

Clinical Development

Indacaterol maleate 110 mcg/glycopyrronium bromide 50 mcg (QVA149)

Clinical Trial Protocol CQVA149ACA01 / NCT02202616

POWER: Prospective Cohort Study for the Real – Life Effectiveness
Evaluation of Glyc**O**pyrronium **W**ith Indacat**E**Rol combination in the
management of COPD in Canada

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List of abbreviations

AE	Adverse event
b.i.d.	Twice a day
CRF	Case Report/Record Form (paper or electronic)
CPO	Country Pharma Organization
CRO	Contract Research Organization
DS&E	Drug Safety & Epidemiology
ECG	Electrocardiogram
EDC	Electronic Data Capture
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS	Inhaled Corticosteroids
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Randomization Technology
o.d.	Once a day
p.o.	Oral
SAE	Serious adverse event

Glossary of terms

Assessment	A procedure used to generate data required by the study
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 <i>includes</i> 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 <i>does not include</i> other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage
Subject Number	A number assigned to each patient who enrolls into the study
Part	A subdivision of a single protocol into major design components. These parts often are independent of each other and have different populations or objectives. For example, a single dose design, a multiple dose design that are combined into one protocol, or the same design with different patient populations in each part.
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)
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study/investigational treatment was discontinued whichever is later
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), active drug run-ins or background therapy
Study/investigational treatment discontinuation	Point/time when patient permanently stops taking study/investigational treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points
Pack-Years	Number of Packs per day multiplied by the number of years smoking.

Amendment 1

Amendment rationale

According to the study protocol, the primary study objective is to evaluate the real-life effectiveness of QVA149 in the management of patients with COPD as assessed with the mean change in trough FEV₁ from baseline to 16 weeks. As a secondary objective, the impact of QVA149 on the mean change in trough FEV₁ from baseline to 4 weeks is to be assessed. The sponsor would like to clarify that trough FEV₁ is defined as the measurement made pre-dose. The purpose of this change is to ensure that there is no confusion with regards to the definition of the primary endpoint.

In addition, the minimum duration of on-going treatment with tiotropium or fixed dose combination of LABA/ICS, specifically combinations fluticasone propionate/salmeterol, while demonstrating persistence of symptoms indicating change of treatment to combination therapy, required for inclusion in the study has been reduced from 3 months to 6 weeks. The reason for this change is the fact that the benefits of tiotropium monotherapy or fixed dose combination of LABA/ICS are apparent within 6 weeks of treatment.

For drugs marketed in Canada, domestic reports of unusual failure in efficacy must be reported to the Marketed Health Product Directorate within 15 calendar days of the receipt of information by the Market Authorization Holder, (Novartis Canada). The protocol is therefore revised to add the obligation of reporting unusual Lack Of Efficacy, within 24 hours of becoming aware of such event to the local Novartis Drug Safety and Epidemiology department, for further processing.

Changes to the protocol

The described changes in the aforementioned amendment rationale are implemented throughout the protocol:

- Change “trough FEV₁” to “trough FEV₁ (pre-dose)” to clarify the definition of trough FEV₁ throughout the protocol.
- Change inclusion criterion #5 in the Inclusion Criteria sections of the Synopsis and section 4.1 of the protocol from “*On-going treatment with tiotropium or fixed dose combination of LABA/ICS, specifically combinations fluticasone propionate/salmeterol for a minimum of **three months** but demonstrating persistence of symptoms indicating change of treatment to combination therapy **using a CAT score > 10*” to “*On-going treatment with tiotropium or fixed dose combination of LABA/ICS, specifically combinations fluticasone propionate/salmeterol for a minimum of **6 weeks** but demonstrating persistence of symptoms indicating change of treatment to combination therapy **using a CAT score > 10*”.
- The safety reporting section 7 was modified to include the definition of Unusual Lack of Efficacy for the study medication, and describe the reporting requirement associated with this reportable Adverse Event, (section 7.4).

The opportunity was also taken to make the following changes:

- The 3rd paragraph of Section 5.5.9, stating that *"Patients who discontinue QVA149 treatment should NOT be considered withdrawn from the study. See Section 6 for the required assessments of these patients after discontinuation of QVA149 treatment."* was removed, as there are no further follow-up visits being done on patients who discontinue treatment with QVA149, except for a last evaluation, to be done, if possible, as per routine clinical care.
- The 3rd paragraph of Section 5.5.9, referenced above, was replaced by: *"If premature discontinuation of study occurs, after Visit 2, the patient should return to the clinic as soon as possible for a last follow-up visit, as per routine clinical care."* Section 6.1 was modified to specify the CRFs to be completed, for patients who discontinue the study after Visit 2 and after having received a first dose of study medication,
- Specifications were added to Section 6.4.3 to clarify the requirements for the assessor performing the Baseline Dyspnea Index –Transitional Dyspnea Index (BDI-TDI) interview.
- The patient population was further defined in the protocol synopsis and in protocol Section 4, to specify the FEV₁ range defining the moderate to severe airflow limitations according to the Global Initiative for Chronic Obstructive Lung Disease.
- The Assessment Schedule (Table 6-1) has been updated to add footnote 5, to clarify that no study medication should be taken at the last study visit, (Visit 5) and to specify that the last dose of study medication will be taken 24 hours before the last study visit, (Visit 5).
- The opportunity was also taken to correct any typographical errors and provide further clarification where required.

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.

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 require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

Protocol synopsis

Protocol number	CQVA149ACA01
Title	Prospective Cohort Study for the Real – Life Effectiveness Evaluation of GlycOpyrronium With IndacatERol in combination in the management of COPD in Canada (POWER)
Brief title	POWER - Effectiveness of Glycopyrronium with Indacaterol combination in COPD.
Sponsor and Clinical Phase	Novartis, Phase IV
Investigation type	Drug
Study type	Interventional
Purpose and rationale	<p>Chronic Obstructive Pulmonary Disease (COPD) affects over 770,000 Canadians or 4% of those over the age of 35 years. The symptoms include shortness of breath, cough and sputum production with progressive deterioration that eventually leads to early mortality.</p> <p>Long acting bronchodilators such as long acting anticholinergics and long acting β_2-agonists are recommended first line treatments for the treatment of COPD patients with persistent symptoms. Guidelines position the use of Inhaled Corticosteroids (ICS) in patients with frequent exacerbations – defined as more than one in the previous year. Although the majority of patients have few (or no) exacerbations, the current practice shows that more than 65% of patients are on triple therapy and that there is a gap in applying the guidelines.</p> <p>Indacaterol is the first long-acting β_2-agonist (LABA) bronchodilator providing 24-hour bronchodilation with once-daily dosing in patients with moderate to severe COPD. The efficacy and tolerability of indacaterol in COPD have been previously evaluated in placebo-controlled studies. In these studies the daily dose of indacaterol tested was 75 mcg, 150 mcg, 300 mcg and 600 mcg once daily.</p> <p>Glycopyrronium bromide is a long acting muscarinic antagonist (LAMA) that has been approved as a once-daily inhaled maintenance therapy for COPD. The data from</p>

