NOVARTIS

Clinical Development

QVA149/ indacaterol maleate/glycopyrronium bromide

Clinical Trial Protocol CQVA149AKR01/ NCT02566031

A randomized, multicenter, open-label, parallel-group, 12-week study to assess the efficacy and safety of switching from tiotropium to QVA149 (indacaterol maleate/glycopyrronium bromide) in symptomatic mild to moderate COPD patients

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List of abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate aminotransferase
ATS	American Thoracic Society
BDI	Baseline Dyspnea Index
BTPS	Normal body temperature (37°C), ambient pressure, saturated with water vapor
CAT	COPD Assessment Test
CCV	Cardio-cerebrovascular Event
COPD	Chronic Obstructive Pulmonary Disease
eCRF	Electronic Case Report/Record Form
DS&E	Drug Safety & Epidemiology
ECG	Electrocardiogram
EDC	Electronic Data Capture
ERS	European Respiratory Society
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
hCG	Human Chorionic Gonadotropin
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS	Inhaled Corticosteroid
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Randomized Technology
IUD	Intrauterine Device
IUS	Intrauterine System
LABA	Long Acting Beta-2 Agonist
LAMA	Long Acting Muscarinic Antagonist

[redacted]

LOCF	Last Observation Carried Forward
MDI	Metered Dose Inhaler
mMRC	Modified Medical Research Council
PSW	Premature Study Withdrawal
QoL	Quality of Life
QT	Time between start of Q wave and end of T wave in heart's electrical cycle
QTc	Corrected QT
QTcF	Fridericia corrected QT formula
SABA	Short Acting Beta-2 Agonist
SAE	Serious Adverse Event
SDDPI	Single Dose Dry Powder Inhaler
SGRQ	St. George's Respiratory Questionnaire
SmPC	Summary of Product Characteristics
SUSARs	Suspected Unexpected Serious Adverse Reactions
TDI	Transitional Dyspnea Index
TURP	Transurethral Resection of Prostate

[redacted]

Glossary of terms

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

[redacted]

Protocol synopsis

Protocol number	CQVA149AKR01
Title	A randomized, multicenter, open-label, parallel-group, 12-week study to assess the efficacy and safety of switching from tiotropium to QVA149 (indacaterol maleate/glycopyrronium bromide) in mild to moderate symptomatic COPD patients.
Brief title	Study of efficacy and safety of switching from tiotropium to QVA149 in patients with symptomatic mild to moderate COPD.
Sponsor and clinical phase	Novartis, Phase IV
Investigation type	Drug
Study type	Interventional
Purpose and rationale	Bronchodilator medications are central to symptom management in chronic obstructive pulmonary disease (COPD). According to local market research data in Korea, 70 to 80% of COPD patients using an inhaled mono-bronchodilator still have the same or more symptoms despite treatment compared to when they were first diagnosed. Tiotropium is the most widely used mono-bronchodilator in Korea. Combining bronchodilators of different pharmacological classes may improve efficacy and decrease the risk of side effects compared to increasing the dose of a single bronchodilator. QVA149 is a novel, inhaled fixed dose combination of the long acting beta-2 agonist (LABA) indacaterol (QAB149) and the long acting muscarinic antagonist (LAMA) glycopyrronium (NVA237) for once-daily maintenance treatment of COPD. QVA149 was first marketed in Europe and Japan in 2013 and has since been marketed in many other countries worldwide including South Korea (since May 2014). In this study, the efficacy and safety of QVA149 will be compared to that of tiotropium in COPD patients with mild to moderate airflow limitation with low exacerbation risk and who are currently receiving tiotropium but still symptomatic, which is defined as COPD assessment test (CAT) scores ≥ 10. The main purpose of this study is to show that QVA149 (110/50 µg) once daily results in better lung function and airflow compared to tiotropium 18 µg once daily in patients with mild to moderate symptomatic COPD; and to assess the effect of both treatments on symptom burden, breathlessness, and use of rescue medication in these patients.
Primary objective	• To demonstrate superiority of QVA149 (110/50 µg) once daily compared to tiotropium 18 µg once daily in terms of trough forced expiratory volume in 1 second (FEV_1) (mean of 45 min and 15 min pre-dose) following 12 weeks of treatment in mild to moderate symptomatic COPD patients.
Secondary objectives	To evaluate the effect of QVA149 (110/50 µg) as compared to tiotropium 18 µg on: • Pre-dose trough FEV_1 at Week 4.

[redacted]

	• Total transitional dyspnea index (TDI) focal score at Week 12. • Symptom control as assessed by total CAT score at Week 12. • Rescue medication used reported by the patients at Week 12. • Safety and tolerability.
[redacted]	
Study design	This is a randomized, multicenter, open-label, parallel-group, 12-week study to assess the efficacy and safety of QVA149 (indacaterol maleate/glycopyrronium bromide) versus tiotropium in mild to moderate symptomatic COPD patients.
Population	The study population will consist of approximately 389 male and female adults aged 40 or older, with a confirmed clinical diagnosis of COPD and post-bronchodilator FEV_1 ≥ 50% of the predicted normal value and post-bronchodilator FEV_1/forced vital capacity (FVC) < 0.7 (COPD Grade 1 or 2 by severity of airflow limitation (GOLD 2015) and a smoking history of at least 10 pack years.
Inclusion criteria	Patients eligible for inclusion in this study have to fulfill all of the following criteria: 1. Written informed consent must be obtained before any assessment is performed. 2. Male or female adults aged ≥ 40 years, who have signed an Informed Consent Form (ICF) prior to initiation of any study-related procedure. 3. Confirmed diagnosis of COPD and post-bronchodilator FEV_1 ≥ 50% of the predicted normal value and post-bronchodilator FEV_1/FVC < 0.7 (COPD Grade 1 or 2 by severity of airflow limitation (GOLD 2015). Current or ex-smokers who have a smoking history of at least 10 pack years. (Ten pack-years are defined as 20 cigarettes a day for 10 years, or 10 cigarettes a day for 20 years etc.) 4. Patients with CAT score ≥ 10 at Visit 0 and Visit 1. 5. Patients who are on and have been on tiotropium 18 µg monotherapy for the past 3 months prior to Baseline (Visit 1). 6. 0 or 1 COPD exacerbation in the previous 12 months prior to baseline (Visit 1) (not leading to hospital admission).
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. **General exclusion criteria** 1. Treatment with any inhaled corticosteroid (ICS) in the 3 months prior to Visit 1. 2. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the

[redacted]

	termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test. 3. 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 6 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 months 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 6 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. 4. Presence of any contraindication, warning, precaution, hypersensitivity to LABA and LAMA. 5. History or current diagnosis of clinically significant electrocardiogram (ECG) abnormalities including: • 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*. 6. Patients who have not achieved an acceptable spirometry result at (Visit 10) in accordance with American Thoracic Society (ATS)/ European Respiratory Society (ERS) criteria for acceptability and

[redacted]

	repeatability. 7. Patients with Type I or uncontrolled Type II diabetes. 8. Patients with narrow-angle glaucoma, symptomatic prostatic hyperplasia or bladder-neck obstruction or moderate to severe renal impairment or urinary retention. (Patients with a transurethral resection of prostate (TURP) are excluded from the study. Patients who have undergone full re-section of the prostate may be considered for the study, as well as patients who are asymptomatic and stable on pharmacological treatment for the condition). 9. History of malignancy of any organ system, treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases with the exception of localized basal cell carcinoma of the skin. 10. Patients with a history of clinically significant diseases that, in the opinion of the Investigator, would put the safety of the patients at risk through study participation, or would compromise patient compliance or preclude completion of the study. 11. Uncontrolled hypothyroidism and hyperthyroidism, hypokalemia. 12. Patients with neurological, endocrine, immunological, psychiatric, gastrointestinal, hepatic, or hematological abnormalities which, in the opinion of the Investigator, could interfere with the assessment of the efficacy and safety of the study treatment. 13. Patients who are, in the opinion of the investigator, known to be unreliable or non-compliant. **COPD specific exclusion criteria** 1. Patients requiring long-term oxygen therapy prescribed for > 12 hours per day. 2. COPD exacerbation between Visits 0 and 1. Patients can be re-screened after a minimum of 6 weeks after resolution of the exacerbation if the exacerbation did not require hospitalization. If a patient has an exacerbation that requires hospitalization between Visit 0 and Visit 1 then he/she is not eligible to re-screen. 3. Onset of respiratory symptoms, including a COPD diagnosis prior to age 40 years. 4. Patients with a history of respiratory infection within 4 weeks prior to Visit 0. Patients who develop a respiratory tract infection between Screening and prior to treatment will not be eligible but will be permitted to be re-enrolled 4 weeks after the resolution of the respiratory tract infection. 5. Concomitant pulmonary disease (e.g. pulmonary tuberculosis (unless confirmed by chest X-ray to be no longer active), lung fibrosis, sarcoidosis, interstitial lung disease, primary pulmonary hypertension, clinically significant bronchiectasis). 6. Patients with lung lobectomy, or lung volume reduction or lung transplantation 7. Prior or current diagnosis of asthma. **Medication exclusion** 1. Treatments for COPD and allied conditions: the following class of medications should be washed out prior to randomization (Visit 1) or prohibited during the study period (Table 5-1 in main protocol).

[redacted]

	2. Patients who need the following treatments for COPD and allied conditions unless they have been stabilized for the specified period and the stated conditions have been met (Table 5-2 in main protocol). 3. Patients who have had live attenuated vaccinations within 30 days prior to the screening visit. Inactivated influenza vaccination, pneumococcal vaccination or any other inactivated vaccine is acceptable provided it is not administered within 48 hours prior to screening and randomization visits. 4. Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of Visit 1, whichever is longer. 5. Patients unable to use a dry powder inhaler (e.g. single-dose dry powder inhaler (SDDPI), HandiHaler®) device or pressurized metered dose inhaler (MDI) (rescue medication).
Investigational and reference therapy	Investigational therapy: • QVA149 110/50 µg capsules once daily for inhalation supplied in blisters, delivered via manufacturer's proprietary inhalation device. Reference therapy: • tiotropium 18 µg capsules once daily for inhalation supplied in commercially available blisters, delivered via proprietary inhaler (HandiHaler®).
Efficacy assessments	Efficacy will be assessed using the following parameters: • Pre-dose (average of -45 min and -15 min) trough FEV_1 following 12-week treatment of QVA149 (110/50 µg) compared to tiotropium 18 µg. • Trough FEV_1 (pre-dose) at Week 4 after treatment. • Mean number of puffs of rescue medication use per day and days without rescue medication over the 12-week treatment period using patient diary. • Baseline dyspnea index (BDI)/TDI focal score at Week 12. • CAT score at Week 12. • [redacted]
Safety assessments	Safety will be assessed by the monitoring of adverse events (AEs), serious adverse events (SAEs), ECGs, vital signs and routine laboratory analyses.
[redacted]	
Data analysis	The primary objective of this study is to demonstrate the superiority of QVA 110/50 µg once daily compared to tiotropium 18 µg once daily in terms of trough forced expiratory volume in one second following 12 weeks of treatment. This will be analyzed for the Full Analysis Set using an analysis of covariance (ANCOVA) model, with treatment, smoking status as fixed effects, baseline trough FEV_1 as a covariate and center as a random effect. The superiority of QVA to tiotropium will be demonstrated if the p-value is less than 0.05 and the confidence interval lies entirely to the right of (higher than) 0 mL.

[redacted]

	In addition, the following variables will also be analyzed in a similar manner: pre-dose trough FEV_1 at Week 4; TDI focal score at Week 12; symptom control as assessed by total CAT score [redacted]; and rescue medication use reported by patients at Week 12. All safety endpoints (i.e. AEs, laboratory data, vital signs, and ECG) will be summarized by treatment for all patients in the safety set.
Key words	COPD, open-label, QVA149, symptomatic, tiotropium

[redacted]

Rationale for Amendment 1 (09-September-2015)

This amendment has been prepared to clarify prohibited medications and allowable concurrent medications which were strongly recommended by the investigators. The study has not yet started and this will not have any major impact on the study population and study results. The opportunity was also taken to remove ICS use in statistical analysis plan which was erroneously included.

[redacted]

Rationale for Amendment 2 (09-November-2015)

This amendment has been prepared to clarify some of the study procedures that would not affect primary and key secondary endpoints such as window period (Visit 2, 3), blood chemistry and SAE reporting details.

The study has not yet started and this will not have any major impact on the study population and study results. The opportunity was also taken to update patient diary in Appendix 3.

[redacted]

Rationale for Amendment 3 (10-Dec-2015)

This amendment has been prepared to change several study procedures such as window period of visit 2/3, reversibility test and providing investigational drug. The study has not yet started patient recruitment and this will not have any major impact on the study population and study results.

[redacted]

Rationale for Amendment 4 (18-Jun-2018)

This amendment has been prepared to reduce sample size due to low enrollment rate.

This amendment also incorporated some minor typographical errors corrections. Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions

Changes to the Protocol:

- Protocol author was changed.
- Due to low enrollment rate, sample size will be reduced to 182 patients in each treatment arm to a total of 364 patients, and the expected treatment difference between QVA149 110/50 µg once daily and tiotropium 18 µg was changed from 80 mL to 82 mL of pre-dose trough FEV1(L) after 12 weeks of treatment , in order to achieve 80% power on a 2-sided test with 5% level of significance. Assuming a dropout rate of 11%, approximately 409 patients will be enrolled in the study.
- Visit number correction
  - Screening period was changed from “Visit 1” to “Visit 0”
  - Visit 1 was amended to Visit 0 in Exclusion criteria: “Patients who have not achieved an acceptable spirometry result at (Visit ~~1~~0) in accordance with American Thoracic Society (ATS)/ European Respiratory Society (ERS) criteria for acceptability and repeatability.”
- Abbreviations in blood chemistry section were defined

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amended protocol are non-substantial and do not require IRB/IEC approval prior to implementation.

[redacted]

Rationale for Amendment 5 (13-Aug-2018)

This amendment has been prepared to correct the sample size calculation error in amendment 04. Changes to the Protocol:

- Due to low enrollment rate, sample size will be reduced to 173 patients in each treatment arm to a total of 346 patients, and the expected treatment difference between QVA149 110/50 µg once daily and tiotropium 18 µg was changed from 80 mL to 82 mL of pre-dose trough FEV1 (L) after 12 weeks of treatment, in order to achieve 80% power on a 2-sided test with 5% level of significance. Assuming a dropout rate of 11%, approximately 389 patients will be enrolled in the study.

