhaler that comes with your new medication pack. Dispose of each inhaler after 30 days of use.
Do not store the capsules in the inhaler.
Always keep the inhaler and capsules in a dry place, and avoid very hot or cold temperatures.
Do not take the inhaler apart.

How to clean your inhaler
Never wash your inhaler with water. If you want to clean your inhaler, wipe the mouthpiece inside and outside with a clean, dry, lint-free cloth to remove any powder residue. Keep the inhaler dry.

[redacted]

Instructions for use of the Accuhaler®

Instructions for use

- Your doctor, nurse or pharmacist should show you how to use your inhaler. They should check how you use it from time to time. Not using the Seretide Accuhaler properly or as prescribed may mean that it will not help your asthma or COPD as it should.
- The Accuhaler device holds blisters containing Seretide as a powder.
- There is a counter on top of the Accuhaler which tells you how many doses are left. It counts down to 0. The numbers 5 to 0 will appear in red to warn you when there are only a few doses left. Once the counter shows 0, your inhaler is empty.

Using your inhaler

1 To open your Accuhaler, hold the outer case in one hand and put the thumb of your other hand on the thumbgrip. Push your thumb away from you as far as it will go. You will hear a click. This will open a small hole in the mouthpiece.

2 Hold your Accuhaler with the mouthpiece towards you. You can hold it in either your right or left hand. Slide the lever away from you as far as it will go. You will hear a click. This places a dose of your medicine in the mouthpiece.

Every time the lever is pulled back a blister is opened inside and the powder made ready for you to inhale. Do not play with the lever as this opens the blisters and wastes medicine.

3 Hold the Accuhaler away from your mouth, breathe out as far as is comfortable. Do not breathe into your Accuhaler.

4 Put the mouthpiece to your lips; breathe in steadily and deeply through the Accuhaler, not through your nose.
Remove the Accuhaler from your mouth.
Hold your breath for about 10 seconds or for as long as is comfortable.
Breathe out slowly.

5 Afterwards rinse your mouth with water and spit it out. This may help to stop you getting thrush and being hoarse.

6 To close the Accuhaler, slide the thumbgrip back towards you, as far as it will go. You will hear a click.
The lever will return to its original position and is reset.
Your Accuhaler is now ready for you to use again.

How to clean your inhaler

Wipe the mouthpiece of the Accuhaler with a dry tissue to clean it.

[redacted]

Instructions for use of the HandiHaler®

FOR ORAL INHALATION ONLY
DO NOT SWALLOW CAPSULES
Read all instructions before use.
This leaflet provides summary information about the inhaler. Before you start to use the inhaler, read this leaflet carefully and keep it for future use.

Your inhaler is a plastic device to be used only with the provided capsules. Please return the device, together with unused capsules to the study site at your next visit.

Becoming familiar with the inhaler:

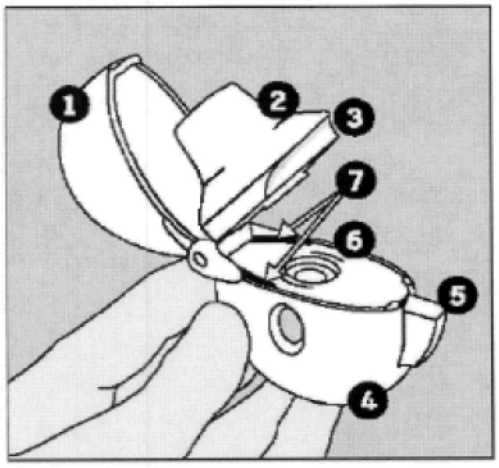


Figure A
Remove the inhaler from the pouch and become familiar with its components. (Figure A)

1. dust cap
2. mouthpiece
3. mouthpiece ridge
4. base
5. green piercing button
6. center chamber
7. air intake vents

[redacted]

Opening the inhaler:

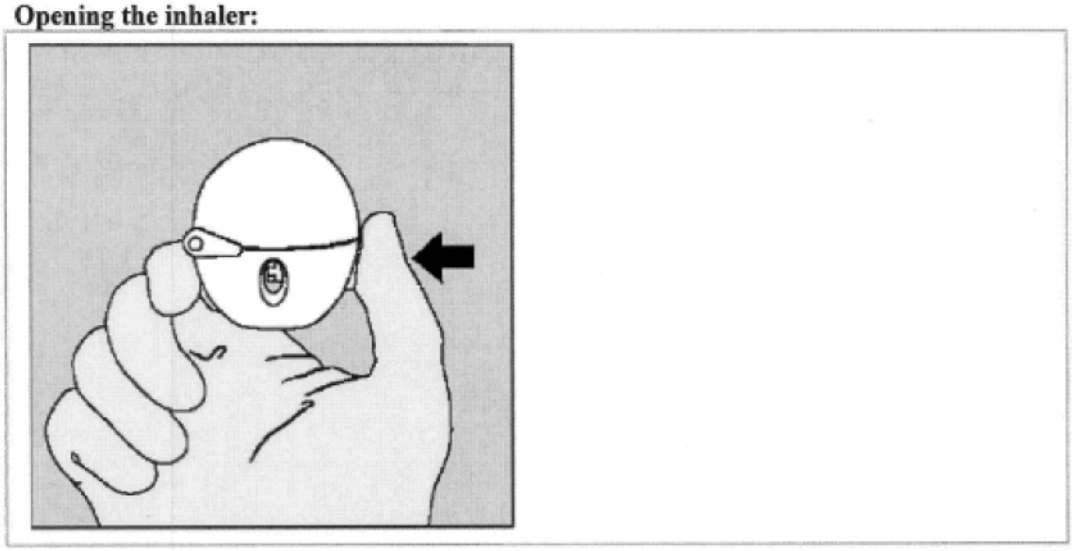


Figure 1
OPEN the dust cap by pressing the green piercing button. (Figure 1)

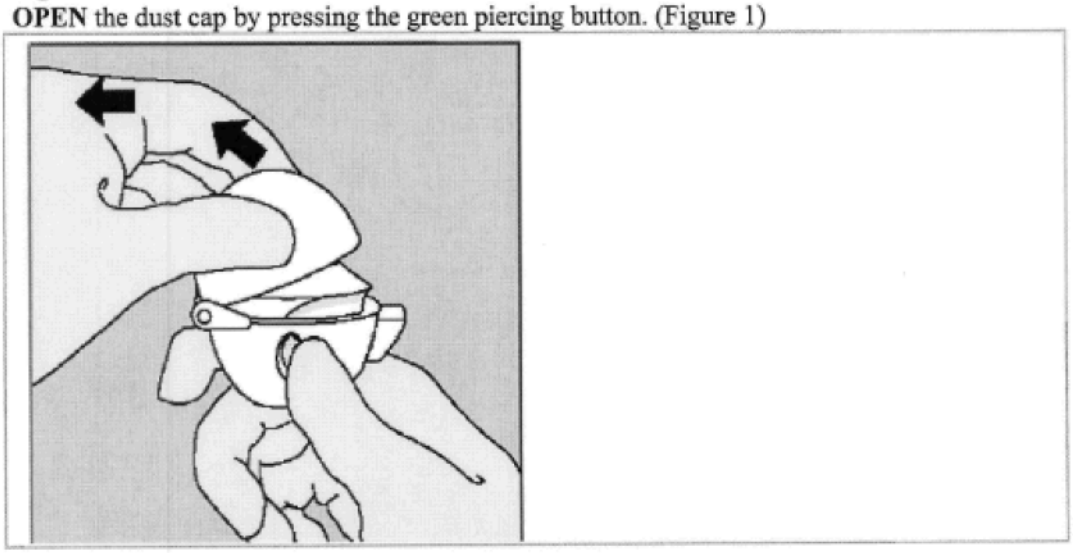


Figure 2
Pull the dust cap upwards to expose the mouthpiece. (Figure 2)

[redacted]

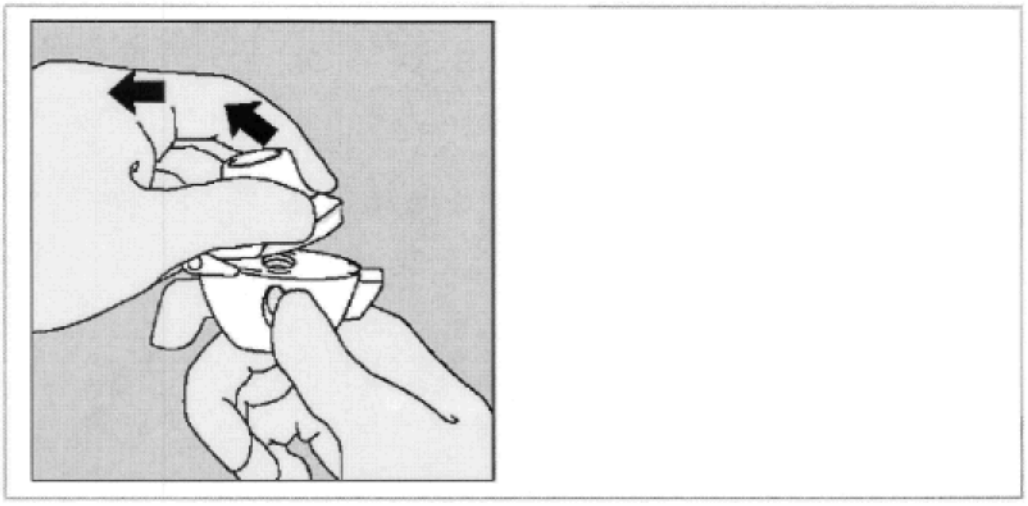


Figure 3
Open the mouthpiece by pulling the mouthpiece ridge upwards. (Figure 3)