	<p>randomized clinical trials (GLOW 1, 2 and 3) have shown that glycopyrronium is superior to placebo and non – inferior to tiotropium with respect to improved lung function, shortness of breath, exacerbations, use of rescue medication, improved quality of life and improved exercise tolerance ^(20,21,22). The safety profile and tolerability of glycopyrronium was similar to that of placebo in these trials. These results would support the use of glycopyrronium as first line monotherapy as well as part of combination therapy for the management of patients with COPD.</p> <p>QVA149 is the combination of both indacaterol 110 mcg and glycopyrronium 50 mcg that have showed significant improvement of lung function and clinical outcomes compared to standard care (23, 24). Results from ILLUMINATE and SHINE showed that FEV₁ was superior and clinically meaningful with QV149 compared than with fixed combination or with tiotropium respectively. Results from the trials also have shown a safety and tolerability profile similar to placebo, monotherapy or fixed dose combination versus QVA149 therapy ^(23, 24).</p> <p>To date, there are no real – life Canadian studies evaluating the effectiveness of indacaterol in combination with glycopyrronium bromide in the management of symptomatic patients when treated with tiotropium or fixed dose LABA/ICS specifically the combination of fluticasone propionate/salmeterol. In addition, data on the effectiveness and tolerability of this regimen under routine clinical care as administered by general practitioners and community physicians in the Canadian setting are not available.</p> <p>The purpose of this prospective interventional study is to evaluate the effectiveness of QVA149 on FEV₁, COPD symptoms, quality of life in COPD patients managed under a routine clinical care setting in Canada.</p>
Primary Objective(s) and Key Secondary Objective	<ol style="list-style-type: none"> 1. To evaluate the real-life effectiveness of QVA149 (indacaterol 110 mcg/glycopyrronium 50 mcg) in the management of patients with COPD who have symptoms defined as CAT score >10 with tiotropium monotherapy; effectiveness will be assessed as the mean change in trough FEV₁ (pre-dose) from baseline to 16 weeks. 2. To evaluate the real-life effectiveness of QVA149 (indacaterol 110 mcg/glycopyrronium 50 mcg) in the

	management of patients with COPD who have symptoms defined as CAT score > 10 while on treatment with FDC of fluticasone propionate/salmeterol; effectiveness will be assessed as the mean change in trough FEV ₁ (pre-dose) from baseline to 16 weeks.
Secondary Objectives	<p>In COPD patients that are managed in the routine clinical setting and are symptomatic while on treatment with tiotropium monotherapy or FDC of fluticasone propionate/salmeterol:</p> <ol style="list-style-type: none"> 1. To evaluate the impact of QVA149 on the mean change in trough FEV₁ (pre-dose) from baseline to 4 weeks. 2. To evaluate the impact of QVA149 on dyspnea as measured by the Baseline and Transition Dyspnea Index (BDI/TDI) at 4 and 16 weeks. 3. To evaluate the impact of QVA149 on patient quality of life as measured by the COPD Assessment Questionnaire (CAT) at baseline, week 4 and 16 weeks. <p>Exploratory objectives:</p> <p>In COPD patients that are managed in the routine clinical setting and are symptomatic while on treatment with tiotropium monotherapy or FDC of fluticasone propionate/salmeterol;</p> <ul style="list-style-type: none"> • To evaluate the impact of QVA149 on patient quality of life as measured by the Medical Outcomes Study Short Form – 36 (MOS - SF-36) and the Dimension Health Status Questionnaire (EQ-5D) at 4 (EQ-5D only) and 16 weeks of treatment. • To describe the patient and physician satisfaction with QVA149 treatment compared to previous therapies.
Study design	This is a single cohort, prospective post approval study conducted on approximately 710 patients with COPD treated by approximately 100 community and hospital based general practitioners and specialists across Canada. The study will enroll patients that have not responded to their current treatment of tiotropium alone or with fixed a dose combination of fluticasone propionate/salmeterol. All patients will be treated with QVA149 and will be followed for 16 weeks. With evaluations at -1 week, baseline 4, 12 and 16 weeks.
Population	The study will enroll adult patients with confirmed COPD, with

	<p>moderate to severe airflow limitations, according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD 2010), (specifically with baseline trough FEV₁ (pre-dose) values of $30\% \leq \text{FEV}_1 < 80\%$), that have not responded to their current treatment on tiotropium alone or on a fixed dose combinations of fluticasone propionate/salmeterol. Only patients for whom the physician has decided to change treatment due to lack of efficacy will be eligible to be enrolled in the study. The decision and choice of changing treatment must be reached prior to enrolling the patient in the study.</p>
Inclusion criteria	<ol style="list-style-type: none"> 1. Patient diagnosed and treated for moderate to severe COPD according to the Global Initiative for Chronic Obstructive Lung Disease according to physician's assessment.* Patient must have moderate to severe airflow limitation indicated by a trough FEV₁, (pre-dose) $\geq 30\%$ and $< 80\%$, obtained at the baseline, Visit 2. 2. Male or Female patients. 3. Age > 40 years. 4. Smoking history of > 10 pack – years. 5. On-going treatment with tiotropium or fixed dose combination of LABA/ICS, specifically combinations of fluticasone propionate/salmeterol for a minimum of 6 weeks, but demonstrating persistence of symptoms indicating change of treatment to combination therapy **using a CAT score > 10. 6. Treatment with QVA149 is indicated as per the product monograph and appropriate for the patient as per the judgment of the treating physician. 7. Patient has signed informed consent agreeing to participate in the study and undergo the study treatments and allowing the use of their data for the purposes of the study. 8. Patient is expected to be available for 16 weeks after study enrolment <ul style="list-style-type: none"> * Assessed as per routine care or as documented in the patient's chart. ** As determined and decided by the treating physician prior to enrolment of the patient in the study.
Exclusion criteria	<ul style="list-style-type: none"> • Patients not willing to sign an informed consent.