[redacted]

1 Introduction

1.1 Background

Chronic Obstructive Pulmonary Disease (COPD) 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. It is a leading cause of morbidity and mortality worldwide and results in an economic and social burden that is both substantial and increasing. The prevalence and burden of COPD are projected to increase in the coming decades due to continued exposure to COPD risk factors and the changing age structure of the world's population with more people living longer. Goals for treatment of stable COPD are to reduce symptoms and future risks. Pharmacological therapy in COPD is used to relieve symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines describe that the selection of treatment regimen needs to be patient-specific as the relationship between severity of symptoms, airflow limitation, and severity of exacerbations will differ between patients (GOLD Guidelines, 2015).

Bronchodilator medications are central to symptom management in COPD. According to local market research data in Korea (Ipsos Korea 2014), 70 to 80% of COPD patients using an inhaled mono-bronchodilator still have the same or more symptoms despite treatment compared to when they were first diagnosed. A similar observation was reported in a primary care setting in the United Kingdom (UK) where a high proportion of GOLD Stage 2 COPD patients were symptomatic on their current treatment management (Price et al 2014). Tiotropium is the most widely used mono-bronchodilator in Korea. Combining bronchodilators of different pharmacological classes may improve efficacy and decrease the risk of side effects compared to increasing the dose of a single bronchodilator. The GOLD guidelines recommend the combined use of short-acting beta2 agonists (SABAs) or long-acting beta2 agonists (LABAs) and anticholinergics if symptoms are not improved with single agents (GOLD Guidelines, 2015).

QVA149 is a novel, inhaled fixed dose dual bronchodilator combination of the LABA indacaterol (QAB149) and the long acting muscarinic antagonist (LAMA) glycopyrronium (NVA237) for once-daily maintenance treatment of COPD. QVA149 was first marketed in Europe and Japan in 2013 and has since been marketed in many other countries worldwide including South Korea (since May 2014). QVA149 was the first once-daily dual bronchodilator to gain European Commission approval in Sep 2013 as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. In Japan, once-daily QVA149 (glycopyrronium 50 µg/indacaterol 110 µg) delivered through the Breezhaler® device, was simultaneously approved in Sep 2013 for the relief of various symptoms due to airway obstruction in COPD. The approvals of QVA149 in Europe and Japan were based on the comprehensive IGNITE Phase III clinical trial program, one of the largest international trial programs in COPD comprising 11 studies in total with more than 10,000 patients from 52 countries.

[redacted]

The Phase III clinical trials have shown that QVA149 provides significant and sustained improvement in lung function and health status compared with its mono components and tiotropium while having a similar safety profile (Bateman et al 2013, Beeh et al 2014, Wedzicha et al 2013).

In this study, the efficacy and safety of QVA149 will be compared to that of tiotropium in COPD patients with mild to moderate airflow limitation with low exacerbation risk (Patient Group B by GOLD Guideline 2015) and who are currently receiving tiotropium but still symptomatic, which is defined as COPD assessment test (CAT) scores ≥ 10. According to GOLD guideline 2015, CAT scores ≥ 10 are associated with significantly impaired health status. Patients will be randomized and treated with either QVA149 or tiotropium monotherapy for 12 weeks.

1.2 Purpose

The purpose of this Phase IV study is to show that QVA149 (110/50 µg) once daily results in better lung function and airflow compared to tiotropium 18 µg once daily in patients with mild to moderate symptomatic COPD; and to assess the effect of both treatments on symptom burden, breathlessness, and use of rescue medication in these patients.

2 Study objectives

2.1 Primary and key secondary objectives

To demonstrate superiority of QVA149 (110/50 µg) once daily compared to tiotropium 18 µg once daily in terms of trough forced expiratory volume in 1 second (FEV_1) (mean of 45 min and 15 min pre-dose) following 12 weeks of treatment in mild to moderate symptomatic COPD patients.

2.2 Secondary objectives

To evaluate the effect of QVA149 (110/50 µg) as compared to tiotropium 18µg on:

- Pre-dose trough FEV_1 at Week 4.
- Transitional dyspnea index (TDI) focal score at Week 12.
- Symptom control as assessed by total CAT score at Week 12.
- Rescue medication used reported by the patients at Week 12.
- Safety and tolerability.

[redacted]

3 Investigational plan

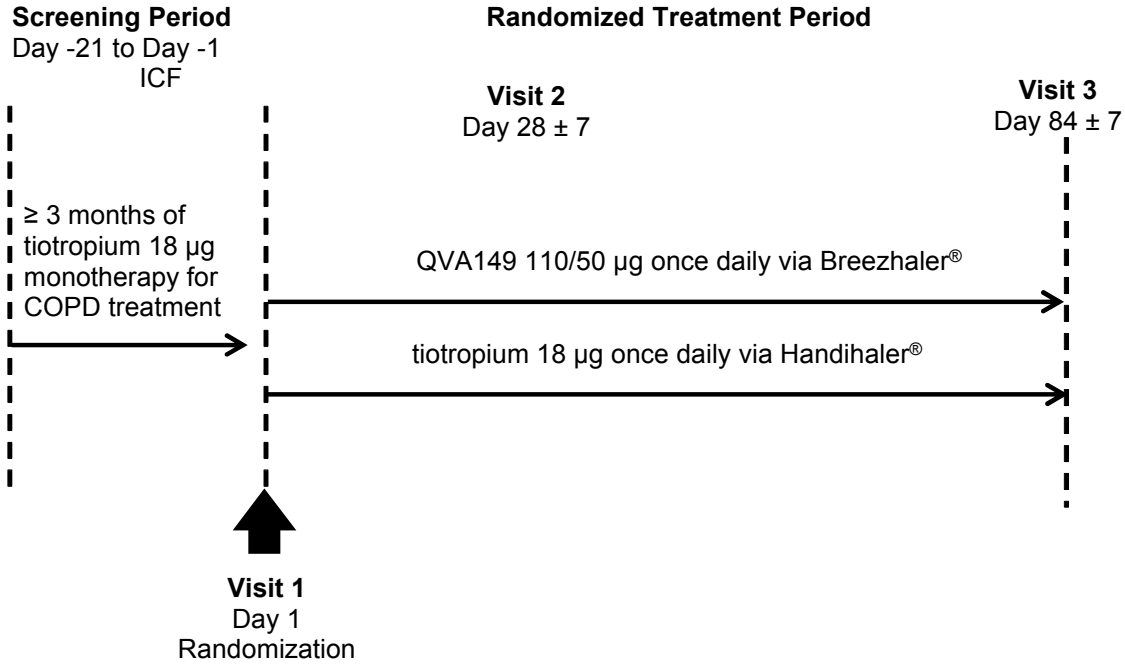
3.1 Study design

This is a randomized, multicenter, open-label, parallel-group, 12-week study to assess the efficacy and safety of QVA149 (indacaterol maleate/glycopyrronium bromide) versus tiotropium in symptomatic mild to moderate COPD patients. A screening period of 3 weeks (21 days) will be used to assess patient eligibility. At the Baseline visit (Visit 1/ Day 1), eligible patients will be randomized to one of the following treatment groups and treated for 12 weeks:

- QVA149 (110/50 µg once daily)
- tiotropium 18 µg once daily.

The assessment to address the primary objective will be performed at Week 12. The study design is presented in Figure 3-1. Further details are provided below.

Figure 3-1 Study design



Screening Period (Day -21 to Day -1)

During the 21-day screening period (Visit 0), informed consent will be obtained and inclusion/exclusion criteria will be assessed. Current COPD medications will be reviewed. If the patient is taking a COPD therapy prohibited by the protocol, that COPD therapy will be adjusted to an allowable COPD therapy. Patient demographics, medical history including history of cardiovascular risk factors, COPD exacerbation history as well as smoking history will be collected. Vital signs will be checked and a 12-lead electrocardiogram (ECG) will be performed. Furthermore, blood and urine samples will be collected for analysis and a

[redacted]

pregnancy test with urine sample will be applied at this visit. Patients are required to be taking tiotropium monotherapy for ≥ 3 months prior to randomization.

Spirometry measurements will be taken to assess patient eligibility for the study and to assess the post-bronchodilation FEV_1 10 to 15 mins after inhalation of 4 x 100 µg puffs of salbutamol.

To allow for a reliable reversibility test and classification of airflow limitation according to GOLD 2015 (Appendix 4), the test has to be performed 24 hours after the last dose inhalation of tiotropium.

At the start of screening (Visit 0), patients will be provided with salbutamol inhaler, which they will be instructed to use throughout the study as rescue medication. Patients will be asked, where possible, not to take rescue medication within the 6 hours prior to and during the study visit. If rescue medication is taken within 6 hours, the visit should be re-scheduled and the number of puffs of rescue medication taken recorded in the patient diary (Appendix 3). Any rescue medication taken within the study visit will be recorded in the spirometer and the number of puffs will be recorded in the patient diary.

A patient diary (Appendix 3) will be distributed and patients will be asked to document the use of rescue medication throughout the study.

The CAT will be collected; patients must have a CAT score ≥ 10 to be included in this study.

The interval between Visit 0 and Visit 1 is an individual screening period used to determine eligibility of the patients for the study and is dependent on the current medication and the time it takes until the laboratory evaluation is available.

Randomization

At Visit 1 (Day 1), patient eligibility will be checked versus the study inclusion/exclusion criteria. Medical history and medication history will be checked and current medications will be reviewed and adjusted. A physical examination will be performed and vital signs will be checked.

The CAT will be collected; patients must have a CAT score ≥ 10 to be included in this study.

At Visit 1 (Day 1), spirometry measurements will be taken to assess the FEV_1 between 45 and 15 minutes prior to dosing. The first dose of study drug will be administered in the clinic at Visit 1 (Day 1). Patients will be instructed *not* to take their study medication at home on the day of the clinic visit as this will be administered in the clinic.

All patients should refrain from strenuous activity, avoid caffeine and alcohol for 4 hours prior to spirometry and should not smoke at least 1 hour before spirometry.

A baseline dyspnea index (BDI) assessment [redacted] will also be performed. All patients who meet the inclusion/exclusion eligibility criteria will be randomized equally to receive either QVA149 or tiotropium.

Patients will be required to take their study drug once a day between 08:00 am and 11:00 am. Subsequent clinic visits should be scheduled such that individual patients are re-assessed at approximately the same time each day.

[redacted]

Patients will attend a further 2 visits on Day 28 (Visit 2) and Day 84 (Visit 3) and should be seen for all visits on the designated day or as close as possible to that day. Visit window ± 7 days will be allowed. Spirometry tests to assess the FEV_1 between 45 and 15 minutes prior to dosing will be performed for all patients at Visit 2 and Visit 3 (primary endpoint). In addition, TDI and CAT assessments will be performed at these visits. Other assessments will be performed as outlined in Table 6-1.

[redacted]

3.2 Rationale of study design

QVA149 is marketed in Korea (as well as the UK, Japan and other countries worldwide) as a once-daily bronchodilator for the maintenance treatment of COPD.

A multicenter, randomized, open-label parallel design was considered appropriate to demonstrate the superiority of QVA149 (110/50 µg once daily) versus tiotropium (18 µg once daily) in patients with mild to moderate symptomatic COPD in this Phase IV study.

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

The dose/regimen and route of administration of QVA149 in this study is indacaterol maleate/glycopyrronium bromide 110/50 µg for once-daily inhalation using a single-dose dry powder inhaler (SDDPI) device is in accordance with the clinical trial program with QVA149 and with the product label (Summary of Product Characteristics for XOTERNA ™ BREEZHALER®). The selection of QVA149 dose in the clinical trial program (110/50 µg once daily) was based on data from the QAB149 and NVA237 monotherapy programs. Those programs identified the doses as 150 µg once daily for QAB149, and 50 µg once daily for NVA237. However, in formulating the QVA149 combination product, an increase in fine particle (respirable) fraction was observed for the QAB149 component (compared with the monotherapy). As a consequence, to ensure that the fine particle dose of QAB149 delivered to the lung from the combination matches that delivered from the monotherapy, the dose for the QAB149 component of QVA149 was reduced to 110 µg.

The tiotropium dose of 18 µg once daily selected for this study is the licensed dose and the standard treatment for COPD. The duration of 12 weeks is considered an adequate time to establish the superiority of QVA149 over tiotropium as it is a clinically meaningful period to assess lung function. Furthermore, patients assigned to QVA149 will already have received tiotropium for at least 12 weeks prior to entering the study, which is long enough to allow patient familiarization with both treatments [redacted].

3.4 Rationale for choice of comparator

According to the current GOLD guidelines (GOLD Guidelines, 2015) one of the first choice treatment options for COPD patients categorized in Group B is monotherapy with a LAMA. This study will test the effect of an alternative therapy as recommended in the guidelines

[redacted]

consisting of a LABA/LAMA combination (QVA149) in terms of lung function [redacted] in patients who are symptomatic despite maintenance treatment with a LAMA. As tiotropium is currently the most widely used LAMA in COPD treatment in Korea, this drug was chosen as the most suitable comparator in this study.

3.5 Purpose and timing of interim analyses/design adaptations

Not applicable.

3.6 Risks and benefits

The latest Developmental Safety Update Report (DSUR: Issue 004) indicated no new benefits or safety concerns during the reporting period (25-Oct-2013 to 24-Oct-2014). The key benefits of QVA149 in patients with COPD, as reported in the latest DSUR, are as follows:

- Improvement of lung function/bronchodilation (increase in FEV_1).
- Improvement of dyspnea (TDI).
- Reduction of COPD symptoms (over treatment period).
- Reduction of COPD exacerbations.
- Improvement of health status (St. George's Respiratory Questionnaire (SGRQ) total score).
- Use of rescue medication (over treatment period).

Combining 2 bronchodilators with different pharmacodynamics properties has demonstrated enhanced efficacy compared with single agents and placebo without increasing adverse effects. QVA149, administered once-daily, provided superior improvements in lung function in comparison with placebo as well as its mono-components, indacaterol and glycopyrronium. Improvement in pre-dose trough FEV_1 was both statistically and clinically significant (ε100 mL in COPD) over placebo; versus active comparators, it approached clinical significance. Furthermore, lung function improvements with QVA149 were superior in terms of peak FEV_1 and, in a subset of patients monitored over 24 hours, throughout the day. Similar findings were observed in all relevant subgroups analyzed. Improvements in lung function versus placebo were greater in patients with moderate versus severe COPD; however, statistically and clinically significant improvements in trough FEV_1 were seen for both moderate and severe patient subgroups. Improvements in lung function were not influenced by patient age, sex or concurrent use of inhaled corticosteroids. Furthermore, these improvements in lung function were maintained throughout the 26-week and up to a 64-week treatment period. The onset of action of QVA149 was confirmed to be rapid, with effects seen at 5 minutes after the first dose, similar to that of SABAs.