Inserting the capsule into the inhaler:

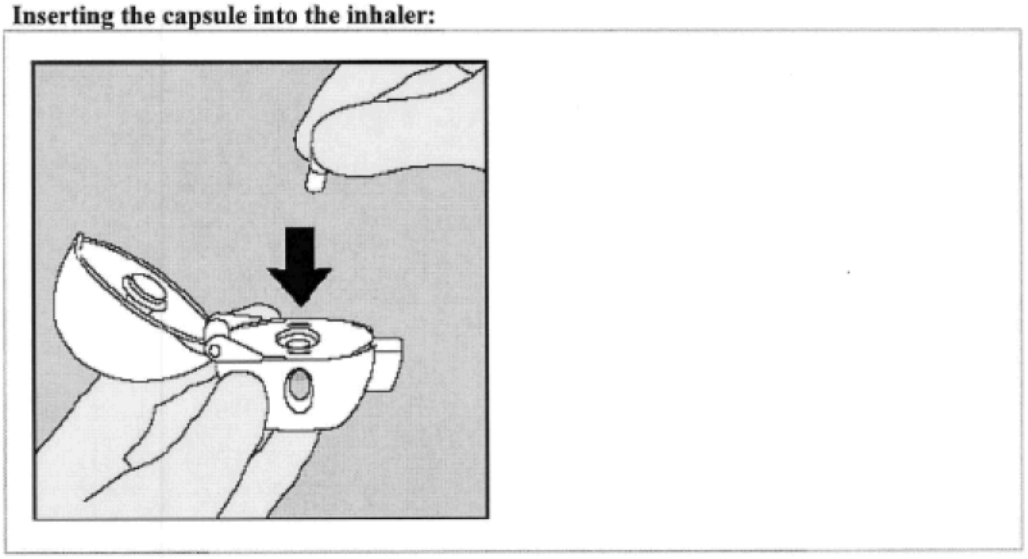


Figure 4
INSERT the capsule in the center chamber of the inhaler. It does not matter which end of the capsule is placed in the chamber. (Figure 4)

[redacted]

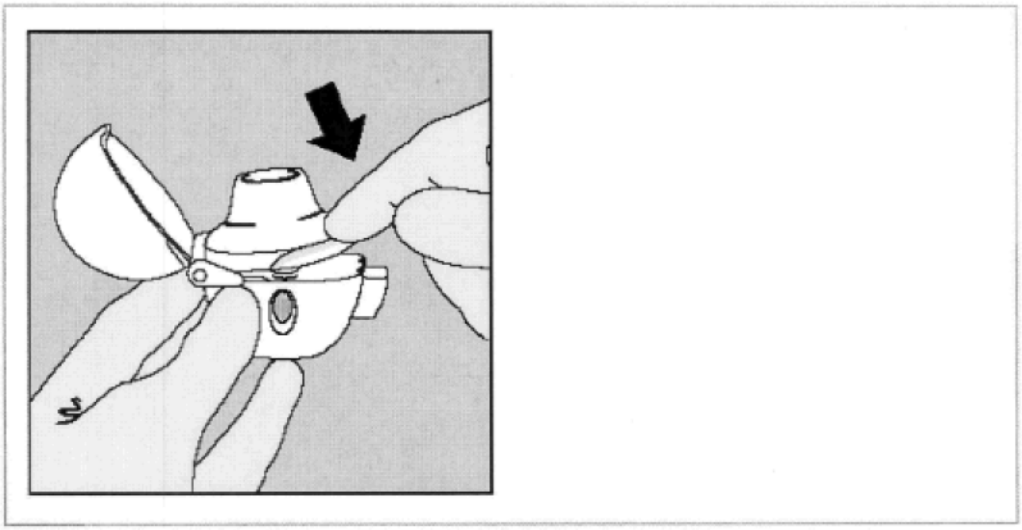


Figure 5
Close the mouthpiece **firmly until you hear a click,** leaving the dust cap open. (Figure 5)
Be sure that the mouthpiece sits firmly against the gray base.

Taking your dose:

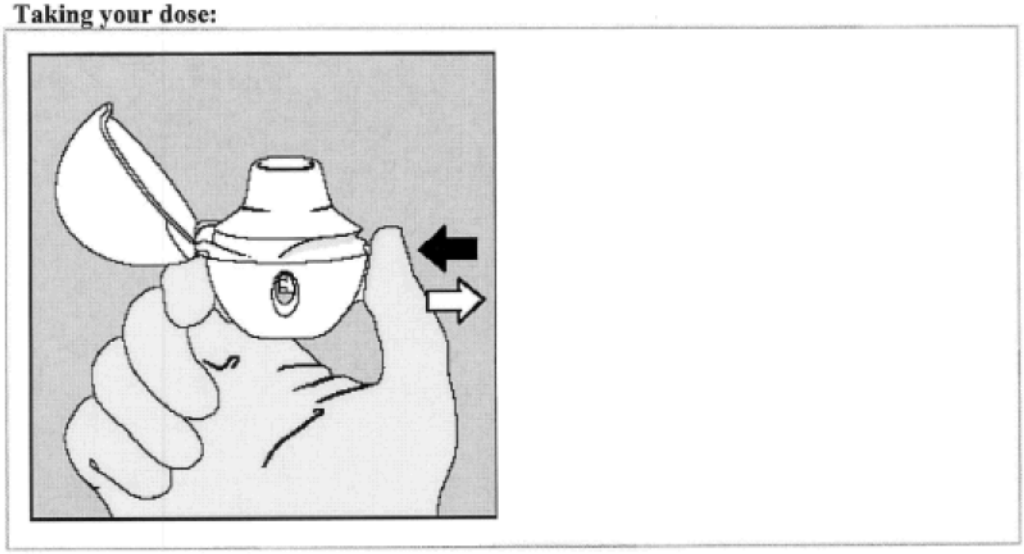


Figure 6
Hold the inhaler with the mouthpiece upwards.
PRESS the green piercing button until it is flush against the base, and release. This makes holes in the capsule and allows the medication to be released when you breathe in. (Figure 6)
DO NOT PRESS THE GREEN PIERCING BUTTON MORE THAN ONE TIME.

[redacted]

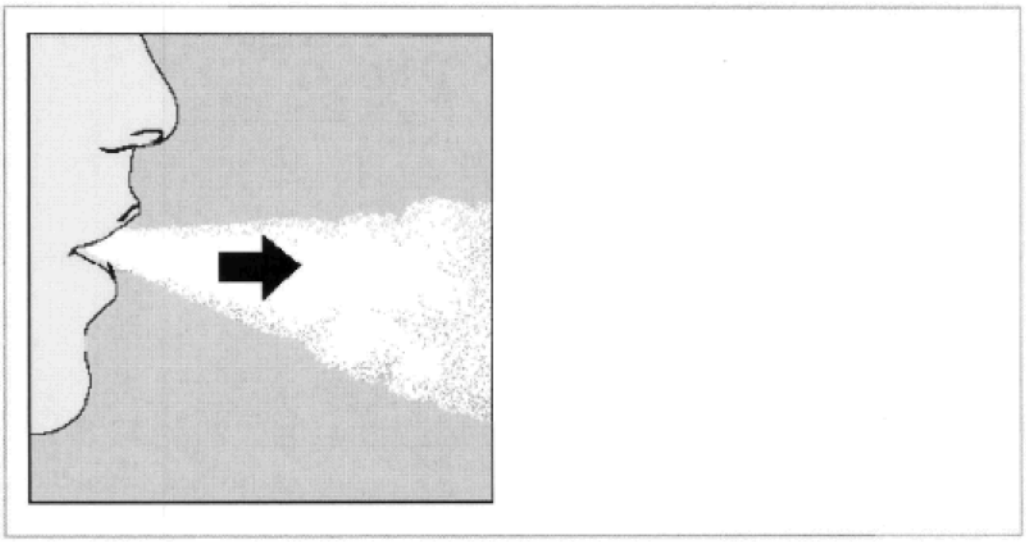


Figure 7

Breathe out completely. (Figure 7)

Important: Do not breathe (exhale) into the inhaler mouthpiece at any time.