	<ul style="list-style-type: none">• Patients on maintenance treatment including triple therapy (LABA/LAMA/CS) for COPD• Patients with a diagnosis of asthma or history of asthma.• Patients who have had two or more moderate to severe exacerbations during the last 12 months prior to study enrolment. A moderate COPD exacerbation is defined by requirement for treatment with systemic corticosteroids or antibiotics or both. A severe COPD exacerbation is defined by hospitalization, including an emergency room visit of longer than 24 h.• Patients who had an exacerbation within 6 weeks prior to enrolment.• Patients who as per physician clinical judgment will require ICS treatment co-administered with QVA149 during the study period.• Patients with other chronic respiratory conditions that may affect the outcome of treatment including but not limited to lung cancer.• Patients with cancer or other condition that, in the opinion of the investigator will prevent them from participating in the study.• Patients participating in an investigational drug trial.• Patients with hypersensitivity to indacaterol maleate, glycopyrronium bromide or to any of their components.
Investigational and reference therapy	All patients will be treated with indacaterol 110 mcg/glycopyrronium 50 mcg combinations as per the Canadian Product Monograph. Study drug will be provided by the sponsor during the course of the study.
Efficacy assessments	The primary efficacy endpoint will be the change from baseline in trough FEV ₁ (pre-dose) at 16 weeks of treatment measured at the physician's office using a portable spirometer.
Safety assessments	<p>Information about all AEs, whether volunteered by the patient, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded on an Adverse Event Case Report Form and will be followed up as appropriate.</p> <p>All serious adverse events will also be reported to Novartis Drug Safety & Epidemiology (DS&E) within 24 hours of the investigator (or designee) being aware of the serious adverse event. Specific definitions of adverse events, and serious adverse events, are outlined below, along with reporting</p>

	criteria required by Novartis.
Other assessments	<p>Secondary Effectiveness Endpoints:</p> <ul style="list-style-type: none">• Change from baseline in trough FEV₁ (pre-dose) at 4 weeks of treatment.• Change from baseline in the CAT score at baseline and 16 weeks of treatment.• Change in the Transition Dyspnea Index (TDI) after 16 weeks of treatment. <p>Exploratory Endpoints:</p> <ul style="list-style-type: none">• Change from baseline to 16 weeks in Quality of Life and Functional Status as measured by the Medical Outcomes Study Short Form – 36 (MOS - SF-36) and the Dimension Health Status Questionnaire (EQ-5D).• Patient and Physician Global Satisfaction with COPD treatment measured at 4, 12 & 16 weeks.
Data analysis	<p>The primary effectiveness outcome measure of the study will be the change from baseline to 16 weeks in trough FEV₁ (pre-dose) measurements in patients treated with indacaterol / glycopyrronium combination. This will be assessed by the mean change in FEV₁ between week 16 and the baseline visits. The precision of the estimate will be assessed with the 95% confidence interval. Multivariate methods and sub group analyses will be used to identify possible determinants of the change in FEV₁ at 16 weeks of treatment. Similar descriptive methods will be used to address the secondary and exploratory objectives of the study.</p>
Key words	COPD, indacaterol, glycopyrronium, FEV ₁ , Quality of Life, Effectiveness, Safety.

1 Introduction

1.1 Background

Chronic Obstructive Pulmonary Disease (COPD) affects over 770,000 Canadians or 4% of those over the age of 35 years. The symptoms include shortness of breath, cough and sputum production with progressive deterioration that eventually leads to early mortality. The disease is the leading cause of all hospitalizations in Canada with direct health care costs being over 1.5 billion dollars per year⁽¹⁻⁷⁾. To date there is no cure for COPD and patient management is focused on managing symptoms, reducing the severity and frequency of exacerbations and improving the patient's quality of life⁽⁸⁻¹¹⁾.

Long acting bronchodilators such as long acting anticholinergics and long acting β_2 -agonists are recommended first line treatments for the treatment of COPD patients with persistent symptoms. Guidelines position the use of ICS in patients with frequent exacerbations – defined as more than one in the previous year. Although the majority of patients have few (or no) exacerbations, current practice shows that more than 65% of patients are on triple therapy indicating that there is a gap in applying the guidelines⁽¹²⁻¹⁷⁾.

Indacaterol is the first long-acting β_2 -agonist (LABA) bronchodilator providing 24-hour bronchodilation with once-daily dosing in patients with moderate to severe COPD. The efficacy and tolerability of indacaterol in COPD have been previously evaluated in placebo-controlled studies. In these studies the daily dose of indacaterol tested was 75 mcg, 150 mcg, 300 mcg and 600 mcg once daily^(18-19,25,28). Glycopyrronium bromide (GB) is a long acting muscarinic antagonist (LAMA) that has been approved as a once-daily inhaled maintenance therapy for COPD. The data from randomized clinical trials (GLOW 1, 2 and 3) have shown that GB is superior to placebo and non – inferior to tiotropium with respect to improved lung function, shortness of breath, exacerbations, use of rescue medication, improved quality of life and improved exercise tolerance^(20,21,22). The safety profile and tolerability of GB was similar to that of placebo in these trials. These results support the use of GB as first line monotherapy as well as part of combination therapy for the management of patients with COPD.

QVA149 is a combination of both indacaterol 110 mcg and glycopyrronium 50 mcg and has demonstrated significant improvement of lung function and clinical outcomes compared to standard of care (23, 24). Results from ILLUMINATE and SHINE showed that treatment with QVA149 was associated with clinically important and statistically significantly higher improvement in FEV₁ when compared to fixed dose combination salmeterol – fluticasone and tiotropium monotherapy.^(23, 24)

1.2 Purpose

To date, there are no real – life Canadian studies evaluating the effectiveness of indacaterol in combination with glycopyrronium bromide in the management of symptomatic patients when treated with tiotropium or fixed dose LABA/ICS (specifically the combination of fluticasone propionate/salmeterol). In addition, data on the effectiveness and tolerability of this regimen under routine clinical care as administered by general practitioners and community physicians in the Canadian setting are not available.

The purpose of this prospective interventional study is to evaluate the effectiveness of QVA149 on FEV₁; COPD symptoms, and quality of life in COPD patients managed under a routine clinical care setting in Canada.

2 Study objectives

2.1 Primary objectives

1. To evaluate the real-life effectiveness of QVA149 (indacaterol 110 mcg/glycopyrronium 50 mcg) in the management of patients with COPD who have symptoms defined as CAT score >10 with tiotropium monotherapy; effectiveness will be assessed as the mean change in trough FEV₁ (pre-dose) from baseline to 16 weeks.
2. To evaluate the real-life effectiveness of QVA149 (indacaterol 110 mcg/glycopyrronium 50 mcg) in the management of patients with COPD who have symptoms defined as CAT score >10 while on treatment with FDC of fluticasone propionate/salmeterol; effectiveness will be assessed as the mean change in trough FEV₁ (pre-dose) from baseline to 16 weeks.

2.2 Secondary objectives

In COPD patients that are managed in a routine clinical setting and are symptomatic while on treatment with tiotropium monotherapy or FDC of fluticasone propionate/salmeterol:

1. To evaluate the impact of QVA149 on the mean change in trough FEV₁ (pre-dose) from baseline to 4 weeks.
2. To evaluate the impact of QVA149 on dyspnea as measured by the Baseline and Transition Dyspnea Index (BDI/TDI) at 4 and 16 weeks.
3. To evaluate the impact of QVA149 on patient quality of life as measured by the COPD Assessment Questionnaire (CAT) at 4 and 16 weeks.