These beneficial effects of QVA149 on lung function were paralleled by statistically significant improvements in other clinically important endpoints: dyspnea, patient symptoms, health status and reduced rescue medication use. QVA149 was significantly superior to placebo for both the TDI and quality of life (QoL) measured by the SGRQ total score at Week 26 and up to 64 weeks; no other active treatment achieved a significant improvement in SGRQ versus placebo. Furthermore, a significantly higher proportion of patients on QVA149 achieved a clinically meaningful improvement in TDI (> 1 unit) and SGRQ (> 4 units) versus placebo. In a study specifically designed to examine the effect of QVA149 on exacerbations, QVA149 significantly reduced the rate of moderate to severe COPD exacerbations by 12%

[redacted]

compared with NVA237 (study CQVA149A2304). Furthermore, QVA149 significantly reduced the rate of all exacerbations (mild/moderate/severe) as compared to NVA237 by 15%. The 'Number Needed to Treat' to prevent one additional moderate or severe exacerbation over 1 year in the QVA149 group was determined as 8 versus NVA237. Reducing the number of exacerbations substantially impacts on patient's overall well-being and may affect disease progression.

The safety profile of QVA149 is determined by the safety associated with its monotherapy components, indacaterol and glycopyrronium. Thus, a safety review needs to consider both pharmacological classes, i.e. β2-adrenergic agonists as well as antimuscarinics. A desired outcome in combining bronchodilators with different pharmacodynamic properties would be an increase in the degree of bronchodilation without an increase in adverse effects. Under consideration of the importance of the cardio-cerebrovascular (CCV) safety concerns associated with the use of both β2-adrenergic agonists and antimuscarinics, the key risks of QVA149 in patients with COPD are as follows:

- Cardiac arrhythmia.
- Cardiac failure.
- Cerebrovascular events.
- Ischemic heart disease.
- Myocardial infarction.
- Atrial fibrillation/flutter.

In the development program to date, the rates between QVA149 and placebo were found to be balanced across all risks. All CCV risks are identified risks (as per the Risk Management Plan).

QVA149 combines different pharmacological mechanisms resulting in greater and more sustained bronchodilation as compared to monotherapy. This therapeutic principle may also decrease the risk of AEs associated with increasing doses of single bronchodilators, or other treatment options such as combinations with inhaled corticosteroids (ICS).

The key benefits of QVA149 in COPD patients continue to be statistically significant and clinically meaningful with respect to improvements of airway obstruction, relief of dyspnea, reduction of rescue medication use, improvements in QoL, and the reduction of COPD exacerbations. The degree of CCV risk for QVA149 is comparable to those of the monotherapy components; no additive or potentiating effects have been observed or reported.

In summary, strong evidence from clinical trials support the concept that dual bronchodilation via QVA149 provides significantly improved clinical efficacy in patients with COPD as compared to monotherapy with LABAs or LAMAs. Of note, the safety profile of the fixed-dose combination is comparable to that of the monotherapy components, indacaterol and glycopyrronium, and often not different from placebo.

4 Population

The study population will consist of approximately 389 male and female adults aged 40 or older, with a confirmed clinical diagnosis of COPD and post-bronchodilator $FEV_1 \geq 50\%$ of

[redacted]

the predicted normal value and post-bronchodilator $FEV_1/FVC < 0.7$ (COPD Grade 1 or 2 by severity of airflow limitation (GOLD Guidelines, 2015)) and a smoking history of at least 10 pack years.

4.1 Inclusion criteria

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

1. Written informed consent must be obtained before any assessment is performed.
2. Male or female adults aged ≥ 40 years, who have signed an Informed Consent Form (ICF) prior to initiation of any study-related procedure.
3. Confirmed diagnosis of COPD and post-bronchodilator $FEV_1 \geq 50\%$ of the predicted normal value and post-bronchodilator $FEV_1/FVC < 0.7$ (COPD Grade 1 or 2 by severity of airflow limitation (GOLD Guidelines, 2015). Current or ex-smokers who have a smoking history of at least 10 pack years. (Ten pack-years are defined as 20 cigarettes a day for 10 years, or 10 cigarettes a day for 20 years etc.)
4. Patients with CAT score ≥ 10 at Visit 0 and Visit 1.
5. Patients who are on and have been on tiotropium 18 µg monotherapy for the past 3 months prior to baseline (Visit 1).
6. 0 or 1 COPD exacerbation in the previous 12 months prior to baseline (Visit 1) (not leading to hospital admission).

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.

General exclusion criteria

1. Treatment with any ICS in the 3 months prior to Visit 1.
2. 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 human chorionic gonadotropin (hCG) laboratory test.
3. 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 6 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 months prior to Screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient.

[redacted]

- 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 6 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.

4. Presence of any contraindication, warning, precaution, hypersensitivity to LABA and LAMA.
5. History or current diagnosis of clinically significant ECG abnormalities including:
   - 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*.
6. Patients who have not achieved an acceptable spirometry result at (Visit 0) in accordance with American Thoracic Society (ATS)/ European Respiratory Society (ERS) criteria for acceptability and repeatability.
7. Patients with Type I or uncontrolled Type II diabetes.
8. Patients with narrow-angle glaucoma, symptomatic prostatic hyperplasia or bladder-neck obstruction or moderate to severe renal impairment or urinary retention. (Patients with a transurethral resection of prostate (TURP) are excluded from the study. Patients who have undergone full re-section of the prostate may be considered for the study, as well as patients who are asymptomatic and stable on pharmacological treatment for the condition).
9. History of malignancy of any organ system, treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases with the exception of localized basal cell carcinoma of the skin.
10. Patients with a history of clinically significant diseases that, in the opinion of the Investigator, would put the safety of the patients at risk through study participation, or would compromise patient compliance or preclude completion of the study.
11. Uncontrolled hypothyroidism and hyperthyroidism, hypokalemia.
12. Patients with neurological, endocrine, immunological, psychiatric, gastrointestinal, hepatic, or hematological abnormalities which, in the opinion of the Investigator, could interfere with the assessment of the efficacy and safety of the study treatment.

[redacted]

13. Patients who are, in the opinion of the investigator, known to be unreliable or non-compliant.

COPD specific exclusion criteria

1. Patients requiring long-term oxygen therapy prescribed for > 12 hours per day.
2. COPD exacerbation between Visit 0 and 1. Patients can be re-screened after a minimum of 6 weeks after resolution of the exacerbation if the exacerbation did not require hospitalization. If a patient has an exacerbation that requires hospitalization between Visit 0 and Visit 1 then he/she is not eligible to re-screen.
3. Onset of respiratory symptoms, including a COPD diagnosis prior to age 40 years.
4. Patients with a history of respiratory infection within 4 weeks prior to Visit 0. Patients who develop a respiratory tract infection between Screening and prior to treatment will not be eligible but will be permitted to be re-enrolled 4 weeks after the resolution of the respiratory tract infection.
5. Concomitant pulmonary disease (e.g. pulmonary tuberculosis (unless confirmed by chest X-ray to be no longer active), lung fibrosis, sarcoidosis, interstitial lung disease, primary pulmonary hypertension, clinically significant bronchiectasis).
6. Patients with lung lobectomy, or lung volume reduction or lung transplantation
7. Prior or current diagnosis of asthma.

Medication exclusion

1. Treatments for COPD and allied conditions: the following class of medications should be washed out prior to randomization (Visit 1) or prohibited during the study period (see Table 5-1).
2. Patients who need the following treatments for COPD and allied conditions (e.g. allergic rhinitis) unless they have been stabilized for the specified period and the stated conditions have been met (see Table 5-2).
3. Patients who have had live attenuated vaccinations within 30 days prior to the screening visit. Inactivated influenza vaccination, pneumococcal vaccination or any other inactivated vaccine is acceptable provided it is not administered within 48 hours prior to screening and randomization visits.
4. Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of Visit 1, whichever is longer.
5. Patients unable to use a dry powder inhaler (e.g. SDDPI, HandiHaler®) device or pressurized metered dose inhaler (MDI) (rescue medication).

5 Treatment

5.1 Protocol requested treatment

5.1.1 Investigational treatment

- QVA149 110/50 µg capsules once daily for inhalation supplied in blisters, delivered via the manufacturer's proprietary inhalation device.

[redacted]

QVA149 capsules will be supplied by Novartis Drug Supply Management as open-label medication packs, providing sufficient quantity of medication to ensure therapy according to the protocol. Under no circumstances is an alternative inhalation device to be used for the administration of QVA149 capsules; the manufacturer's proprietary inhalation device.

5.1.2 Reference treatment

- tiotropium 18 µg capsules once daily for inhalation supplied in commercially available blisters, delivered via proprietary inhaler (HandiHaler®).

A sufficient quantity of open-label medication will be provided to each patient to ensure therapy according to the protocol. Only the HandiHaler® device should be used for the administration of tiotropium.

5.1.3 Additional study treatment

Rescue medication with salbutamol, a SABA, is permitted in this study (Section 5.5.6). At Visit 0, all patients will be provided with a SABA (salbutamol) which they will be instructed to use throughout the study as rescue medication on an 'as needed basis'. Patients should be instructed to abstain from taking rescue salbutamol within 6 hours of the start of each visit unless absolutely necessary. If rescue medication is taken within 6 hours of a spirometry visit, the visit should be re-scheduled and the number of puffs of rescue medication taken recorded in the patient diary.

Use of rescue medication (number of puffs taken in the previous 24 hours) will be recorded daily in the morning by the patient in the patient diary.

Salbutamol (100 µg will be supplied to the investigator sites locally by Novartis.

Concomitant medications and prohibited medications are described in Section 5.5.7 and Section 5.5.8, respectively.

5.2 Treatment arms

Patients will be assigned to treatment for 12 weeks with either open-label QVA149 110/50 µg or tiotropium 18 µg in a 1:1 ratio as follows:

- Open-label QVA149 110/50 µg once daily delivered via SDDPI.
- tiotropium 18 µg once daily delivered via the manufacturer's proprietary inhalation device (Handihaler®).

5.3 Treatment assignment, randomization

At Visit 1, all eligible patients will be randomized via the interactive randomized technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming 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 study drug to be dispensed to the patient.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient

[redacted]

randomization list will be produced 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 study drug packs containing each of the study drugs.

The randomization scheme for patients will be reviewed and approved by a qualified team member.

5.4 Treatment blinding

Not applicable.

5.5 Treating the patient

5.5.1 Patient numbering

Each patient is uniquely identified by a Patient Number which is composed by the center number assigned by Novartis and a sequential number assigned by the investigator. Once assigned to a patient, the Patient Number will not be reused.

Upon signing the ICF, the patient is assigned the next sequential number by the investigator. The investigator or his/her staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. The site should select the eCRF book with a matching Patient Number from the Electronic Data Capture (EDC) system to enter data. If the patient fails to be treated for any reason, the IRT must be notified within 2 days that the patient was not treated. The reason for not being treated will be recorded in the Screening Phase Disposition eCRF.

5.5.2 Dispensing the investigational treatment

Each study site will be supplied by Novartis with the following open-label study treatment:

- QVA149 110/50 µg will be supplied as medication packs containing blister strips of capsules and one SDDPI device.
- Tiotropium 18 µg will be supplied as medication packs containing blister strips of capsules and one HandiHaler® device.

Sufficient medication will be dispensed at Visit 1 (Day 1) and Visit 2 (Day 28) to cover the treatment period between patient visits and to allow for late visits and other unforeseen events.

The investigational treatment packaging has a 2-part label. A unique medication (kit) number is printed on each part of this label which corresponds to one of the 2 treatments. 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.

[redacted]

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

At randomization - Visit 1

Investigator staff will contact the IRT to randomize the patient and identify the specific medication pack number assigned to patients randomized to the QVA149 or tiotropium.

One open-label medication box containing QVA149 or tiotropium will be dispensed at this visit for patients randomized to QVA149 or tiotropium, respectively.

Visit 2 and Visit 3

The patient's study drug supplies should be checked at each visit and the Drug Accountability Log (Section 5.5.3) completed for that patient, as necessary.

Additional study drug should be dispensed when scheduled according to the Assessment Schedule (Table 6-1) and at other times, if required, due to unexpected events. Study center personnel should ensure that patients always have more than sufficient study medication to last until the next scheduled visit and must always call the IRT to obtain the specific medication pack numbers to be issued before dispensing supplies.

The duration between visits is 4 weeks (Visit 1 to Visit 2) and up to 8 weeks (Visit 2 to Visit 3). Sufficient tiotropium medication packs must be dispensed to last the duration between visits.

One SDDPI inhaler will be included in the QVA149 medication packs.

One Handihaler® inhaler will be included in the tiotropium medication packs.

At Visit 1 and Visit 2, all patients will be provided with 2 packs of study medication according to randomized treatment arms. At Visit 2, patients must bring back all used and unused study medication. After checking compliance, unused study medication will be returned to the patient. At Visit 3, all used and unused study medication must be returned.

5.5.3 Handling of study treatment

5.5.3.1 Handling of investigational treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all investigational treatment should be stored according to the instructions specified on the labels. 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 study treatment but no information about the patient except for the medication number. Study treatment should not be stored above 25°C and should be protected from moisture.

The investigator must maintain an accurate record of the shipment and dispensing of investigational treatment in a drug accountability log. Monitoring of drug accountability will be performed by the field monitor during site visits and at the completion of the trial. Patients

[redacted]

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.

5.5.4 Instructions for prescribing and taking study treatment

QVA149 110/50 µg and tiotropium bromide 18 µg will be provided as open-label study treatment.

Medication labels will comply with the legal requirements and be printed in the local language. They will supply no information about the patient. The storage conditions for study drug will be described on the medication label.

Patients will be instructed to come to the clinic in appropriate time to complete pre-dosing assessments and to allow randomized study medication to be taken in the morning between 08:00 and 11:00. Patients must be instructed to withhold the use of SABA (rescue medication) for at least 6 hours prior to all clinic visits, unless the use is absolutely necessary.