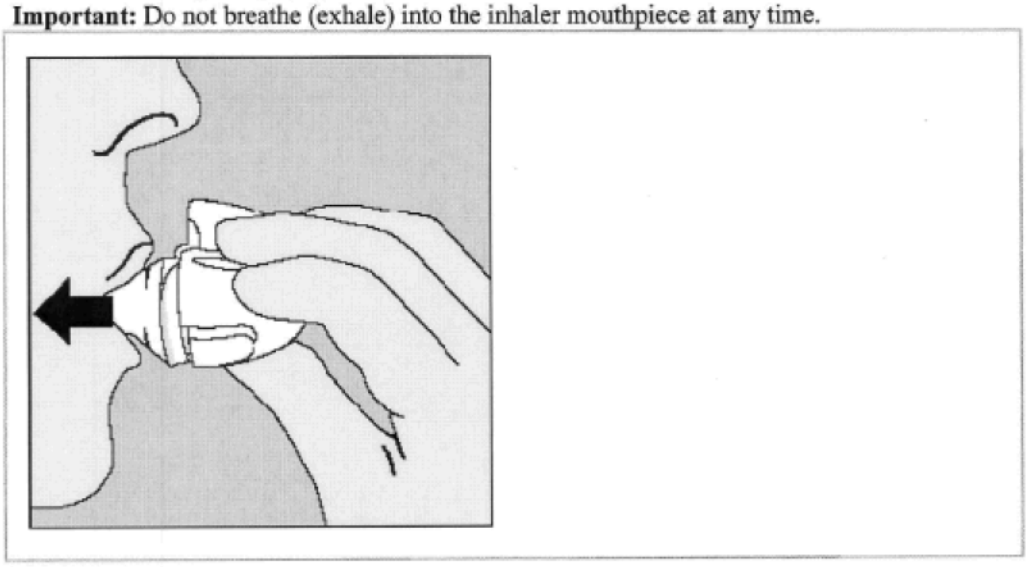


Figure 8

INHALE

- Hold the inhaler by the gray base. Do not block the air intake vents.
- Raise the inhaler device to your mouth and close your lips tightly around the mouthpiece.
- **Keep your head in an upright position. The inhaler should be in a horizontal position.** (Figure 8)
- Breathe in **slowly and deeply** but at a rate **sufficient to hear or feel the capsule vibrate**

[redacted]

- Breathe in until your lungs are full.
- Hold your breath as long as is comfortable and at the same time take the inhaler out of your mouth. Resume normal breathing.

To ensure you get the full dose from the capsule, you must again breathe out completely and inhale once again as previously described (Figure 8).

DO NOT PRESS THE GREEN PIERCING BUTTON AGAIN.

If you do not hear or feel the capsule vibrate, **Do Not Press The Green Piercing Button Again** but instead tap the inhaler gently on a table, holding it in an upright position. Check to see that the mouthpiece is completely closed. Then breathe in again – slowly and deeply. If you still do not hear or feel the capsule vibrate after repeating the above steps, please consult your doctor, nurse or pharmacist at the study site.

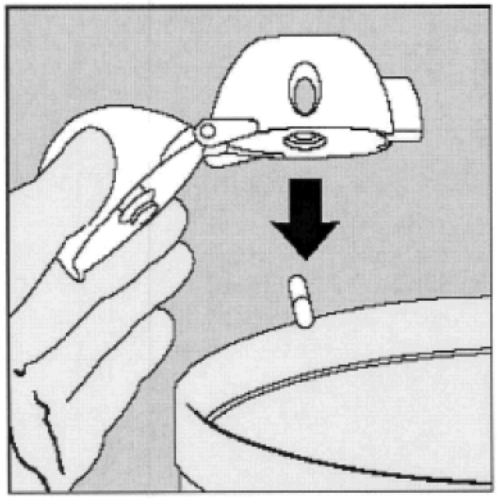


Figure 9

After you have finished taking your dose, open the mouthpiece again. Tip out the used capsule and discard. (Figure 9)

[redacted]

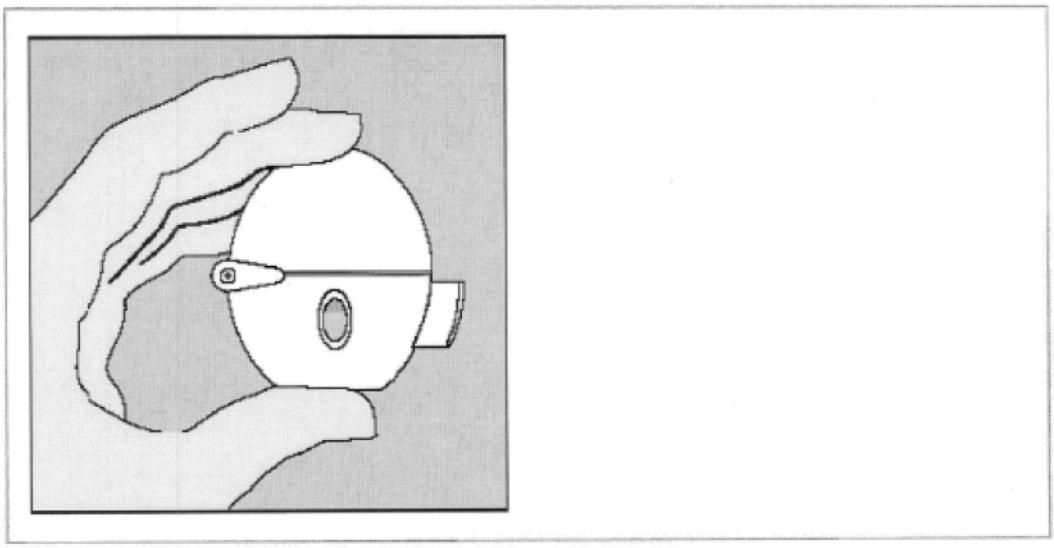


Figure 10
Close the mouthpiece and dust cap for storage of your inhaler. (Figure 12)

Do not store the used or unused capsules in the inhaler.

As with all prescription medications, keep this out of the reach of children

[redacted]

17 Appendix 5: Guidelines for Administering the SGRQ-C Questionnaire

Before the Trial Begins

Study coordinators should familiarize themselves with the questionnaires and training materials in the trial, and identify any items where a patient's response might highlight issues of potential concern.