2.3 Exploratory objectives

In COPD patients that are managed in a routine clinical setting and are symptomatic while on treatment with tiotropium monotherapy or FDC of fluticasone propionate/salmeterol;

- To evaluate the impact of QVA149 on patient quality of life as measured by the Medical Outcomes Study Short Form – 36 (MOS - SF-36) and the Dimension Health Status Questionnaire (EQ-5D), 4 (EQ-5D only) and at 16 weeks of treatment.
- To describe the patient and physician satisfaction with QVA149 treatment at 4, 12, and 16 weeks.

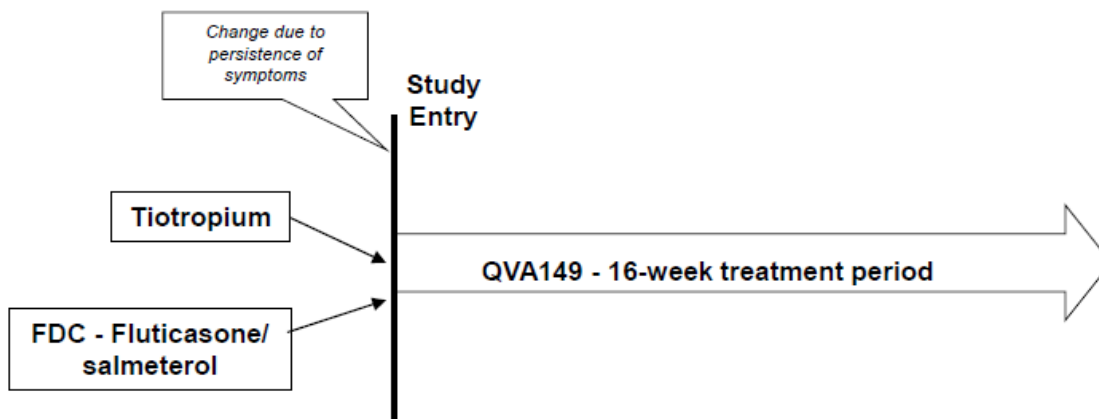
3 Investigational plan

3.1 Study design

This is a real – life, prospective post approval study conducted on approximately 710 patients diagnosed with COPD and treated by approximately 100 general practitioners and community specialists across Canada. The study will enroll patients who are symptomatic while on current monotherapy with tiotropium alone or FDC (fluticasone propionate/salmeterol) with a 3:2 ratio. Only patients for whom the physician has decided to change treatment due to the persistence of symptoms (based on CAT score) despite treatment will be eligible to be enrolled in the study. On-going treatment will be interrupted for 24 hours for patients treated with Tiotropium and 12 hours for patients on FDC treatment. Subsequently all patients will be treated with QVA149 for 16 weeks as part of the active treatment in the study in order to describe the course of treatment, change in treatments and disease outcomes including incidence of exacerbations.

The following diagram describes the study design:

Figure 1.
Study Design



3.2 Rationale of study design

This is a single cohort prospective study that is aimed at assessing the effectiveness of Indacaterol/glycopyrronium combination in COPD patients that have failed to respond to previous treatment with tiotropium monotherapy or with an ICS/LABA fixed dose combination. Given that the objective of the study is to describe the incremental benefit of indacaterol/glycopyrronium combination on respiratory function in this patient population that has failed previous treatment, the single cohort design is appropriate. In this study the pre-treatment respiratory function of the patient will serve as the control against which the incremental effect of the interventional treatment will be assessed. Furthermore, this design best emulates the routine care setting in which physicians will decide the switch patients from one treatment to another when adequate therapeutic response cannot be achieved.

The open label design of the study may make it susceptible to ascertainment bias given that the patients and physicians will be aware of the fact that a new treatment regimen will be used. However, standardization of the efficacy endpoint assessments including FEV₁ and the use of validated tools to measure patient centric outcomes will reduce this bias. Confounding by indication will be reduced by the fact that the decision to change treatment will have been reached prior to enrolment of the patient in the study and it will be on the basis of a-priori established criteria indicating treatment failure. Random confounding will be prevented by the fact that patients will act as their own controls.

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

All patients will be treated with the indacaterol 110 mcg /glycopyrronium 50 mcg combination in accordance with the approved Canadian product labeling and monograph.

3.4 Rationale for choice of comparator

Not Applicable

3.5 Purpose and timing of interim analyses/design adaptations

An interim analysis will be performed when 300 patients will have completed their Visit 3.

3.6 Risks and benefits

The risk to subjects in this trial will be minimized by compliance with the inclusion/exclusion criteria, close clinical monitoring and use of the study medications according to the product monograph and label under the supervision of the treating physician. Potential benefits to the patients may be related to steroid sparing. More specifically, the benefits of ICS over and above LAMA / LABA combinations in the management of COPD are debatable while the increased risk for adverse outcomes related to long term use of corticosteroids is well documented. Therefore, the benefit – risk ratio for LAMA – ICS/ LABA combination may be suboptimal for patients with COPD. Treatment with Indacaterol/glycopyrronium combination does not involve the use of ICS and hence may provide a corticosteroid free treatment to COPD patients without compromising therapeutic efficacy.

4 Population

The target population of the current study is patients with moderate to severe COPD, according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD 2010), (specifically with baseline trough FEV₁ (pre-dose) values of FEV₁ 30% ≤ FEV₁ < 80%), that have not achieved therapeutic response with respect to control of their symptoms while on treatment with tiotropium as monotherapy or a FDC of fluticasone propionate/salmeterol. COPD patients that are intolerant to tiotropium or the FDC of fluticasone propionate/salmeterol are included in the target population. For these patients a change in treatment is indicated. The study will exclude patients with more than one previous exacerbation in the previous year to ensure that homogeneous cohorts of low exacerbation risk patients are included in the study. Approximately 710 patients will be recruited from the practices of about 100 general practitioners and community physicians or specialists will be enrolled in the study.

4.1 Inclusion criteria

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

1. Patient diagnosed and treated for moderate to severe COPD according to the Global Initiative for Chronic Obstructive Lung Disease according to physician's assessment*. Patient must have moderate to severe airflow limitation indicated by a trough FEV₁ (pre-dose) ≥ 30% and <80%, obtained at the baseline, Visit 2.
2. Male or Female patients.
3. Age > 40 years.
4. Smoking history of > 10 pack – years.
5. On-going treatment with tiotropium or fixed dose combination of LABA/ICS, specifically combinations fluticasone propionate/salmeterol for a minimum of 6 weeks but demonstrating persistence of symptoms indicating change of treatment to combination therapy **using a CAT score > 10.