At Visit 1 (Day 1), patients will be randomized to one of the 2 treatment arms.

Patients will be instructed on how to use the study treatment SDDPIs. The instructions for use for the SDDPI for QVA149 110/50 µg administration are presented in Appendix 6. The instructions for use for the proprietary inhaler (Handihaler®) for tiotropium bromide 18 µg administration are presented in Appendix 7.

At Visit 2 and Visit 3 (randomized treatment) the study medication will be administered in the clinic by the investigator between 08:00 and 11:00 h, after completion of all pre-dose procedures.

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

All used and unused study medication must be returned by the patient at Visit 2 and Visit 3.

The date and time of dose administration at each clinic visit will be recorded on the Dosage Administration Record eCRF.

All medication kits assigned by the IRT will be recorded in the IRT.

5.5.5 Permitted dose adjustments and interruptions of study treatment

No adjustments to the study drug dosage or dosing scheme are permitted, other than temporarily interrupting study medication during the treatment period due to an AE (including mild COPD exacerbations), if necessary.

However, 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 should be

[redacted]

discussed with the Novartis Medical Monitor to determine the patient's eligibility to continue study participation.

These changes must be recorded on the Dosage Administration Record eCRF.

5.5.6 Rescue medication

At Visit 0, all patients will be provided with a salbutamol (containing chlorofluorocarbon-free propellant – hydrofluorocarbon 134a) inhaler, which they will be instructed to use throughout the study as rescue medication. Nebulized albuterol is not allowed as a rescue medication. Salbutamol (100 µg) will be supplied to the investigator sites locally by Novartis. Patients should be instructed to abstain from taking rescue salbutamol within 6 hours of the start of each visit unless absolutely necessary.

If rescue medication is taken within 6 hours prior to spirometry at Visit 1 or prior to administering study medication at any of the scheduled visits, the visit should be rescheduled to the next possible day. The investigator must use their judgment when deciding how many times a visit for an individual patient should be rescheduled for Visit 2 and Visit 3.

In the event that a patient uses a dose of rescue medication after taking study medication at that visit or during any other visits then the visit should continue as planned but the approximate time taken will be captured through the spirometer if taken during a study visit and the number of puffs collected in the Patient Diary.

5.5.7 Concomitant treatment

All medications and significant non-drug therapies administered 30 days prior to Visit 0 (Day -21 to Day -1) and Visit 1 (Day 1) will be recorded in the eCRF.

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

5.5.8 Prohibited treatment

The classes of medications listed in Table 5-1 **are NOT allowed to be taken during the study unless part of the study medication e.g. tiotropium.** Some medications (Table 5-2) 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 medications

Class of medication	Minimum washout period prior to Randomization (Visit 1)
Non-potassium sparing diuretics (unless administered as a fixed dose combination with a potassium conserving drug)	7 days
Cardiac antiarrhythmics class Ia, III	7 days,

[redacted]

	Amiodarone 3 months
Any other drug with potential to significantly prolong the QT interval (e.g. mizolastin) (macrolide antibiotics recommended under Section 6.4.6 for the treatment of COPD exacerbation are allowed)	14 days or 5 half-lives, whichever is longer
Other investigational drugs (Please note that investigational drugs should be washed out prior to V1)	30 days or 5 half-lives, whichever is longer
Systemic non-selective beta- blocking agents	7 days
Tricyclic antidepressants, Serotonin Norepinephrine reuptake inhibitors (SNRIs), Monoamine oxidase inhibitors	14 days
Other noradrenaline reuptake inhibitors	7 days
Theophylline and other Xanthines	7 days
Systemic anticholinergics	7 days
Short acting anticholinergics	8 hours
Short-acting β2 agonists (other than study rescue medication)	6 hours
Phosphodiesterase inhibitors (PDE-4), (e.g. roflumilast)	7 days
Parenteral or oral corticosteroids (allowed for the treatment of COPD exacerbation but should be discontinued at the resolution of the exacerbation)	30 days
Intra-muscular depot corticosteroids	3 months

Table 5-2 Medication allowed under certain conditions

Class of medication	**Condition**
Selective serotonin reuptake inhibitors (SSRIs)	Treatment regimen has been stable for at least one month prior to screening visit and during the study Screening ECG is normal with no clinical evidence of prior ECG abnormalities
Inactivated vaccine	Not administered within 48 hours prior to a study visit
Cromoglycate, Leukotriene antagonists, Ketotifen, Nedocromil	In constant doses and dose regimens for at least 5 days prior to Screening

5.5.9 Discontinuation of study treatment and premature patient withdrawal

Patients who discontinue their randomized study regimen should remain in the study, if possible, and receive standard therapy, according to local practice, until completing the study at Week 12. Visits and assessments for such patients are described in Table 6-1.

The study drug must be discontinued and the patient withdrawn from the trial if the investigator determines that continuing it would result in a significant safety risk for the patient.

Study treatment *must* be discontinued and the patient withdrawn from the trial under the following circumstances:

[redacted]

- Withdrawal of informed consent.
- Adverse events for which continued inhalation of the study drug would be detrimental.
- Abnormal test procedure results indicating risk for the patient on continued inhalation of the study drug.
- Pregnancy.
- If a COPD exacerbation is being treated with intra-muscular depot corticosteroids (e.g. Depo-Medrone®).

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

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

If a patient experiences a COPD exacerbation he/she will be treated as deemed appropriate by the investigator. Guidance for treating exacerbations is described under Section 6.4.6. Following treatment for the exacerbation the patient will be expected to continue in the study if, in the opinion of the investigator, he/she can be safely returned to their pre-exacerbation concomitant medications.

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

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

The Investigator must also notify the IRT of the premature withdrawal.

For patients who are lost to follow-up (i.e. those 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 documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc.

Patients who are prematurely withdrawn from the study will not be replaced by an equal number of newly enrolled patients.

5.5.10 Emergency breaking of treatment assignment

Not applicable.

5.5.11 Study completion and post-study treatment

Completion of the study for an individual patient will be when he/she has completed 12 weeks of treatment (through Visit 3). Completion of the study will be when all randomized patients have completed the study or have been prematurely withdrawn.

[redacted]

Patients completing the 12-week treatment period will not be given further access to the study drug.

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.

When the patient has completed all scheduled study assessments, the Investigator must call the IRT to record the patient completion.

5.5.12 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and treated as described in Section 5.5.9 (premature patient withdrawal). 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 Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) of the early termination of the trial.

6 Visit schedule and assessments

Table 6-1 lists all of the assessments and indicates with an "X or S" the visits at which they are performed. All data obtained from these assessments must be supported in the patient's source documentation. At a minimum, patients will be contacted for safety evaluations (AEs/SAEs, death) during the 30 days following the last study visit. Documentation of attempts to contact the patient should be recorded in the source documentation.

Patients should be seen for all visits on the designated day or as close to it as possible. Visit window ± 7 days will be allowed. These visits must be scheduled to start in the morning between 8:00 and 11:00 h. All data obtained from these assessments must be supported in the patient's source documentation.

All patients are screened for study suitability. At Visit 0, informed consent is obtained and patients registered with the IRT by center personnel. The current COPD medications are reviewed and if necessary arrangements made to adjust prohibited COPD therapy to allowable COPD therapy. Medical history including history of cardiovascular risk factors will also be collected at this visit. Patients will undergo investigations including beta-2 agonist reversibility tests.

Patients who meet the inclusion/exclusion criteria at the screening visit will be given a patient diary to capture daily symptoms and rescue medication use at Visit 0.

At Visit 1, patients who still fulfil the inclusion/exclusion criteria will be randomized to QVA149 110/50 µg or tiotropium 18 µg once daily via the IRT.

Patients must be reminded not to take study medication prior to **ALL** clinic visits, as this dose will be administered in clinic after all pre-dose measurements have been performed.

This data is to be captured on the eCRF.

The site must register the patient's premature withdrawal with the IRT.

[redacted]

When the following assessments are scheduled to be performed at the same time point, the order of priority will be as follows: CAT, ECG, pulse rate, blood pressure, and blood sample/urine samples, spirometry. Spirometry measurements should occur at the scheduled time points and other tests should be performed as close as possible to the spirometry times.

Patients will be asked to refrain from the following prior to spirometry:

- Caffeine-containing beverages (such as coffee, tea, cola) and food (such as chocolate), and ice cold beverage for 4 hours prior to spirometry.
- Alcohol for 4 hours prior to spirometry.
- Strenuous physical activity for 12 hours prior to spirometry.
- Exposure to environmental smoke, dust or areas with strong odors.

Patients should not smoke for at least 1 hour before the scheduled time of the clinic visit and should be asked to refrain from smoking during the visit until all assessments are completed for the visit.

[redacted]

Table 6-1 Assessment schedule

Study Period	**Screen**	**RND**	**Treatment**		**PSW**
Visit Number	**0**	**1**	**2**	**3**	
Visit	**SCR**	**BL**	**W4**	**W12**	
Day	**-21 to -1**	**1**	**28 ±7**	**84 ± 7**	
Informed consent form[1]	X				
Medical history and medication history	X	X			
Height and Weight[2]		X		X	X
Smoking history	X				
Review/adjustment of current medication	X	X			
Pregnancy test[3]	X			X	X
Laboratory evaluations[4]	X		X	X	X
Demographics	X				
Vital signs[5]	X	X	X	X	X
12-lead ECG	X		X	X	X
Inclusion/exclusion criteria	X	X			
Reversibility test	X				
Issue & instruct on paper diary	X				
Review diary		X	X	X	X
Spirometry		X	X	X	X
Provide rescue medication	X	As needed			
Check use of rescue medication		X	X	X	X
Randomization		X			
Instruction on inhaler usage		X			
Study drug dose administration record		X	X	X	
BDI assessment		X			
TDI assessment			X	X	X
CAT assessment	X	X	X	X	X
COPD exacerbation	X	X	X	X	X
[redacted]					
Adverse events[6]		X	X	X	X
[redacted]					
Concomitant medication		X	X	X	X
Surgical and medical procedures	As needed				
Record any patient deaths	As applicable				
Withdrawal of informed consent	As needed				
Week 12 period completion[7]		As needed		X	
Physical examination		S		S	S
IRT call	S	S	S	S	S
Dispense study treatment		S	S		

[redacted]

Abbreviations: BDI: baseline dyspnea index, CAT: COPD assessment test, COPD: chronic obstructive pulmonary disease, ECG: electrocardiogram, IRT: interactive randomized technology, [redacted], PSW: premature study withdrawal, RND: randomization, RDN: randomization, TDI: transitional dyspnea index

X=assessment for all patients in study regardless of on or off randomized study regimen, to be recorded in clinical data base

S=assessment to be recorded on source documentation

1. Informed consent should be obtained prior to performing any study-related procedures.
2. Height and weight will be recorded on Day 1. Weight will be recorded again at Week 12 and in the event of premature study withdrawal.
3. It will be conducted only in women of childbearing potential and the urine test can be performed according to local practice. Local result must be available and negative prior to randomization.
4. Laboratory evaluations:

   Hematology: white blood cells (WBC) (total and differential), red blood cells, hemoglobin, hematocrit, platelets.

   Blood chemistry: Albumin, alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), calcium, total cholesterol, lactate dehydrogenase (LDH), magnesium, phosphate, sodium, potassium, creatinine, γ-GT, blood glucose, total protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), low-density lipoprotein-cholesterol (LDL-C) and high-density lipoprotein-cholesterol (HDL-C).

   Urinalysis: pH, specific gravity, protein, glucose, ketones, bilirubin, blood, urobilinogen, nitrate, and WBC.
5. For vital signs, systolic blood pressure, diastolic blood pressure and heart rate will be assessed.
6. Every SAE, occurring after informed consent and until 30 days after the patient has stopped study participation (defined as time of last dose of study drug taken or last visit, whichever is later) must be reported to Novartis).
7. All subjects are expected to continue in the study to Week12 regardless of whether they are on or off randomized study regimen, if subjects discontinue randomized study regimen they should continue on standard of care and attend study visits to W12, if possible. For all subjects completing the study to Week 12 or discontinuing from the study prior to Week 12, the W12 Period completion form should be completed, regardless of on or off-treatment status.

6.1 Information to be collected on screening failures

All patients who have signed informed consent but not entered into the next period will have the study completion page for the Screening period, demographics (date of birth, age, sex, race and ethnicity), inclusion/exclusion and SAE data collected. The Patient Number and primary reason for not continuing the study will also be recorded. Adverse events that are not SAEs will be followed by the Investigator and collected only in the source data.

All patients who have signed informed consent and are entered into the next period of the study will have all AEs **occurring after informed consent is signed** recorded on the AE eCRF.

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

[redacted]

6.2 Patient demographics/other baseline characteristics

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

- Date of birth
- Sex
- Height
- Weight
- Date of diagnosis of COPD
- Relevant medical history. History of cardiovascular risk factors will also be collected.
- Smoking history (1 pack year = 20 cigarettes/day × 1 year or 10 cigarettes/day × 2 years)
- Prior concomitant medications (COPD related and non-COPD related)
- Baseline physical examination (not databased other than in the context of relevant medical history)
- Vital signs
- ECG findings
- Screening spirometry (FEV_1 and FVC).
- FEV_1 and FVC after reversibility test with 4 × 100 µg puffs of salbutamol.

6.3 Treatment exposure and compliance

The time of study drug administration at each dosing visit will be collected on the eCRF. For assessments where spirometry is performed, the time of dosing is to be taken from the spirometer. The date of last use of study drug will be recorded on the study phase completion page.

Study drug compliance will be assessed by the investigator and/or center personnel at designated visits by recording capsule counts from the previously dispensed blister strips for the Novartis SDDPI and HandiHaler® as well as from the information provided by the patient/caregiver. This information should be captured in the source documentation at each visit.

The total number of doses of study drug administered since the last dispensing visit will be recorded at Visit 2 and 3 for each patient on the eCRF.

In addition, the use of rescue medication will be documented in the patient diary and transferred at the following visit to the eCRF. All medications taken after the start of study drug use, the reason for prescribing the medication and the start and end dates will be collected in the source documents and recorded on the respective pages of the eCRF.

6.4 Efficacy

6.4.1 Spirometry measurements

All clinic visits will start in the morning. The following spirometry measurements will be taken: FEV_1 and FVC.