Before Completion

Explain to the patient why they are completing the questionnaires, and how important it is for us to understand how they feel about their illness and the effect it has on their daily life. Ask the patient to complete the questionnaires as honestly as possible and stress that there are no right or wrong answers simply the answer that the patient feels applies to them. Explain that they should answer every question and that someone will be close at hand to answer any queries.

Patients should be provided with the correct questionnaires at the appropriate visits, and in the appropriate language (The same language should be used by the patient for all visits).

Patients should have adequate space and time to complete the forms.

Patients should be provided with a firm writing surface (such as a table or a clip board).

Questionnaires should be completed before the clinical assessments

During Completion

The administrator may clarify the questions but may not influence the response. The questionnaires are designed to elicit the patient's opinion of his/her health, not someone else's opinion of it. If the spouse or partner has accompanied the patient they should be asked to wait in a separate area. Do not allow patients to take the questionnaires home to be completed.

Ensure there is only one response for each question

Also see 'Addressing Problems and Concerns' on the next page.

After Completion

Check for completeness but not for content.

Check for multiple responses that were made in error

File completed questionnaires in the patient study file notebooks provided for the study.

Any response which may directly impact on or reflect the patient's medical condition (e.g. noting of depression) should be communicated by the study coordinator to the investigator.

Addressing Problems and Concerns

Occasionally a patient may have concerns or questions about the questionnaires administered. Guidance related to some of the most common concerns and questions are given below.

[redacted]

The patient does not want to complete the questionnaire(s).

Tell the patient that completion of the questionnaire(s) is voluntary. The goal is to better understand the physical, mental, and social health problems of patients. Emphasize that this information is as important as any of the other medical information, and that the questionnaire(s) is simple to complete. Suggest that the questionnaire(s) may be different from anything the respondent has filled in the past. If the patient still declines, retrieve the questionnaires. Record the reason for the decline, and thank the patient.

The patient is too ill or weak to complete the questionnaire(s).

In these instances, the coordinator may obtain patient responses by reading out loud each question, followed by the corresponding response categories, and entering the patient's response. No help should be provided to the patient by any person other than the designated study coordinator. The coordinator should not influence patient responses. The study coordinator cannot translate the question into simpler language and it has to be read verbatim.

The patient wants someone else to complete the questionnaire(s).

In no case should the coordinator or anyone other than the patient provide responses to the questions.

The patient does not want to finish completing the questionnaire(s).

If non-completion is a result of the patient having trouble understanding particular items, ask the patient to explain the difficulty. Re-read the question for them *verbatim*, but do not rephrase the question. Guidance notes on queries of understanding for specific questions from the SGRQ-C User Manual are provided below. If the respondent is still unable to complete the questionnaire, accept it as incomplete. Thank the patient.

The patient is concerned that someone will look at his/her responses.

Emphasize that all responses are to be kept confidential. Point out that their names do not appear anywhere on the questionnaire, so that their results will be linked with an ID number and not their name. Tell the patient that his/her answers will be pooled with other patients' answers and that they will be analyzed as a group rather than as individuals. Tell the patient that completed forms are not routinely shared with treating staff, and that their responses will only be seen by you (to check for completeness), and possibly the investigator. Any response which may directly impact on or reflect their medical condition (e.g. noting of severe depression) will be communicated by the coordinator to the physician.

The patient asks the meaning of a question / item.

While completing a questionnaire, some patients might ask the meaning of specific items so that they can better understand and respond. If this happens, assist the patient by rereading the question for them *verbatim*. If the patient asks to interpret the meaning of an item, do not try to explain it, but suggest that he/she use his/her own interpretation of the question. Patients should answer the questions based on what *they* think the questions mean. However there are some guidance notes in the SGRQ-C User Manual regarding queries relating to specific questions that may be of use. They are provided below:

[redacted]

Responding to a patient's queries regarding completion of the questionnaire

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

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

1. In Part 1 of the questionnaire, emphasize to patients that you are interested in how much chest trouble they have recently. The exact period is not important. We are looking for an impression or perception of health.
2. An attack of chest trouble (Part 1, Question 5) is any episode of worse symptoms that constitutes an attack *in the patient's own judgment*. Not just severe attacks as judged by medical staff.
3. COPD can vary day-to-day. Part 2 is concerned with the patient's current state (i.e. on average over 'these days'), not necessarily just today.
4. For Part 1 Question 6, emphasize that you are interested in the number of good days that they have had.
5. In Part 2, Questions 8 and 14 require a single response, but Questions 9 to 13 require a response to every question. It may be worth emphasizing this to the patient.
6. Many patients do not engage in physical activity. It is important to determine whether this is because they do not wish to (in which case the answer would be 'False') or cannot engage in these activities because of their chest trouble (in which case the answer would be 'True').
7. Responses to Questions 12 and 13 concern limitations due to breathing difficulties and not any other problems. If the patient does not engage in an activity for another reason, they should tick 'False'.