6. Treatment with QVA149 is indicated as per the product monograph and appropriate for the patient as per the judgment of the treating physician.
7. Patient has signed informed consent agreeing to participate in the study and undergo the study treatments and allowing the use of their data for the purposes of the study.
8. Patient is expected to be available for 16 weeks after study enrolment

* *Assessed as per routine care or as documented in the patient's chart.*

** *As determined and decided by the treating physician prior to enrolment of the patient in the study.*

4.2 Exclusion criteria

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

1. Patients not willing to sign an informed consent.
2. Patient on maintenance treatment including triple therapy (LABA +LAMA+ICS) for COPD
3. Patients with a diagnosis of asthma or history of asthma.
4. Patients who have had two or more moderate to severe exacerbations during the last 12 months prior to study enrolment. A moderate COPD exacerbation is defined by requirement for treatment with systemic corticosteroids or antibiotics or both. A severe COPD exacerbation is defined by hospitalization, including an emergency room visit of longer than 24 h.
5. Patients who had an exacerbation within the previous 6 weeks to enrolment.
6. Patients who as per physician clinical judgment will require ICS treatment co-administered with QVA149 during the study period.
7. Patients with other chronic respiratory conditions that may affect the outcome of treatment including but not limited to lung cancer.
8. Patients with cancer or other condition that, in the opinion of the investigator will prevent them from participating in the study.
9. Patients participating in an investigational drug trial.
10. Patients with hypersensitivity to indacaterol maleate, glycopyrronium bromide or to any of their components and any excipients of their formulations.
11. Use of other investigational drugs within 30 days of enrollment in the study.
12. Patients who are unable or unwilling to comply with study procedures, attend scheduled study visits, complete questionnaires and daily diaries, or who may otherwise be unable to comply with the study requirements.

13. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
14. 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 subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
 - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
 - Male sterilization (at least 6 m prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
 - 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. 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.
 - Placement of an intrauterine device (IUD) or intrauterine system (IUS)

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

5 Treatment

5.1 Protocol requested treatment

5.1.1 Investigational treatment

All patients will be treated with receive Indacaterol (as maleate)/ glycopyrronium (as bromide) inhalation powder hard capsules 110 mcg/50mcg per capsule with ULTIBRO[®] BREEZHALER[®]. The product will be obtained from commercial stocks and sent to individual investigational site once all regulatory documents and those individual site preparation activities are completed.

ULTIBRO[®] is a registered trademark. BREEZHALER[®] is a registered trademark.

5.1.2 Additional study treatment

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

5.2 Treatment arms

All patients will be treated with indacaterol 110 mcg/glycopyrronium bromide 50 mcg. This is a single cohort open label study in which no randomization for treatment allocation applies.

5.3 Treatment assignment, randomization

This is a single cohort open label study in which no randomization for treatment allocation applies. Selection bias will be prevented by enrolling sequential eligible patients at each site.

5.4 Treatment blinding

Not applicable.

5.5 Treating the patient

5.5.1 Patient numbering

Each patient is uniquely identified by a Subject Number which is composed of the 4-digit site number assigned by Novartis and a sequential 5-digit number assigned to each patient by the investigator. Once assigned to a patient, the Subject Number will not be reused. If a patient had initially failed based on eligibility and is further re-screened, a new Subject Number should be used for this patient.

Upon signing the informed consent form during the first Visit, the patient is assigned the next sequential Subject Number by the investigator. If the patient fails to be treated for any reason, the investigator will complete the Study Completion / Premature Discontinuation CRF and the reason for not being treated will be entered.

5.5.2 Dispensing the investigational treatment

Each study site will be supplied by Novartis with investigational treatment in packaging from commercial stock with additional labels to comply with Novartis requirements for drugs used for clinical research purpose.

5.5.3 Handling of study treatment

5.5.3.1 Handling of investigational treatment

Investigational treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and 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 investigational treatment but no information about the patient except for the unique study identification number.

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

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

5.5.4 Instructions for prescribing and taking study treatment

Indacaterol 110 mcg/50 mcg glycopyrronium, i.e. ULTIBRO[®] BREEZHALER[®]. will be taken once daily as indicated in the Canadian product monograph.

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

5.5.5 Permitted dose adjustments and interruptions of study treatment

For patients who are unable to tolerate the protocol-specified dosing scheme should discontinue QVA149 treatment and be discontinued from the trial.

5.5.6 Rescue medication

In the current study use of inhaled SABA, theophylline will be allowed. Use of rescue medication must be recorded on the COPD Concomitant medications section in the CRF.

5.5.7 Concomitant treatment

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

5.5.8 Prohibited Treatment

Corticosteroids should not be prescribed to the study patient during the trial. If it is determined as per clinical judgment that a patient needs to be treated with corticosteroids the patient should be discontinued from the trial.

5.5.9 Discontinuation of study treatment and premature patient withdrawal

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, fail to return for visits, or become lost to follow-up for any other reason.

If premature withdrawal occurs for any reason, the investigator must make every effort to determine the primary reason for a patient's premature withdrawal from the study and record this information. QVA149 treatment must be discontinued.

The investigator should discontinue QVA149 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 or if the patient no longer fulfills the study inclusion and exclusion criteria, namely the use of ICS during the trial.

If premature discontinuation of study occurs, after Visit 2, the patient should return to the clinic as soon as possible for a last follow-up visit, as per routine clinical care.

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

Patients completing 16 weeks of treatment will be considered as completing the study. The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

5.5.12 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 for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

6 Visit schedule and assessments

Table 6-1 lists all of the assessments and indicates with an "x" when the visits are performed. Patients should be seen for all visits on the designated day with an allowed "visit window" of "5" days, or as close to it as possible.

Table 6-1 Assessment schedule

Visit number	1¹	2	3	4	5
Time of Visit (weeks)	-1	0	4	12	16
Time window		(-6 days)¹	(±5 days)	(±5 days)	(±2 days)
Informed consent	X				
Demographics	X				
Inclusion & Exclusion Criteria	X				
Physical Examination	X ²	X ³	X ³	X ³	X ³
Medical History	X				
COPD History	X				
Smoking History	X				
Alcohol Use History	X				
Concomitant Medication Use	X	X	X	X	X
Current Treatment for COPD	X				
Previous Treatment for COPD	X				
Instruction to interrupt COPD medication (tiotropium or LABA/ICS) before V ₂	X				
Urine pregnancy test for women with childbearing potential	X				X
Pre-dose FEV ₁		X	X		X
BDI		X			
TDI			X		X
CAT	X		X		X
Sf-36, EQ-5D		X	X ⁴		X
Treatment Compliance (Missed Doses)			X	X	X
Physician Global Satisfaction			X	X	X
Patient Global Satisfaction			X	X	X
Adverse Events		X	X	X	X
Drug Accountability		X	X	X	X ⁵

1. *The visit 1 is a screening visit. Patients may come back for their visit 2 for 24 hours after interrupting their COPD medication with Tiotropium or 12 hours if they are on a FDC. The visit 2 should not occur later than 6 days after the visit 1.*
2. *Physical examinations per routine care.*
3. *Changes in physical examination only*
4. *At visit 3 only the EQ-5D questionnaire should be completed*
5. *The last dose of study medication will be taken 24 hours before the last study visit, (Visit 5).*

6.1 Information to be collected on screening failures

All patients who have signed informed consent but not completing the trial beyond V1 will have CRF completed for the demographics, inclusion/exclusion, and SAE data collected. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data. Patients who discontinue the study after Visit 2 and after having received a first dose of study medication, should have the study completion/discontinuation page completed, in addition to the above listed CRF.