[redacted]

- At Visit 0, spirometry measurements will be taken to assess patients eligibility for the study and to assess the post-~~bronchodilation FEV1~~bronchodilation FEV1 10 to 15 min after inhalation ~~of~~ 4of 4 x 100 μ g puffs of salbutamol.

The results of the spirometry measurement must meet ATS/ERS criteria for acceptability and repeatability for the patient to continue in the study (see Appendix 2).

A single spirometry manoeuver will be performed on those patients who withdraw prematurely.

All spirometry measurements taken after Visit 1 should be performed as close as possible, and ideally within 1 hour, of the time that they were performed at the randomization visit (Visit 1).

For all clinic spirometry assessments, 3 acceptable maneuvers should be performed for each time-point. The FEV_1 and FVC values recorded must be the highest values measured irrespective of whether or not they occur on the same curve. All displaceable volumes will be reported in liters (L) at the following conditions: normal body temperature (37°C), ambient pressure, saturated with water vapor (BTPS).

Pulmonary function assessments will be performed using spirometry. For this purpose the spirometer will be customized and programmed according to the requirements of the study protocol in accordance with ATS standards (Miller et al, 2005), including predicted reference values. In order to reduce the variability of observations, this equipment must be used for all measurements during the study. Whenever possible the same staff member should evaluate and coach a given patient at each visit throughout the study and be consistent in their patient handling. In addition, the spirometer should be calibrated every morning before taking any spirometric measurements for this study. Calibration reports should be stored as source data.

However, the deviation caused by a different equation of each participating center (Morris, Knudson, Korean equation, etc) will be accepted.

Refer to the Spirometry Guidance for further details on spirometry and reversibility testing (Appendix 2).

6.4.2 Baseline/transitional dyspnea index

Patients must be interviewed by a trained assessor who will grade the degree of impairment due to dyspnea at Visit 1 (BDI) and at Visit 2 and 3 and at the time of discontinuation for patients who discontinue prematurely (TDI).

Preferably, the same assessor should complete all the BDI/TDI assessments for an individual patient. These assessments must be undertaken prior to the spirometry and study drug administration.

Details of the BDI and TDI (Mahler and Wells, 1988) are provided in Appendix 1.

6.4.3 Chronic obstructive pulmonary disease assessment

The CAT is a short instrument used to quantify the symptom burden of COPD and will be used to assess the health status impairment of patients in this study (Jones et al, 2009) first at Visit 1 to determine patient eligibility (must have a score of at least 10). The CAT consists of 8 items, each presented as a semantic 6-point differential scale, providing a total score out of

[redacted]

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 of individual items.

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

The CAT questionnaire (see Appendix 8) is completed by the patient at the beginning of the study visit before any other assessment to avoid influencing the responses. Completed CAT questionnaires will be reviewed by the investigator and data entered into eCRF. The investigator should review not only the responses to the questions in the questionnaire but also for any unsolicited comments written by the patient. Investigators should not encourage the patients to change the responses reported in the questionnaire.

[redacted]

6.4.5 Rescue medication use

Each patient will be provided with salbutamol to use as rescue medication. If a patient requires the use of salbutamol as rescue medication due to an increase in COPD symptoms, the number of inhalations taken during the previous 24-hour period will be recorded in the paper diary. Instructions regarding the use of rescue medication are outlined in Section 5.5.6.

6.4.6 Chronic obstructive pulmonary disease exacerbations

A COPD exacerbation is defined as:

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

- dyspnea
- sputum volume
- sputum purulence

OR

A worsening of any 1 major symptom together with an increase in severity of any 1 of the following minor symptoms **for at least 2 consecutive days**:

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

[redacted]

A COPD exacerbation is considered of **moderate severity** if treatment with systemic glucocorticosteroids or antibiotics or both was required and **severe** if hospitalization was required. An emergency room visit of longer than 24 hours will be considered a hospitalization. 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 he/she deems appropriate. However, the following regimen is recommended for the treatment of an exacerbation:

- A 2 week oral course of prednisolone (or equivalent), 30mg/day in Week 1, followed by 20 mg/day in Week 2, and/or an oral 7 day course of amoxicillin 500 mg 3 times daily (alternatively augmentin 625 mg 3 times daily or clarithromycin 500 mg twice daily).

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.

If systemic corticosteroids are taken within 7 days prior to any study visit, the visit must be rescheduled to allow a washout of 7 days.

The start date for a COPD exacerbation recorded in the eCRF should be the first day of symptom worsening of 2 or more major symptoms or 1 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 should where possible attend the clinic for assessment of the episode.

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.

All COPD exacerbations should only be recorded on the COPD exacerbation eCRF and not on the AEs eCRF.

Any reported AEs or SAEs of pneumonia must be confirmed by chest X-ray.

6.4.7 Appropriateness of efficacy assessments

The efficacy assessments (BDI/TDI, CAT, FEV_1, rescue medication) planned for this study are standard efficacy assessments in COPD clinical trials.

6.5 Safety

- Adverse events
- Physical examination
- Urine pregnancy test (females of childbearing potential)
- ECG
- Vital signs
- Laboratory tests: biochemistry, hematology and urine.

[redacted]

6.5.1 Physical examination

A complete physical examination will be performed at Visit 1 (Day 1) and Visit 3 (Day 84). In case of early withdrawal, a physical examination should be performed at the premature study withdrawal visit. It will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, and extremities; and vascular and neurological systems. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic examinations 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 drug must be included in the Relevant Medical History/Current Medical Conditions screen on the patient's eCRF. Significant findings after the start of study drug which meet the definition of an AE must be recorded on the AE screen of the patient's eCRF.

6.5.2 Vital signs

Vital signs will include 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 position for at least 10 minutes. The patient's condition must be monitored to rule out any clinically relevant arrhythmia. The investigator needs to monitor the pulse rate for any missed beats or ectopics.

Vital signs will be obtained at Visit 0; Visit 1, 2 and 3; and once in the event of premature study withdrawal.

Clinically notable vital signs will be determined in accordance with the investigator's decision.

6.5.3 Height and weight

Height (in cm) and weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be recorded at Visit 1 (Day 1). Weight will be recorded again at Visit 3 (Day 84), and in the event of premature study withdrawal.

6.5.4 Laboratory evaluations

Laboratory evaluations and analyses will be performed locally at the site level.

In the event of premature study withdrawal, a laboratory sample for hematology, chemistry, and urinalysis will be obtained at the end of study visit. Clinically notable laboratory findings will be determined in accordance with the investigator's decision.

6.5.4.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count will be measured at Visit 0 (Day -21 to Day -1), Visit 2 (Day 28) and Visit 3 (Day 83).

6.5.4.2 Clinical chemistry

Albumin, alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), calcium, total cholesterol, lactate dehydrogenase (LDH), magnesium, phosphate, sodium, potassium,

[redacted]

creatinine, γ-GT, blood glucose, total protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), low-density lipoprotein-cholesterol (LDL-C) and high-density lipoprotein-cholesterol (HDL-C) will be measured at Visit 0 (Day -21 to Day -1), Visit 2 (Day 28) and Visit 3 (Day 83). If the total bilirubin concentration is increased above 1.5 times the upper limit of normal (ULN) range, direct bilirubin should be measured.

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

6.5.4.3 Urinalysis

Urinalysis will be measured at Visit 0 (Day -21 to Day 1), Visit 2 (Day 28) and Visit 3 (Day 83).

Testing will include: pH, specific gravity, protein, glucose, ketones, bilirubin, blood, urobilinogen, nitrate, and WBC.

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 AE, is identified.

6.5.5 Electrocardiogram

At Visit 0, a single screening ECG will be measured to test for eligibility for trial inclusion. ECGs will also be performed at Visit 2 and Visit 3. In the event of premature study withdrawal, a single ECG will be measured. All ECGs should include all 12 standard leads.

If a patient experiences a clinically significant change in cardiac rhythm or other clinically significant cardiovascular abnormality, the investigator should consider withdrawing the patient from the study.

6.5.6 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 local laboratory at Visit 0 (Day -21 to Day -1) and Visit 3 (Day 84) or at premature withdrawal. A positive urine pregnancy test requires the patient to be discontinued from the trial. No assessments of fertility will be performed. See Section 5.5.9 and Section 7.3 for more details.

6.5.7 Appropriateness of safety measurements

The safety assessments selected are standard for clinical trials in COPD.

6.6 Other assessments

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

6.6.1 Resource utilization

Not applicable.

[redacted]

6.6.2 Health-related quality of life

Not applicable.

6.6.3 Pharmacokinetics

Not applicable.

6.6.4 Pharmacogenetics/pharmacogenomics

Not applicable.

6.6.5 Other biomarkers

Not applicable.

[redacted]

[redacted]

7 Safety monitoring

7.1 Adverse events

An AE is any untoward medical occurrence (i.e., any unfavorable and unintended sign (including abnormal laboratory findings), symptom or disease) in a subject or clinical investigation subject *after providing written informed consent* for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The occurrence of AEs 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 AEs 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 AEs.

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

- the severity grade:
  - mild: usually transient in nature and generally not interfering with normal activities.
  - moderate: sufficiently discomforting to interfere with normal activities.
  - severe: prevents normal activities.
- its relationship to the study treatment (suspected/not suspected).

[redacted]

- its duration (start and end dates) or if the event is ongoing an outcome of "not recovered/not resolved" should be reported.
- whether it constitutes a serious adverse event (SAE).
- action taken regarding study treatment.
- whether other medication or therapies have been taken (concomitant medication/non-drug therapy).
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown).

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

- is fatal or life-threatening.
- results in persistent or significant disability/incapacity.
- constitutes a congenital anomaly/birth defect.
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent.
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission.
  - social reasons and respite care in the absence of any deterioration in the patient's general condition.
- is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.

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

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

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

Once an AE 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.

[redacted]

Information about common side effects already known about the investigational drug can be found in the Package Insert. 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 AE (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information should be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

7.2 Serious adverse event reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days after the patient has stopped study participation (defined as time of last dose of study drug taken or last visit, whichever is later) must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30-day 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 SAE Report Form. The investigator must assess the relationship to *each specific component of study treatment,* complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours after awareness of the SAE to the local Novartis Drug Safety and Epidemiology (DS&E) Department. The telephone and fax number of the contact persons in the local DS&E Department, 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 eCRF 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. Information about all SAEs (either initial or follow up information) is collected and recorded in English on the paper SAE Report Form. The Investigator must assess the relationship to each specific component of the study treatment (if the study treatment consists of several components).

SAEs (initial and follow-up) that are recorded *on the paper SAE form* should be faxed within 24 hours of awareness of the SAE to the local Novartis DS&E Department. The telephone and fax number of the contact persons in the local DS&E department specific to the site, are listed in the investigator folder provided to each ~~site~~(site (Tel. 02-768-9007, Fax. 02-780-8487, Email. safety.kor@novartis.com). The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the eCRF 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

[redacted]

SAEs (initial and follow-up) that are recorded *electronically* in the OC/RDC system should be entered, saved and e-signed within 24 hours of awareness of the SAE or changes to an existing 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 DS&E Department associate may urgently require further information from the investigator for Health Authority reporting. All SAEs will be collected and reported to the competent authorities and relevant ethics committees in accordance with national regulatory requirements in participating countries.

7.3 Pregnancy reporting

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

Pregnancy should be recorded on a Clinical Trial Pregnancy Form in English and reported by the investigator to the local Novartis DS&E Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

7.4 Prospective suicidality assessment

Not applicable.

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 eCRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol and to GCP, 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.

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

[redacted]

information, laboratory data, ECGs, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original ICF signed by the patient (a signed copy is given to the patient).

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

8.2 Data collection

Novartis will supply the investigator site with a computer loaded with EDC software that has been fully validated and conforms to 21 CFR Part 11 requirements. Investigator site staff will not be given access to the EDC system until they have been trained by Novartis personnel. Designated investigator staff will enter the data required by the protocol into the Novartis eCRFs using the Novartis-supplied computer. Automatic validation programs check for data discrepancies in the eCRFs and, by generating appropriate error messages, allow the data to be confirmed or corrected by the investigator staff before transfer of the data to Novartis via a secure Virtual Private Network. The investigator must certify that the data entered are complete and accurate by signing a memo generated at the end of the trial that will be sent to him by Novartis personnel. 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 will review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff 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 AEs will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Data about all study drugs dispensed to the patient and all dosage changes will be tracked using an IRT. The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis.

[redacted]

8.4 Data Monitoring Committee

Not required.

8.5 Adjudication Committee

Not required.

9 Data analysis

9.1 Analysis sets

The following sets will be used for the analysis of data:

- The Randomized set (RAN), will include all randomized patients regardless of whether or not they actually received study treatment.
- The Full analysis set (FAS) will include all randomized patients who received at least one dose of study treatment and have at least one evaluable post-baseline assessment. Following the intent-to-treat principle, patients will be analyzed according to the treatment they were assigned to at randomization.
- The Per-protocol set (PPS) will include all patients in the FAS without any major protocol deviations. Major protocol deviations will be defined prior to database lock. Patients will be analyzed according to the treatment they were assigned to at randomization.
- The Safety set will include all patients who received at least one dose of study treatment. Patients will be analyzed according to the treatment they received.

The analysis of the primary objective will be performed on the FAS. The PPS will be used for the supportive analysis of the primary variable. The FAS will be used for the analysis of all other efficacy variables. The safety set will be used for the analysis of all safety variables.

Note that the FAS and Safety set are the same except that the Safety set allows the inclusion of non-randomized patients who receive study treatment in error. Also the FAS assigns randomized treatment and the Safety set assigns received treatment.

9.2 Patient demographics and other baseline characteristics

Demographic and baseline characteristics including age, sex, race, ethnicity, height, weight, body mass index (BMI), relevant medical history, screening spirometry (FEV_1, FVC, FEV_1/FVC) including short acting bronchodilator reversibility, duration of COPD, baseline COPD severity (mild or moderate), smoking history, prior concomitant medications (COPD related and non-COPD related), vital signs (systolic and diastolic blood pressure, pulse rate), QT using Fridericia's correction and ECG will be summarized for the randomized set by treatments.

9.3 Treatments

The number of patients and the length of time (in days) exposed to each study drug will be summarized by treatment for the Safety set.

[redacted]

Concomitant medications will be summarized by treatment for the safety set. Concomitant COPD related medications will be summarized by pre-specified categories recorded on the CRF, route of administration and ingredient. Concomitant medications not related to COPD will be summarized by the preferred term. Furthermore, concomitant COPD-related and non COPD-related medications were combined in one table and presented by Anatomical Therapeutic Chemical (ATC) class and preferred term.