[redacted]

18 Appendix 6: St. George's Respiratory Questionnaire (SGRQ-C)

(The samples provided here are for illustrative purposes only)

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE
for COPD patients (SGRQ-C)

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life.
We are using it to find out which aspects of your illness cause you most problems, rather than what the doctors and nurses think your problems are.

Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.

ID :_____

Date :_____/_____/_____(dd/mm/yy)

Before completing the rest of the questionnaire:

Please tick in one box to show how you describe your current health:

Very good	Good	Fair	Poor	Very poor
☐	☐	☐	☐	☐

Version: 1.1 (December 2008)

[redacted]

[redacted]

[redacted]

PART 1

Questions about how much chest trouble you have.

Please tick (✓) **ONE** box for each question:

Question 1. I cough:

most days a week ..... ☐ a

several days a week..... ☐ b

only with chest infections..... ☐ c

not at all..... ☐ d

Question 2. I bring up phlegm (sputum):

most days a week ..... ☐ a

several days a week..... ☐ b

only with chest infections ... ☐ c

not at all..... ☐ d

Question 3. I have shortness of breath:

most days a week ..... ☐ a

several days a week..... ☐ b

not at all..... ☐ c

Question 4. I have attacks of wheezing:

most days a week ..... ☐ a

several days a week..... ☐ b

a few days a month..... ☐ c

only with chest infections..... ☐ d

not at all..... ☐ e

Question 5. How many attacks of chest trouble did you have during the last year?

3 or more attacks..... ☐ a

1 or 2 attacks..... ☐ b

none..... ☐ c

[redacted]

Question 6. How often do you have good days (with little chest trouble) ?

No good days..... ☐ a

a few good days..... ☐ b

most days are good..... ☐ c

every day is good..... ☐ d

Question 7. If you have a wheeze, is it worse in the morning?

No..... ☐

Yes..... ☐

[redacted]

PART 2

8. *How would you describe your chest condition?*

Please tick (✓) *ONE*:

Causes me a lot of problems or is the most important problem I have..... ☐ a

Causes me a few problems..... ☐ b

Causes no problem..... ☐ c

9. *Questions about what activities usually make you feel breathless*

For each statement please tick (✓) in the box that applies to you these days:

	True	False
Getting washed or dressed.....	☐	☐ a
Walking around the home.....	☐	☐ b
Walking outside on the level.....	☐	☐ c
Walking up a flight of stairs.....	☐	☐ d
Walking up hills.....	☐	☐ e

10. *Some more questions about your cough and breathlessness*

For each statement please tick (✓) in *the box* that applies to you these days:

	True	False
My cough hurts.....	☐	☐ a
My cough makes me tired.....	☐	☐ b
I am breathless when I talk.....	☐	☐ c
I am breathless when I bend over.....	☐	☐ d
My cough or breathing disturbs my sleep.....	☐	☐ e
I get exhausted easily.....	☐	☐ f

[redacted]

11. ***Questions about other effects that your chest trouble may have on you***

For each statement please tick (✓) in *the box* that applies to you these days:

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

12. ***These are questions about how your activities might be affected by your breathing.***

For each statement please tick (✓) in *the box* that applies to you because of your breathing:

	True	False
I take a long time to get washed or dressed.....	☐	☐ a
I cannot take a bath or shower, or I take a long time.....	☐	☐ b
I walk slower than other people, or I stop for rests.....	☐	☐ c
Jobs such as housework take a long time, or I have to stop for rests....	☐	☐ d
If I walk up one flight of stairs, I have to go slowly or stop.....	☐	☐ e
If I hurry or walk fast, I have to stop or slow down.....	☐	☐ f
My breathing makes it difficult to do things such as walk up hills, carrying things up stairs, light gardening such as weeding, dance, play bowls or play golf	☐	☐ g
My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles per hour, play tennis or swim.....	☐	☐ h

[redacted]

PART 2

13 . *We would like to know how your chest trouble usually affects your daily life.*

For each statement please tick (✓) in *the box* that applies to you *because of your breathing:*

	True	False	
I cannot play sports or games.....	☐	☐	a
I cannot go out for entertainment or recreation.....	☐	☐	b
I cannot go out of the house to do the shopping.....	☐	☐	c
I cannot do housework.....	☐	☐	d
I cannot move far from my bed or chair.....	☐	☐	e

14. *How does your chest trouble affect you?*

Please tick (✓) *ONE*:

It does not stop me doing anything I would like to do.....	☐	a
It stops me doing one or two things I would like to do.....	☐	b
It stops me doing most of the things I would like to do.....	☐	c
It stops me doing everything I would like to do.....	☐	d

Thank you for filling in this questionnaire.