For all patients who have signed informed consent and are continuing study will have all adverse events **occurring after informed consent is signed** recorded on the Adverse Event CRF.

6.2 Patient demographics/other baseline characteristics

For each potentially eligible patient, during the baseline assessment the eligibility criteria will be determined. At the same visit the following data will be collected:

- Date of Birth
- Gender
- Race
- Smoking History and Status:
 - Number of Pack-Years
 - Current Smoker (Y/N)
 - Number of packs / day
- Alcohol Consumption History and Status
 - Number of alcoholic beverages / day
- Medical History
 - Presence of Targeted Chronic Conditions: osteoporosis, diabetes, allergy, dysphonia
- Physical Examination (as per routine care)
 - Vital Signs (Blood Pressure, Pulse)
 - Weight
 - Height
 - BMI (Calculated from Weight and Height)

- Concomitant Medication Use
 - Medication Name
 - Dose
 - Indication
 - Start Date
- COPD History:
 - Duration of the Disease (Time since diagnosis)
 - Prior Treatment with duration and reason for discontinuation
 - Number of Exacerbations during the 12 months prior to entry in the study
- Current COPD treatments:
 - Medication name
 - Dose

6.3 Treatment exposure and compliance

Self-reported compliance with treatment will be ascertained at every visit by determining the number of daily QVA149 doses missed

6.4 Efficacy

The following efficacy assessments will be conducted::

Primary Effectiveness Assessment:

- Pre-dose FEV₁

Secondary Effectiveness Endpoints:

- COPD Assessment Questionnaire (CAT)
- Baseline Dyspnea Index –Transitional Dyspnea Index (BDI-TDI)
- Medical Outcomes Study Short Form 36 (SF-36) and in the Dimension Health Status Questionnaire (EQ-5D)
- Patient and Physician Global Satisfaction with COPD Treatment

6.4.1 FEV₁:

The evaluation of the primary endpoint is based on change from baseline in trough FEV₁ (pre-dose) at 16 weeks of treatment. Investigator should instruct patient to not take their study drug before measuring their FEV₁ at the clinic. Investigators may opt to use the services of spirometry center if readily accessible for FEV₁ measurements. For investigators who have no access to spirometry, portable spirometers will be provided to investigators and they will use this device for all of their patient measurements of FEV₁ during the trial. The devices will be returned to Novartis at the end of the study.

6.4.2 COPD Assessment Test:

Change from baseline in the CAT will be assessed at baseline 4 and 16 weeks. The CAT is an 8 item questionnaire that assesses the impact of COPD on the patient's functional status. The item scores range from 0 to 5 (0 = no impairment). An overall score is calculated by adding the score from each item.

6.4.3 Baseline Dyspnea Index –Transitional Dyspnea Index (BDI-TDI):

The BDI and TDI measure dyspnea symptoms at a single point in time (BDI), and measuring changes in breathlessness from this baseline state over time (TDI). BDI and TDI are scores are obtained by interview conducted by the assessor, at 4 and 16 weeks. The questions assess the patient's subjective experience of breathlessness and its impact on activities of daily living. The assessor is the designated site personnel qualified, with experience in obtaining history of respiratory disease or documented training on administration of BDI-TDI.

6.4.4 Medical Outcomes Study Short Form – 36 (SF-36) and the Dimension Health Status Questionnaire (EQ-5D):

Change in the SF – 36 from baseline will be assessed at 16 weeks. The SF-36 is a self-administered general quality of life assessment tool that consists of 36 items that converge into eight scales measuring Physical Function (PF), Role Limitations caused by Physical Problems (RP), Pain (BP), General Health (GH), Vitality/Energy (VT), Social Function (SF), Mental Health/Emotional Well-Being (MH) and Role Limitations caused by emotional problems/mental health (RE). The eight scales are summarized even more into two dimensions, one assessing physical and the other mental health. The SF-36 has been validated in a large number of disease states and Canadian age – specific normal values are available for comparison. In addition, the tool has been used in several studies assessing quality of life in patients with COPD and can be used to calculate QALY values.

Change in the EQ-5D from baseline will be assessed at 4 and 16 weeks. The EQ-5D is a simple but effective standardized instrument designed for use as a measure of health outcome. There are two parts to this questionnaire. The first, 'health state classification' consists of five questions. The second, 'Visual Analogue Scale Thermometer' consists of a visual analogue scale. This generates a self-rating of current health-related quality of life. EQ-5D enables an accurate self-description of current health-related quality of life to be easily recorded. Self-explanatory instructions to respondents are provided within the questionnaire and it takes about 2 min to complete.

6.4.5 Appropriateness of efficacy assessments

- COPD Assessment Questionnaire (CAT):
 - This is a standardized questionnaire used to assess quality of life and functional capacity in patients with COPD.
- Baseline Dyspnea Index –Transitional Dyspnea Index (BDI-TDI):

- These are measurements assessing the severity of COPD symptoms at baseline and the change in symptoms over time.
- Medical Outcomes Study Short Form 36 (SF-36) and the Dimension Health Status Questionnaire (EQ-5D):
 - The SF-36 and EQ-5D as a general measure of Quality of Life
- Patient and Physician Global Satisfaction with COPD Treatment

6.5 Safety

The safety assessments include adverse events.

6.5.1 Physical examination

A complete physical examination will be conducted if part of regular clinical practice at the baseline visit and may include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. Blood pressure (SBP/DBP) and pulse will also be measured and recorded.

A short physical exam will be conducted at all follow up visits and will include the examination of general appearance and vital signs (blood pressure [SBP and DBP] and pulse).

Information for all physical examinations should be included in the source documentation at the study site. Significant findings that are present prior to signing informed consent must be included in the Medical History part of the CRF. Significant findings made after signing the informed consent which meet the definition of an Adverse Event must be recorded on the Adverse Event section of the CRF.