Treatment compliance will be summarized by treatment for the safety set.

9.4 Analysis of the primary variable

The primary objective of this study is to demonstrate the superiority of QVA 110/50 µg once daily compared to tiotropium 18 µg once daily in terms of trough forced expiratory volume in one second (FEV_1 in Liters) following 12 weeks of treatment.

9.4.1 Variable

The primary variable is pre-dose trough FEV_1 (L) at Week 12, which is defined as the average of FEV_1 values taken at 45 and 15 min prior to the administration of study drug.

The baseline FEV_1 (L) measurement is defined as the average of the FEV_1 values taken at 45 and 15 min prior to the first dose of study drug at Visit 1 (Day 1).

9.4.2 Statistical model, hypothesis, and method of analysis

To demonstrate the superiority of QVA 110/50 µg once daily to tiotropium 18 µg once daily in patients having COPD with mild to moderate airflow limitations, the following hypothesis will be tested using an analysis of covariance (ANCOVA) model for the full analysis set:

H_0: There is no difference in trough FEV_1 (L) at Week 12 for patients treated with QVA versus tiotropium

H_A: There is a difference in trough FEV_1 (L) at Week 12 for patients treated with QVA versus tiotropium

The model will contain treatment and smoking status as fixed effects with baseline trough FEV_1 as a covariate and center as a random effect.

Least squares means and the estimated treatment differences will be displayed along with the associated 95% confidence interval and p-value. The superiority of QVA to tiotropium will be demonstrated if the p-value is less than 0.05 and the confidence interval lies entirely to the right of (higher than) 0 mL.

9.4.3 Handling of missing values/censoring/discontinuations

If any of the values contributing to the trough FEV_1 are collected within 6 hours of rescue medication use or less than 7 days after systemic corticosteroid use then the individual FEV_1 value will be set to missing or if the actual measurement times were outside the 22-25 hour post-dose time window then the individual FEV_1 value will be excluded from analyzed.

If any one of the 45 min or 15 min pre-dose values is missing at Week 12, the remaining non-missing value will be considered as trough FEV_1. If both values are missing, or if the patient

[redacted]

has withdrawn from the trial, regardless of the reason for discontinuation, then missing trough values will be imputed with the last observation carried forward (LOCF) method using the data at Visit 2. If the trough value at Visit 2 is missing, then patient will be excluded from this analysis.

9.4.4 Supportive analyses

Since some patients may discontinue the study prematurely affecting the sample size at Week 12, the following analyses will also be performed as supplementary to support the result of the primary analysis:

1. The primary analysis will be repeated only for patients who have a valid trough measurement at Week 12. Any missing observation at Week 12 will not be imputed.
2. The primary analysis will be repeated for the Per-protocol set. Missing FEV_1 values will be imputed by LOCF method.
3. A sensitivity analysis of trough FEV_1 at Week 12 (with and without imputation by LOCF method) will also be performed by allowing inclusion of values that fell within 6 hours of rescue medication use or within 7 days of systemic corticosteroid use.
4. The following exploratory subgroup analyses for the primary endpoint trough FEV_1 at Week 12 will be performed (using the appropriate interaction term in the model and additional covariate as a fixed effect if necessary) for the full analysis set to explore the treatment effect in:
   - Age group.
   - Sex.
   - Severity of COPD (50% ≤ FEV1 < 60%, FEV1 ≥ 60%).
   - Smoking status at baseline.
   - Exacerbation (exacerbation history in previous year; 0 or 1).
   - Patient's larger value of FEV_1 reversibility after SABA (12% & 200ml increase / 12% increase / 200 mL increase).
   - BMI.
5. In addition, analysis of the log-transformed trough FEV_1 after 12 weeks of treatment for the FAS will be performed using the same ANCOVA model as specified for the primary analysis with the relevant covariates in the model log-transformed as appropriate.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

9.5.1.1 Trough FEV_1 at Week 4

Trough FEV_1 at Week 4 will be summarized using a similar ANCOVA model as specified in the primary analysis. Least squares means and the estimated treatment differences will be displayed along with the 95% confidence interval and p-value.

As an exploratory analysis, similar ANCOVA analysis will be performed for FVC and FEV_1/FVC at Week 4 and Week 12. The model will also contain visit and treatment by visit

[redacted]

interactions as fixed effects. Least squares means and the estimated treatment differences will be displayed along with the 95% confidence interval and p-value.

9.5.1.2 Rescue medication use

Diary data recorded between Visit 0 and Visit 1 will be used to calculate the baseline values.

Patients will be considered as eligible for the analysis if they have at least 7 evaluable diary days in the baseline period and in the post baseline period they have at least 30% of their diary days evaluable and at least 40 evaluable diary days in total.

Daily rescue medication use (number of puffs) over 12 weeks

The total number of puffs of rescue medication used over the last 24 hours will be recorded in the electronic patient diary in the morning. The total number of puffs of rescue medication per day over the full 12 weeks will be calculated and divided by the total number of days with non-missing rescue medication data to derive the mean daily number of puffs of rescue medication taken for the patient. The mean daily number of puffs of rescue medication used over 12 weeks will be summarized by treatments and analyzed using a negative binomial regression model with treatment and smoking status as fixed effects with baseline rescue medication use as a covariates and center as a random effect. Log of exposure to the study drug will be used as the offset variable. Least squares means will be displayed by treatments. The estimated difference between treatments, along with the 95% confidence interval and p-value will also be displayed.

Percentage of 'days with no rescue use' over 12 weeks

A 'day with no rescue use' is defined from diary data as any day where the patient does not use any puffs of rescue medication. The total number of 'days with no rescue use' over the 12 weeks will be divided by the total number of days in order to derive the percentage of 'days with no rescue use'.

The percentage of 'days with no rescue use' will be summarized by treatment and analyzed using the same ANCOVA model as specified for the primary analysis, however, baseline percentage of 'days with no rescue use' will be used instead of baseline FEV_1.

9.5.1.3 Dyspnea index

Dyspnea will be measured at baseline using the BDI and during the treatment period using the TDI, which captures changes from baseline. The BDI and TDI each have 3 domains-functional impairment, magnitude of task and magnitude of effort. The BDI domains are rated from 0 (severe) to 4 (unimpaired) and the rates are summed for the baseline focal score ranging from 0 to 12; the lower the score the worse the severity of dyspnea. The TDI domains are rated from -3 (major deterioration) to 3 (major improvement) and the rates are summed for the transition focal score ranging from -9 to 9; minus scores indicate deterioration. A TDI focal score of 1 is considered to be a clinically significant improvement from baseline.

[redacted]

TDI focal score

The TDI focal score after 12 weeks of treatment will be analyzed using the same ANCOVA model as specified for the primary analysis with the BDI focal score as the baseline covariate. When the data are missing or insufficient for any one of the domains, a focal score cannot be calculated.

Proportion of patients with a clinically important improvement of at least 1 in the TDI focal score

A TDI focal score of ≥1 is considered to be a clinically important improvement from baseline. The proportion of patients who achieve this clinically important improvement will be analyzed using logistic regression. The model will contain same terms as in the primary analysis, with BDI focal score as the baseline covariate. The estimated adjusted odds ratios will be displayed along with the associated 95% confidence intervals and two-sided p-values.

9.5.1.4 COPD Assessment Test

The CAT score at Week 12 will be summarized by treatment and analyzed using the same ANCOVA model as specified for the primary analysis, with the baseline covariate replaced by baseline CAT score. Least squares means will be displayed by treatments. The estimated difference between treatments, along with the 95% confidence interval and p-value will also be displayed.

9.5.2 Safety variables

All safety endpoints (i.e. AEs, laboratory data, vital signs, and ECG) will be summarized by treatment for all patients in the safety set. All data will be included in the summaries and/or analysis regardless of rescue medication use.

Adverse events

All study emergent AEs including COPD exacerbations will be recorded and listed.

Adverse events starting on or after the time of the first dose of study drug and up to 7 days (30 days in case of SAEs) after the last dose of study drug will be classified as a treatment emergent AE and included in all summaries. Any AEs that started during the study before the time of the first dose of study drug will be listed only.

All treatment emergent AEs will be listed.

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

The number and percentage of patients with the most frequent AEs will be summarized by treatment.

The number and percentage of patient mortality and CCV SAE events will be summarized by treatment.

[redacted]

Deaths

All deaths occurring in the study will be listed by patient and summarized by treatments and investigator-reported principal cause. Deaths will be summarized separately based on (A) cases reported during the active treatment period only and (B) cases reported during the active treatment period plus the following 30 days.

Electrocardiogram and vital signs

ECG data and vital signs (sitting systolic/diastolic blood pressures, sitting pulse rate) will be summarized by treatment for each visit separately. The baseline is defined as the measurement taken at Visit 1. The maximum (QTcF, systolic blood pressure, pulse rate) or minimum (diastolic blood pressure) post first dosing will also be summarized. Changes from baseline will also be summarized by treatment.

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

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

Systolic blood pressure

- "Low" criterion: < 75 mmHg, or ≤ 90 mmHg and decrease from baseline ≥ 20 mmHg
- "High" criterion: > 200 mmHg, or ≥ 180 mmHg and increase from baseline ≥ 20 mmHg

Diastolic blood pressure

- "Low" criterion: < 40 mmHg, or ≤ 50 mmHg and decrease from baseline ≥ 15 mmHg
- "High" criterion: > 115 mmHg, or ≥ 105 mmHg and increase from baseline ≥ 15 mmHg

Pulse rate

- "Low" criterion: < 40 bpm, or ≤ 50 bpm and decrease from baseline ≥ 15 bpm
- "High" criterion: > 130 bpm, or ≥ 120 bpm and increase from baseline ≥ 15 bpm

QTc will be calculated from the QT interval and RR (in seconds) using Fridericia's formula: QTc = QT / 3√ RR, where 3√ denotes the cube root. Notable QTc values and changes from baseline will be summarized.

A notable value is defined as a QTc interval of greater than 450 ms. The categories used for the change from baseline in QTc are less than 30 ms, 30 to 60 ms and greater than 60 ms.

Laboratory Data

All laboratory data will be listed with abnormal values. The laboratory values and the change from baseline (Visit 0) for continuous laboratory parameters will be summarized for each visit. A frequency table of results for categorical laboratory parameters will be produced by visit. Shift tables relative to the normal reference ranges will be used to summarize the change from baseline to post-baseline for each laboratory parameter.

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

[redacted]

9.5.3 Resource utilization

Not applicable.

9.5.4 Health-related Quality of Life

Not applicable.

9.5.5 Pharmacokinetics

Not applicable.

9.5.6 Pharmacogenetics/pharmacogenomics

Not applicable.

9.5.7 Biomarkers

Not applicable.

9.5.8 PK/PD

Not applicable.

[redacted]

[redacted]

9.7 Interim analyses

Not applicable.

9.8 Sample size calculation

The primary objective is to demonstrate superiority of QVA149 110/50 µg once daily compared to tiotropium 18 µg once daily in terms of pre-dose trough FEV_1 (L) after 12 weeks of treatment. Based on the results of QVA149A2303 (SHINE) study, it was assumed that the estimated treatment difference between QVA149 and tiotropium is 80 mL and corresponding standard deviation is 271 mL (Bateman et al 2013). In this study, a sample size of 173 patients in each treatment arm with an estimated treatment difference between QVA149 and tiotropium of 82 mL would be required to achieve 80% power on a 2-sided test with 5% level of significance. Assuming a dropout rate of 11%, approximately 389 patients will be enrolled in the study.

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

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

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

[redacted]

duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

10.3 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed ICF must be reviewed and approved by a properly constituted IRB/IEC/REB before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Novartis before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs, 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.

11 Protocol adherence

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

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

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

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/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the

[redacted]

protocol. In such cases, Novartis should be notified of this action and the IRB/IEC/REB at the study site should be informed within 10 working days or less, if required by local regulations.

12 References

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[redacted]

13 Appendices

13.1 Appendix 1: Baseline dyspnea index/transitional dyspnea index

[redacted]

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.

[redacted]

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.

[redacted]

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.

Source: Mahler DA and Wells CK, 1988

[redacted]

13.2 Appendix 2: Spirometry guidance

Spirometry

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 in liters (L) at the following conditions: normal body temperature (37°C), ambient pressure, saturated with water vapor (BTPS).

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.
- Exposure to environmental smoke, dust or areas with strong odors.

Every effort should be made to assure consistent testing conditions throughout the study. The patient should perform spirometry in the seated position with nose clips. 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 and repeatability. Acceptability criteria should be applied before repeatability is determined.

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 may 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 early termination of exhalation (minimum exhalation time of 6 seconds is recommended, unless there is an obvious plateau of reasonable duration (i.e., no volume change for 1 second) or the patient cannot continue to exhale further).

Repeatability

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

Recording of data

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

Predicted normal

The study is using the spirometry at individual site therefore the predicted normal values will be handled at site level.

Reversibility

All reversibility evaluations should follow the recommendations of the ATS/ERS Task force: Standardization of Lung Function Testing (Miller et al, 2005). A baseline spirometry assessment should be performed after a washout period of *at least* 6 hours for short-acting-β2-agonists (SABAs), 48 hours for long-acting β2-agonists (LABAs) and 7 days for long-acting anticholinergics.

Following baseline assessment, perform post-bronchodilation FEV_1 10 to 15 min after inhalation ~~of 4~~of 4 x 100 µg puffs of Salbutamol.

.

Reversibility is calculated as:

$$\frac{100 \times FEV_1 \text{ (post } \beta2\text{-agonists)} - FEV_1 \text{ (baseline)}}{FEV_1 \text{ (baseline)}}$$

13.3 Appendix 3: Patient COPD treatment diary

Instructions for Completing the Diary:

- Please use this diary to record the time when you take your COPD medication.

[redacted]

- Please (√) check if you missed the dose.
- Each morning record the number of puffs of rescue medication taken during the past 24 hours.

- Please bring this diary with you to the visit.
- PLEASE remember to not take any rescue medication 06 hours before a study visit.