Before you finish, would you please check to see that you have answered all the questions.

UK/ English 6/6

[redacted]

VIAPen® (eResearchTechnology GmbH) is a portable data capture tool that enables the simultaneous collection of data electronically and on paper and will be used for completing the patient questionnaires for this study. This maintains the original validated questionnaire and enables the study to be set up without changing the process for traditional PRO collection techniques.

VIAPen® is a digital and a ball pen in one device. The questionnaires are printed on e-paper which is paper with coded dot pattern, invisible to the naked eye and each page has a unique pattern.

While the patient answers the questions by ticking boxes, circling numbers or marking visual analog scales as on a usual paper with a normal pen, the built-in infrared camera in the digital pen automatically records the strokes and the time of the strokes.

After the patient has completed the questionnaire, the digital pen is docked in a cradle attached to a computer and the VIAPen® software reads the captured data and interprets the strokes.

The investigator or delegate checks the results of the automated interpretation for accuracy and completeness. During this process the software creates a digital image and a data set and transfers both into the central study database. A print out of the digital answers is created by the investigator before the data are transmitted. Both the print out as well as the original e-paper are filed in the source documentation at the investigator's site.

[redacted]

19 Appendix 7: COPD Assessment Test (CAT)

Your name:

Today's date:

CAT
COPD Assessment Test

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

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

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

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

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

[redacted]

20 Appendix 8: modified Medical Research Council (mMRC) Dyspnea Scale

Modified Medical Research Council Questionnaire for Assessing the Severity of Breathlessness	
PLEASE TICK IN THE BOX THAT APPLIES TO YOU (ONE BOX ONLY)	
mMRC Grade 0. I only get breathless with strenuous exercise.	☐
mMRC Grade 1. I get short of breath when hurrying on the level or walking up a slight hill.	☐
mMRC Grade 2. I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level.	☐
mMRC Grade 3. I stop for breath after walking about 100 meters or after a few minutes on the level.	☐
mMRC Grade 4. I am too breathless to leave the house or I am breathless when dressing or undressing.	☐

[redacted]

21 Appendix 9: BDI/TDI

Dyspnea Index - Baseline

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Functional Impairment

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

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

Magnitude of Task

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

[redacted]

Dyspnea Index - cont. - Baseline

Magnitude of Effort

- ☐ Grade 4: *Extraordinary*. Becomes short of breath only with the greatest imaginable effort. No shortness of breath with ordinary effort.
- ☐ Grade 3: *Major*. Becomes short of breath with effort distinctly submaximal, but of major proportion. Tasks performed without pause unless the task requires extraordinary effort that may be performed with pauses.
- ☐ Grade 2: *Moderate*. Becomes short of breath with moderate effort. Tasks performed with occasional pauses and requiring longer to complete than the average person.
- ☐ Grade 1: *Light*. Becomes short of breath with little effort. Tasks performed with little effort or more difficult tasks performed with frequent pauses and requiring 50-100% longer to complete than the average person might require.
- ☐ Grade 0: *No Effort*. Becomes short of breath at rest, while sitting, or lying down.
- ☐ W: *Amount Uncertain*. Patient's exertional ability is impaired due to shortness of breath, but amount cannot be specified. Details are not sufficient to allow impairment to be categorized.
- ☐ X: *Unknown*. Information unavailable regarding limitation of effort.
- ☐ Y: *Impaired for Reasons Other than Shortness of Breath*. For example, musculoskeletal problems or chest pain.

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Dyspnea Index - Transition

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Change in Functional Impairment

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

Change in Magnitude of Task

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

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Dyspnea Index - cont. - Transition

Change in Magnitude of Effort

☐ -3: *Major Deterioration*. Severe decrease in effort from baseline to avoid shortness of breath. Activities now take 50-100% longer to complete than required at baseline.

☐ -2: *Moderate Deterioration*. Some decrease in effort to avoid shortness of breath, although not as great as preceding category. There is greater pausing with some activities.

☐ -1: *Minor Deterioration*. Does not require more pauses to avoid shortness of breath, but does things with distinctly less effort than previously to avoid breathlessness.

☐ 0: *No Change*. No change in effort to avoid shortness of breath.

☐ +1: *Minor Improvement*. Able to do things with distinctly greater effort without shortness of breath. For example, may be able to carry out tasks somewhat more rapidly than previously.

☐ +2: *Moderate Improvement*. Able to do things with fewer pauses and distinctly greater effort without shortness of breath. Improvement is greater than preceding category, but not of major proportion.

☐ +3: *Major Improvement*. Able to do things with much greater effort than previously with few, if any, pauses. For example, activities may be performed 50-100% more rapidly than at baseline.

☐ Z: *Further Impairment for Reasons Other than Shortness of Breath*. Patient has reduced exertional capacity, but not related to shortness of breath. For example, musculoskeletal problem ot chest pain.

[redacted]