6.5.2 Vital signs

Blood pressure measurements and pulse will be recorded when assessed as per routine care.

6.5.3 Height and weight

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

6.5.4 Laboratory evaluations

Not applicable.

6.5.4.1 Hematology

Not applicable.

6.5.4.2 Clinical chemistry

Not applicable.

6.5.4.3 Urinalysis

Not applicable

6.5.5 Electrocardiogram (ECG)

Not applicable.

6.5.6 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile (women of child-bearing potential) will have a local urine pregnancy test performed at Screening (Visit₁) and at the end of the trial. If a local urine pregnancy test at screening shows a positive result, then a serum β -hCG test must be done. If positive, the patient should not enter in the study.

6.5.7 Appropriateness of safety measurements

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

6.5.8 Pharmacokinetics

Not Applicable.

6.5.9 Pharmacogenetics /pharmacogenomics

Not Applicable.

6.5.10 Other biomarkers

Not Applicable.

7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease and unusual lack of therapeutic efficacy*) 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. (*Refer to section 7.4 for unusual lack of therapeutic efficacy definition and reporting requirements).

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

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

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

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

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

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

An SAE is any adverse event (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical condition(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.

For QVA149, there are events which are the object of more targeted follow-up activities as per regulatory commitments. The local Novartis DS&E Department will perform the follow-up: on the following events regardless of seriousness:

- Atrial fibrillation
- Cardiac arrhythmias (Brady-Tachy arrhythmias)
- Cardiac Failure
- Cerebrovascular events
- Hyperglycemia
- Intubation, hospitalization and death due to asthma related events in asthma (off label use)
- Ischemic Heart disease
- Myocardial Infarction
- Narrow-angle glaucoma
- QTc prolongation

Unlike routine safety assessments, SAEs, pregnancies and Unusual Lack of Efficacy are monitored continuously and have special reporting requirements; see Section 7.2 and 7.4.

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

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

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

7.2 Serious adverse event reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days after the last study visit must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after the 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

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

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

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

Follow-up information provided should describe whether the event has resolved or continues, if and how it was treated, 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 Product Monograph (new occurrence) and is thought to be related to the investigational treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same investigational treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

7.3 Pregnancy reporting

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

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

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

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

7.4 Lack of Efficacy, (LOE) and LOE reporting

Lack of Efficacy is defined as a technical failure of a compound to meet its efficacy goals, to produce the expected intended effect, and is subject to quality assurance testing to confirm that the manufacturing of the compound is appropriate. Therefore, unusual lack of efficacy should be sent within 24 hours of awareness to the local Novartis Drug Safety and Epidemiology Department at [REDACTED]. The original copy of the e-mail correspondence should be kept at the study site.

Clinical judgment should be exercised by a qualified health care professional to determine if the problem reported is related to the product itself, rather than one of treatment selection or disease progression since health products cannot be expected to be effective in 100% of the patients. One example of unusual failure in efficacy is a previously well-stabilized condition that deteriorates when the patient changes to a different brand or receives a new prescription

The following situations are examples when Unusual Lack of Efficacy is considered:

- The patient's disease was stable and controlled. Suddenly, an unexplainable loss of efficacy is reported, with no change in the drug dosage or the severity of the medical condition.
- The loss of efficacy happened despite proper dosage administration and adequate duration of therapy, as per labeling instructions.
- The loss of efficacy happened after switching to a new batch of medication.
- The loss of efficacy reported is in association with some specific units within the same package / box, only.

7.5 Periodic Reconciliation

Periodic reconciliation between the clinical and safety databases shall be performed at a frequency of at least 6 months, at interim analysis (if applicable) and at the end of the study.

8 Data review and database management

8.1 Site monitoring

Sites will be selected to participate in the study based on their clinical research experience and their responses to the Novartis feasibility questionnaire. Before study initiation, each site will have initiation visit where the CRO monitor will review the protocol and CRFs with the investigators and their staff. Investigator and their staff will also be invited to participate in an Investigator's Meeting. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study 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 information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. Data not requiring a separate written record will be defined before study start and will be recorded directly on the CRFs. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

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

8.2 Data collection

Designated investigator staff must enter the information required by the protocol onto the Novartis paper CRFs. CRO monitors will review the CRFs for completeness and accuracy and instruct site personnel to make any required corrections or additions. The CRFs are forwarded to the Medical Documents Reception Center of Novartis by the investigational site, with one copy being retained at the investigational site. Once the CRFs are faxed to Novartis their receipt is kept and date entered into a database. Original CRF will remain at the site.

8.3 Database management and quality control

Data from the CRFs are entered into the study database by Novartis staff following internal standard operating procedures.

Subsequently, the entered data are systematically checked by Data Management staff, using error messages printed from validation programs and database listings. Other errors or omissions are entered on Data Query Forms, which are returned to the investigational site for resolution. The signed original and resolved Data Query Forms are kept with the CRFs at the investigator site, and a copy is sent to Novartis so the resolutions can be entered into the database. Quality control audits of all key safety and efficacy data in the database are made prior to locking the database.

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

8.4 Data Monitoring Committee

Not required.

8.5 Adjudication Committee

Not required.

9 Data analysis

9.1 Analysis sets

This is a single cohort interventional study. All patients receiving the study treatment and have returned for at least one follow up visit will be included in the Intent to Treat (ITT) analysis set. All patients receiving one dose of the study treatment will be included in the safety data set. All patients fulfilling all the study inclusion and exclusion criteria and have undergone all study visit assessments will be included in the Per-Protocol data set.

9.2 Patient demographics and other baseline characteristics

The patient demographics will be analyzed descriptively. Means, medians, standard deviation and 95% confidence interval of the mean will be used to describe the patient demographics.

9.3 Treatments

Exposure to the study treatment and other concomitant treatments will be ascertained by patient questionnaires and prescription refills.

9.4 Analysis of the primary and key secondary variable(s)

9.4.1 Variable(s)

The primary effectiveness variable will be the absolute change in trough FEV₁ (pre-dose) from baseline to the Week 16 visit.

The following secondary effectiveness variables will also be analyzed:

- Change in trough FEV₁ (pre-dose) between baseline and 4 weeks of treatment.
- Change in COPD Assessment Questionnaire (CAT) between baseline, 4 and 16 weeks of treatment.
- Baseline Dyspnea Index –Transitional Dyspnea Index (BDI-TDI) at baseline, 4 and 16 weeks of treatment.
- Change in the Medical Outcomes Study Short Form 36 (SF-36) and in the Dimension Health Status Questionnaire (EQ-5D) between baseline, 4 (EQ-5D only) and 16 weeks of treatment.
- Change in Patient and Physician Global Satisfaction with COPD Treatment between at 4, 12 and 16 weeks of treatment.