Visit 0 (Screening visit) to Visit 1 (Randomization visit)

RESCUE MEDICATION RECORD

Date	Number of puffs of rescue medication taken in the past 24 hours
__ __ __ __ __ __ __ __ __	__ __ Puffs
__ __ __ __ __ __ __ __ __	__ __ Puffs
__ __ __ __ __ __ __ __ __	__ __ Puffs
__ __ __ __ __ __ __ __ __	__ __ Puffs
__ __ __ __ __ __ __ __ __	__ __ Puffs
__ __ __ __ __ __ __ __ __	__ __ Puffs
__ __ __ __ __ __ __ __ __	__ __ Puffs
__ __ __ __ __ __ __ __ __	__ __ Puffs
__ __ __ __ __ __ __ __ __	__ __ Puffs
__ __ __ __ __ __ __ __ __	__ __ Puffs
__ __ __ __ __ __ __ __ __	__ __ Puffs
__ __ __ __ __ __ __ __ __	__ __ Puffs
__ __ __ __ __ __ __ __ __	__ __ Puffs

Visit 1 (Randomization visit) to Visit 2 (Treatment visit)

Visit 2 (Treatment visit) to Visit 3 (Treatment visit)

[redacted]

MEDICATION RECORD

Study Medication Recording Section		Rescue Medication Recording Section
Date	Time of study medication	Number of puffs of rescue medication taken in the past 24 hours
	☐ Missed	Puffs
	☐ Missed	Puffs
	☐ Missed	Puffs
	☐ Missed	Puffs
	☐ Missed	Puffs
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	☐ Missed	Puffs

13.4 Appendix 4: GOLD guidelines

Classification of severity of airflow limitation in COPD based on post-bronchodilator FEV_1	
	In patients with $FEV_1/FVC < 0.7$
GOLD 1	• $FEV_1 \geq 80\%$ predicted
GOLD 2	• $50\% \leq FEV_1 < 80\%$ predicted
GOLD 3	• $30\% \leq FEV_1 < 50\%$ predicted
GOLD 4	• $FEV_1 < 30\%$ predicted

COPD groupings based on risk level and symptoms	
Group A	**Low risk, less symptoms** Typically GOLD 1 or GOLD 2 (mild or moderate airflow limitation); and/or 0-1 exacerbation per year and no hospitalization for exacerbation; and CAT score < 10 or mMRC grade 0-1
Group B	**Low risk, more symptoms** Typically GOLD 1 or GOLD 2 (mild or moderate airflow limitation); and/or 0-1 exacerbation per year and no hospitalization for exacerbation; and CAT score ≥ 10 or mMRC grade ≥ 2
Group C	**High risk, less symptoms** Typically GOLD 3 or GOLD 4 (severe or very severe airflow limitation); and/or

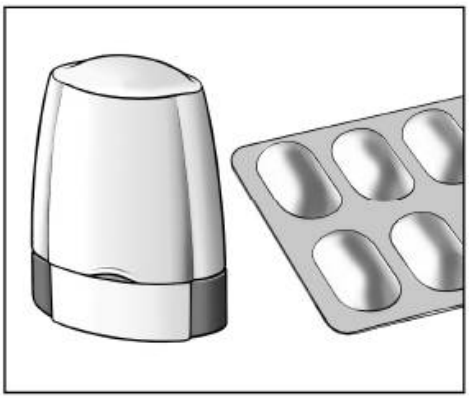
[redacted]

	≥ 2 exacerbations per year or ≥ 1 with hospitalization for exacerbation; and CAT score < 10 or mMRC grade 0-1
Group D	**High risk, more symptoms** Typically GOLD 3 or GOLD 4 (severe or very severe airflow limitation); and/or ≥ 2 exacerbations per year or ≥ 1 with hospitalization for exacerbation and CAT score ≥ 10 or mMRC grade ≥ 2
Abbreviations: CAT: COPD assessment test, GOLD: Global Initiative for Chronic Obstructive Lung Disease, mMRC: modified Medical Research Council	

Source: GOLD Guidelines, 2015.

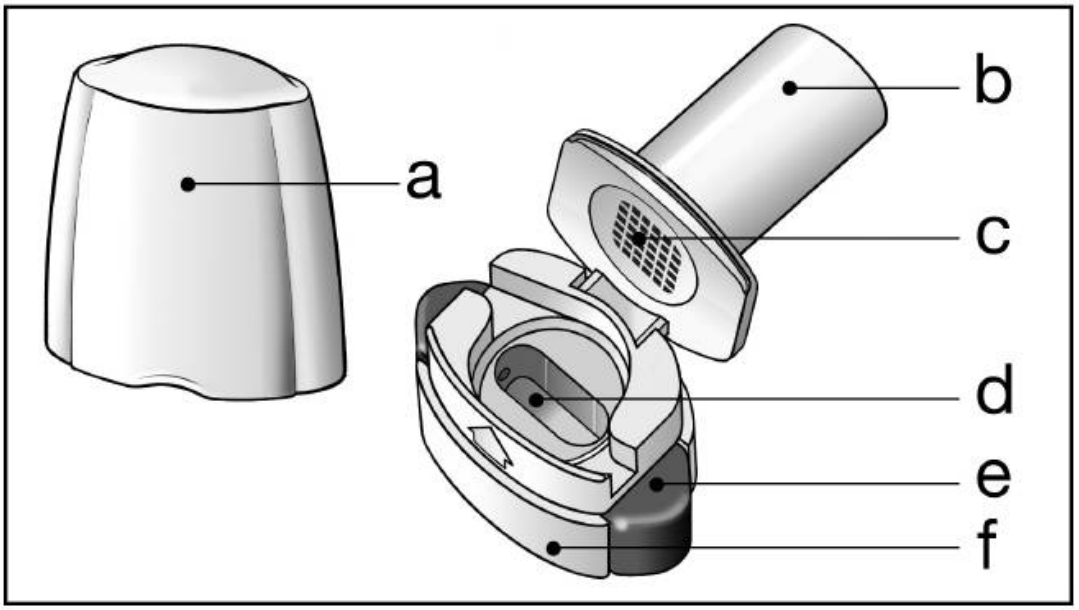
13.6 Appendix 6: Instructions for use of the SDDPI for QVA149 110/50 microgram

Your inhaler



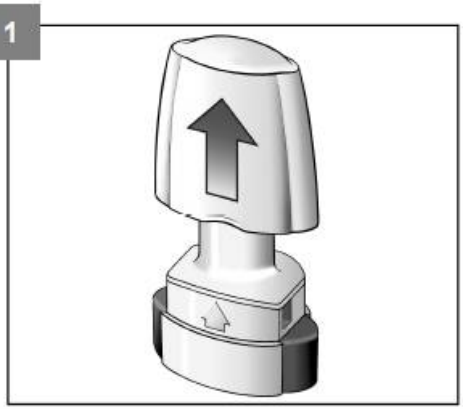
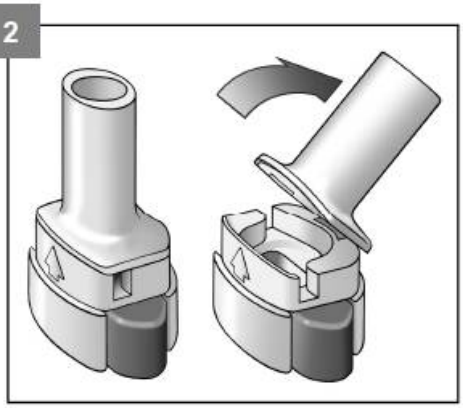
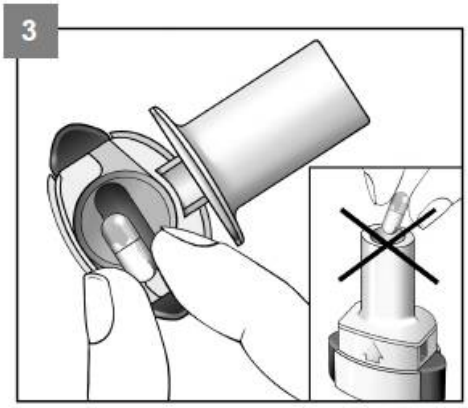
Your inhaler is designed to administer the study drug contained in the capsules. The capsules are packaged in blisters.

Do not swallow capsule.

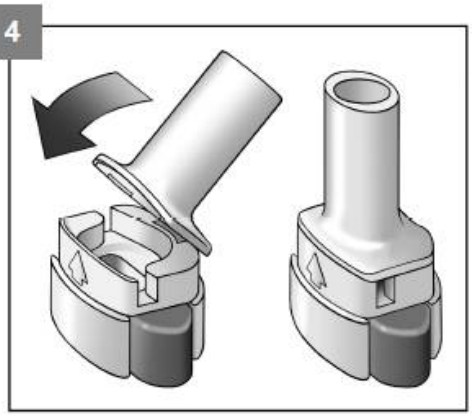
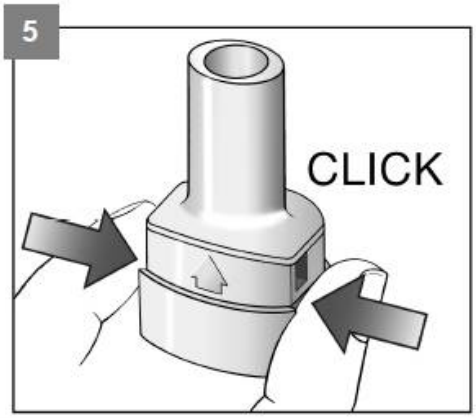
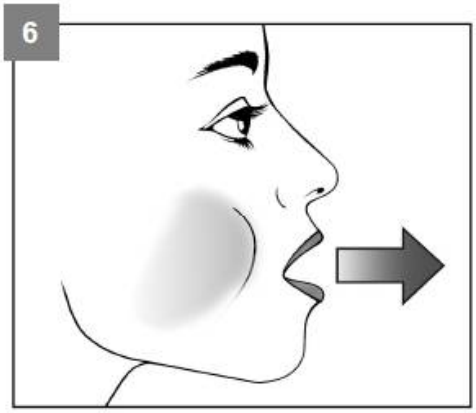


a	Cap	**d**	Capsule cavity
b	Mouthpiece	**e**	Button
c	Screen	**f**	Base

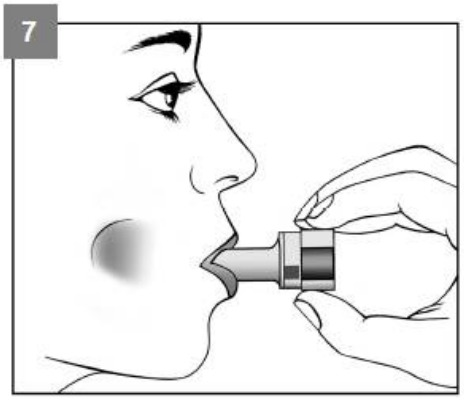
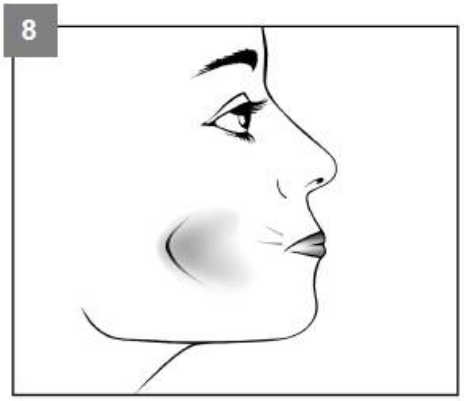
[redacted]

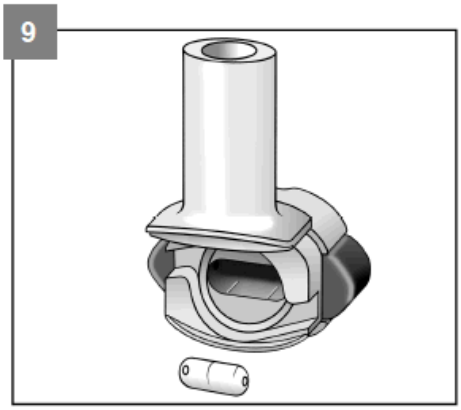
How to use your inhaler	
1 	Pull off cap.
2 	Open inhaler: Hold the base of the inhaler firmly and tilt the mouthpiece in the direction of the arrow to open the inhaler.
3 	Insert capsule: **Immediately before use**, with dry hands, remove one capsule from the blister. Place the capsule into the capsule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

[redacted]

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

[redacted]

7 	Administer study drug: Before breathing in, place the mouthpiece in your mouth and close your lips around the mouthpiece. Hold the inhaler with the buttons to the left and right (not up and down). Breathe in rapidly and steadily, as deeply as you can. **Do not press the buttons**. As you breathe in through the inhaler, the capsule spins around in the cavity and you should hear a whirring noise. You will experience a sweet taste as the medicine goes into your lungs. If you do not hear a whirring noise, the capsule may be stuck in the capsule cavity. If this occurs, open the inhaler and carefully loosen the capsule by tapping the base of the device. **Do not press the buttons repeatedly** to loosen the capsule. Repeat steps 6 and 7 if necessary.
8 	**Continue to hold your breath** as long as comfortably possible while removing the inhaler from your mouth. Then breathe out. Open the inhaler to see if any powder is left in the capsule. If there is powder left in the capsule, close the inhaler and repeat steps 6 to 8. Most people are able to empty the capsule in one or two inhalations.

9 	Remove capsule: After use, open the inhaler, remove the empty capsule by tipping it out, and discard it. Close the inhaler and replace the cap. Never leave a capsule in the inhaler.

[redacted]

Additional information

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

How to clean your inhaler

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

[redacted]

13.7 Appendix 7: Instructions for use of HandiHaler® for tiotropium 18 microgram

Instructions for Use

SPIRIVA® (speh REE vah) **HandiHaler®**
(tiotropium bromide inhalation powder)

Do not swallow SPIRIVA capsules.

Important Information about using your SPIRIVA HandiHaler

- **Do not swallow SPIRIVA capsules.**
- **SPIRIVA capsules should only be used with the HandiHaler device and inhaled through your mouth (oral inhalation).**
- **Do not use your HandiHaler device to take any other medicine.**

First read the Patient Information, then read these Instructions for Use before you start to use SPIRIVA HandiHaler and each time you refill your prescription. There may be new information.

Becoming familiar with your HandiHaler device and SPIRIVA capsules:

Your SPIRIVA HandiHaler comes with SPIRIVA capsules in blister packaging and a HandiHaler device. Use the new HandiHaler device provided with your medicine.

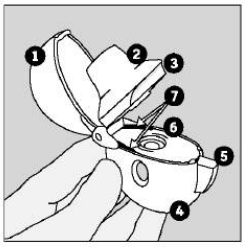


Figure A

The parts of your HandiHaler device include:
(See Figure A)

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

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[redacted]

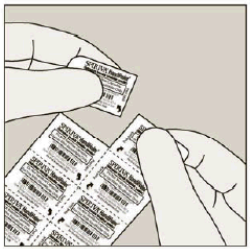

Figure B

Each SPIRIVA capsule is packaged in a blister. (See Figure B)

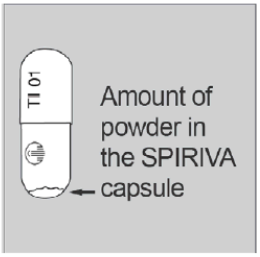

Figure C

- Each SPIRIVA capsule contains only a small amount of powder. (See Figure C) This is 1 full dose.
- **Do not open the SPIRIVA capsule** or it may not work.

Taking your full daily dose of medicine requires 4 main steps.

Step 1. Opening your HandiHaler device:

Figure D

After removing your HandiHaler device from the pouch:

- Open the dust cap (lid) by pressing the green piercing button. (See Figure D)

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[redacted]

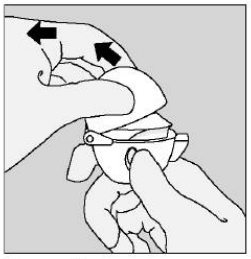

Figure E

- Pull the dust cap (lid) upwards away from the base to expose the mouthpiece. (See Figure E)

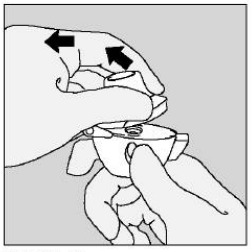

Figure F

- Open the mouthpiece by pulling the mouthpiece ridge up and away from the base so the center chamber is showing. (See Figure F)

Step 2. Inserting the SPIRIVA capsule into your HandiHaler device:

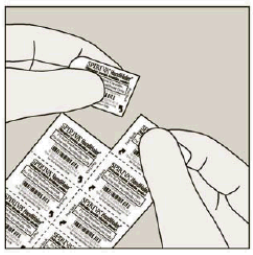

Figure G

Each day, separate only 1 of the blisters from the blister card by tearing along the perforated line. (See Figure G)

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[redacted]

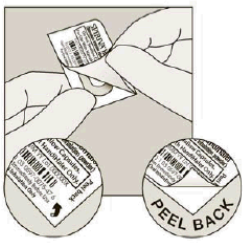

Figure H

Remove the SPIRIVA capsule from the blister:

- **Do not** cut the foil or use sharp instruments to take out the SPIRIVA capsule from the blister.
- Bend 1 of the blister corners with an arrow and separate the aluminum foil layers.
- Peel back the printed foil until you see the whole SPIRIVA capsule. (See Figure H)
- If you have opened more than 1 blister to the air, the extra SPIRIVA capsule should not be used and should be thrown away.

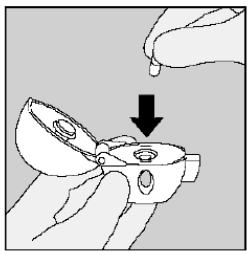

Figure I

Place the SPIRIVA capsule in the center chamber of your HandiHaler device. (See Figure I)

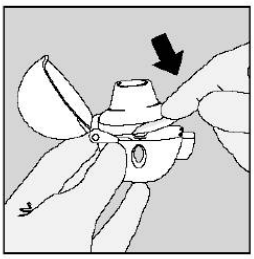

Figure J

Close the mouthpiece firmly against the gray base until you hear a click. Leave the dust cap (lid) open. (See Figure J)

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[redacted]

Step 3. Piercing the SPIRIVA capsule:

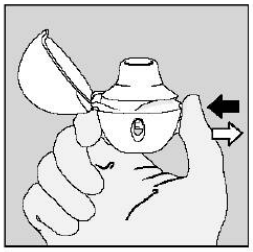

Figure K

- Hold your HandiHaler device with the mouthpiece pointed up. (See Figure K)
- Press the green piercing button once until it is flat (flush) against the base, then release. This is how you make holes in the SPIRIVA capsule so that you get your medicine when you breathe in.
- **Do not** press the green button more than one time.
- **Do not** shake your HandiHaler device.
- The piercing of the SPIRIVA capsule may produce small gelatin pieces. Some of these small pieces may pass through the screen of your HandiHaler device into your mouth or throat when you breathe in your medicine. This is normal. The small pieces of gelatin should not harm you.

Step 4. Taking your full daily dose (2 inhalations from the same SPIRIVA capsule):

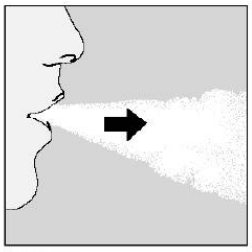

Figure L

Breathe out completely in 1 breath, emptying your lungs of any air. (See Figure L)

Important: Do not breathe into your HandiHaler device.

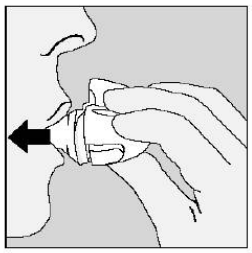

Figure M

With your next breath, take your medicine:

- **Hold your head in an upright position while you are looking straight ahead.** (See Figure M)
- Raise your HandiHaler device to your mouth in a horizontal position. **Do not** block the air intake vents.
- Close your lips tightly around the mouthpiece.
- **Breathe in deeply** until your lungs are full. You should **hear or feel the SPIRIVA capsule vibrate** (rattle). (See Figure M)
- Hold your breath for a few seconds and, at the same time, take your HandiHaler device out of your mouth.
- Breathe normally again.

The rattle tells you that you breathed in correctly. If you do not hear or feel a rattle, see the section, "If you do not hear or feel the SPIRIVA capsule rattle as you breathe in your medicine."

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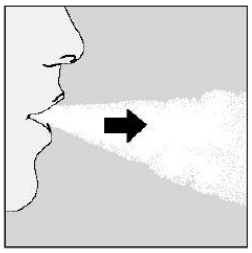

Figure N

To get your full daily dose, you must again, breathe out completely (See Figure N) and for a second time, breathe in (See Figure O) from the same SPIRIVA capsule.

Important: Do not press the green piercing button again.

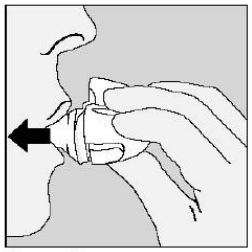

Figure O

Remember: To get your full medicine dose each day, you must breathe in 2 times from the same SPIRIVA capsule. Make sure you breathe out completely each time before you breathe in from your HandiHaler device.

Caring for and storing your SPIRIVA HandiHaler:

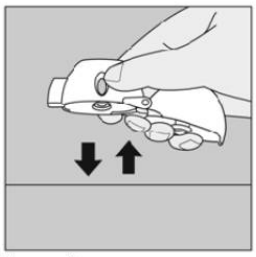

Figure P

- After taking your daily dose, open the mouthpiece and tip out the used SPIRIVA capsule into your trash can, without touching it.
- Remove any SPIRIVA capsule pieces or SPIRIVA powder buildup by turning your HandiHaler device upside down and gently, but firmly, tapping it. (See Figure P) Then, close the mouthpiece and dustcap for storage.
- **Do not** store your HandiHaler device and SPIRIVA capsules (blisters) in a damp moist place. Always store SPIRIVA capsules in the sealed blisters.

If you do not hear or feel the SPIRIVA capsule rattle as you breathe in your medicine:

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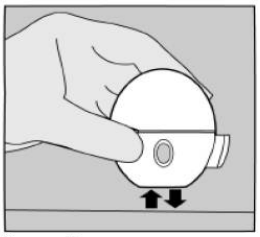

Figure Q

Do not press the green piercing button again.

Hold your HandiHaler device with the mouthpiece pointed up and tap your HandiHaler device gently on a table. (See Figure Q)

Check to see that the mouthpiece is completely closed. Breathe out completely before deeply breathing in again with the mouthpiece in your mouth. (See Figure O)

If you still do not hear or feel the SPIRIVA capsule rattle after repeating the above steps:

- Throw away the SPIRIVA capsule.
- Open the base by lifting the green piercing button and check the center chamber for pieces of the SPIRIVA capsule. SPIRIVA capsule pieces in the center chamber can cause a SPIRIVA capsule not to rattle.
- Turn your HandiHaler device upside down and gently, but firmly, tap to remove the SPIRIVA capsule pieces. Call your doctor for instructions.

Cleaning your HandiHaler device:

Figure R

Clean your HandiHaler device as needed. (See Figure R)

- **It takes 24 hours to air dry your HandiHaler device** after you clean it.
- **Do not** use cleaning agents or detergents.
- **Do not** place your HandiHaler device in the dishwasher for cleaning.

Cleaning Steps:

- Open the dust cap and mouthpiece
- Open the base by lifting the green piercing button.
- Look in the center chamber for SPIRIVA capsule pieces or powder buildup. If seen, tap out.
- Rinse your HandiHaler device with warm water, pressing the green piercing button a few times so that the center chamber and the piercing needle is under the running water. Check that any powder buildup or SPIRIVA capsule pieces are removed.
- Dry your HandiHaler device well by tipping the excess water out on a paper towel. Air-dry afterwards, leaving the dust cap, mouthpiece, and base open by fully spreading it out so that it dries completely.
- **Do not** use a hair dryer to dry your HandiHaler device.
- **Do not** use your HandiHaler device when it is wet. If needed, you may clean the outside of the mouthpiece with a clean damp cloth.

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Helpful Hints to help ensure that you are properly taking your full daily dose of SPIRIVA HandiHaler:

- **Press** the green piercing button 1 **time; Breathe in 2 times; Breathe out completely** before each of the **2** inhalations.
- Always use the new HandiHaler device provided with your medicine.
- Keep your HandiHaler device with the mouthpiece pointed up when pressing the green piercing button.
- **Press the green piercing button 1 time** to pierce the SPIRIVA capsule.
- Do not breathe out into your HandiHaler device.
- Keep your HandiHaler device in a horizontal position and keep your head upright, looking straight ahead, when breathing in.
- Check the center chamber of your HandiHaler device for SPIRIVA capsule pieces or powder build-up. If pieces or powder are seen, tap out before use.
- Clean your HandiHaler as needed and dry thoroughly.

For more information, ask your doctor or pharmacist, or go to www.spiriva.com or call 1-800-542-6257.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

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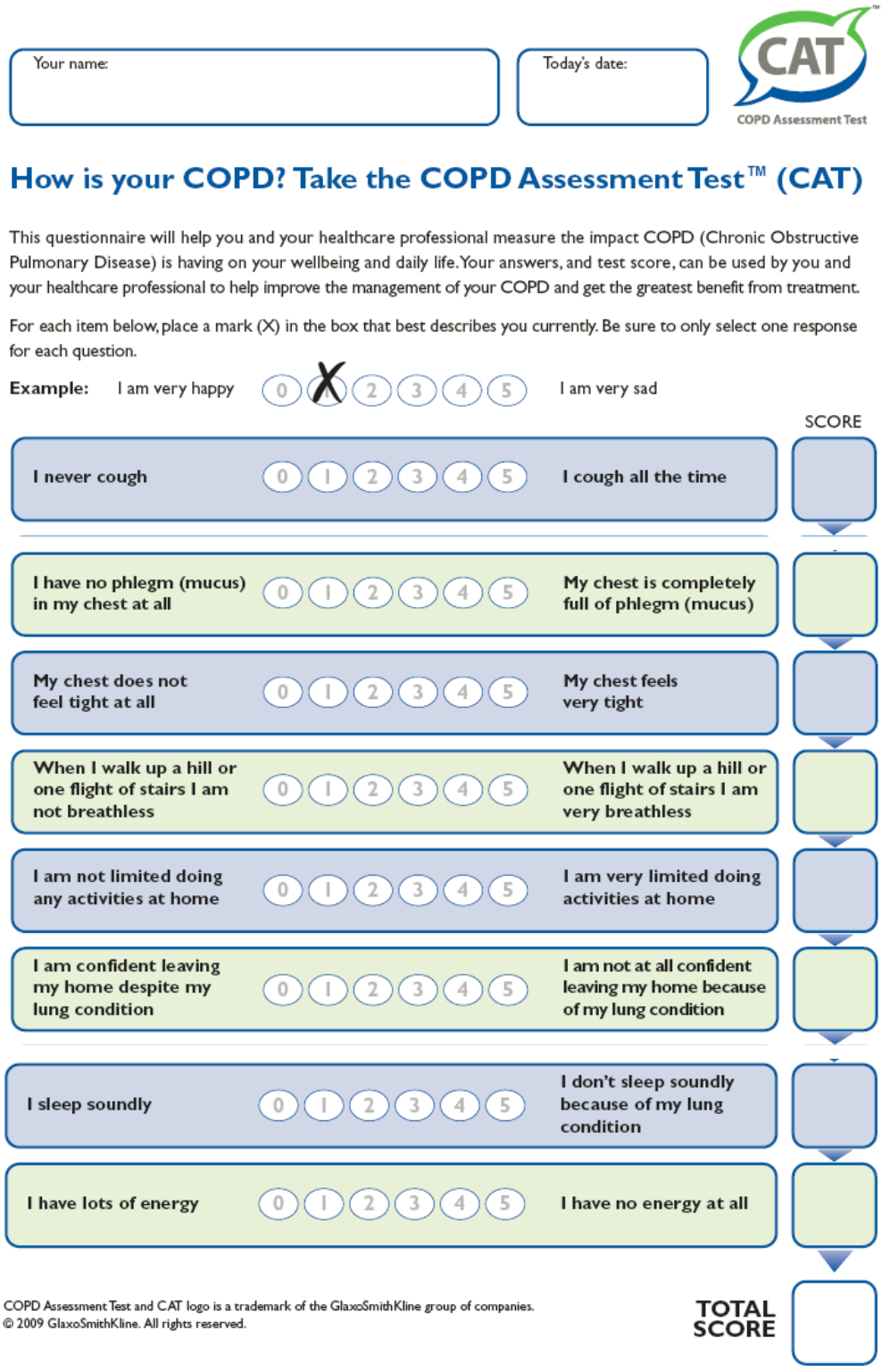
13.8 Appendix 8: COPD Assessment Test (CAT)



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]