9.4.2 Statistical model, hypothesis, and method of analysis

The primary objective of the current study is to describe the effectiveness of treatment of QVA149 in the management of patients with COPD. Effectiveness will be assessed primarily with the change in FEV₁ between baseline and 16 weeks of treatment. Given the descriptive nature of the study there is no a priori-defined hypothesis. The mean change in trough FEV₁ (pre-dose) between baseline and 16 weeks of treatment will be estimated. The 95% confidence interval of the change in FEV₁ will be used to assess the precision of the estimate and to make inferences to the target population. The analysis will be repeated for subgroup of patients classified according to prior COPD treatment, specifically, tiotropium monotherapy or ICS/LABA fixed dose combination.

Between subgroup differences with respect to the effectiveness variables will be assessed descriptively with appropriate bivariate statistical methods, specifically the Student's t-test for independent samples for continuous scale variables and the Chi-Square test for categorical variables.

General linear models with repeated measures and random effects will be used to describe the change in the effectiveness variables over time, to assess the adjusted between subgroup differences and to identify determinants of variability in response to treatment.

9.4.3 Handling of missing values/censoring/discontinuations

There will be no imputation for missing data. The analysis will be conducted on observed cases. However, the mixed effects repeated measures models will compensate for missing data.

9.4.4 Supportive analyses

Not Applicable.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

Similar analyses as those used for the primary objective will be used to assess the secondary objectives pertaining to the secondary effectiveness variables.

9.5.2 Safety variables

All treatment emergent adverse events will be coded and classified according to the MedDRA dictionary of terms. The incidence of adverse events will be reported as the number of patients with more than one event and the number of events per patient. Incidence of adverse events will be described according to severity and causality in relation to the study treatment.

9.5.3 Health-related Quality of Life

All scales of the SF-36 and EQ-5D will be analyzed with emphasis on the physical health dimension. The CAT will be analyzed as a whole.

9.5.4 Pharmacokinetics

Not Applicable.

9.5.5 Pharmacogenetics/pharmacogenomics

Not Applicable.

9.5.6 Biomarkers

Not Applicable.

9.5.7 PK/PD

Not Applicable.

9.6 Interim analyses

An interim analysis will be performed when 300 patients will have completed their V₃.

9.7 Sample size calculation

The primary effectiveness outcome measure of the study will be the change from baseline to 16 weeks in trough FEV₁ (pre-dose) measurements in patients treated with QVA149. Therefore, the study must have sufficient sample size to produce a precise estimate of these changes in FEV₁. Precision is assessed by the width of the 95% confidence interval.

In the SPARK study the mean difference between QVA149 (indacaterol 110 mcg + glycopyrronium) and tiotropium with respect to trough FEV₁ was between 0.060 L – 0.080 L during 64 weeks of treatment. In the SHINE study the difference between tiotropium and QVA149 at 26 weeks was 0.08 L.

In the ILLUMINATE study the difference between QVA149 and fixed dose combination LABA/ICS with respect to FEV₁ at 12 weeks was 0.092 L.

Using the 95% CI and SEM estimates from these studies the calculated SD for the change in FEV₁ at 16 weeks is approximately 0.220 L.

Sample size calculations for the current study are based on the primary objective which is to describe the change in FEV₁ at 16 weeks after the initiation of treatment on indacaterol + glycopyrronium. The precision of the estimated mean change in FEV₁ at 16 weeks, as assessed by the 95% confidence interval, is the parameter driving the sample size.

For the current study we can assume a mean change in FEV₁ at 16 weeks of 0.080 L for the patients previously treated with tiotropium monotherapy and approximately 0.092 L for the patients previously treated fixed dose combination with LABA / ICS.

The sample size requirements of the study have been determined on the basis of the above parameters and in order to achieve a 95% confidence interval of the mean change in FEV₁ at 16 weeks with a width ($\omega/2$) of $\pm 30\%$ of the point estimate. This value is comparable with the results reported in the above clinical trials and provides reasonable precision of the estimated FEV₁ change at 16 weeks. Assuming a 0.080 L mean change in FEV₁ for the patients previously treated with tiotropium the 95% confidence interval for this cohort will be between 0.056 L – 0.104 L; for the patients previously treated with fixed dose combination LABA/ICS assuming a mean change in FEV₁ of 0.092 L the 95% confidence interval will be between 0.064 L and 0.120 L. For purposes of sample size calculations, for both cohorts the SD of the mean change in FEV₁ between baseline and 16 weeks will be assumed to be 0.220 L.

Based on the above criteria and assumptions, for the cohort of patients previously treated with tiotropium the sample size requirement is 323 patients. For the patients previously treated with fixed dose combination LABA/ICS the sample size requirement is 245 patients. The total sample size of the study will be 568. Assuming a 20% attrition rate, the total number of patients recruited will be 710 (404 previously treated with tiotropium and 306 previously treated with fixed dose combination LABA/ICS).

Patient enrolment will be designed to enroll at a 3:2 ratio of patients previously treated with tiotropium to those previously treated with fixed dose combination LABA/ICS per individual site and at the study level. Once study-wise recruitment has been completed for one of the strata, the each site will be instructed to pursue recruitment onto the other stratum only.

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US 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-approved informed consent. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

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

10.3 Responsibilities of the investigator and IRB/IEC

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

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 it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

11.1 Protocol Amendments

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

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Appendix 1: COPT Assessment Test

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

There are eight questions in the CAT. COPD patients should read the two statements for each item, and mark where on the scale (0-5) they fit. Scores for each of the 8 items are summed to give an overall score (out of 40).

The CAT questionnaire:

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 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

Appendix 2: Baseline Dyspnea Index and Transition Dyspnea Index (BTI-TDI)

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

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 categorized.
- ☐ 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 categorized.
- ☐ X: *Unknown*. Information unavailable regarding limitation of magnitude of task.
- ☐ Y: *Impaired for Reasons Other than Shortness of Breath*. For example, musculoskeletal problem or chest pain.

Dyspnea Index - cont. - Baseline**Magnitude of Effort**

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

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Dyspnea Index - Transition*(Reproduced by kind permission of CHEST)***Change in Functional Impairment**

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

Change in Magnitude of Task

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

Dyspnea Index - cont. - Transition**Change in Magnitude of Effort**

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

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Appendix 3: SF-36 version 2 questionnaire






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

Your Health and Well-Being






This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

For each of the following questions, please mark an ☐ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
				
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

2. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
				
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
	▼	▼	▼
a <u>Vigorous activities</u> , such as running, lifting heavy objects, participating in strenuous sports	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
b <u>Moderate activities</u> , such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
c Lifting or carrying groceries	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
d Climbing <u>several</u> flights of stairs	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
e Climbing <u>one</u> flight of stairs	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
f Bending, kneeling, or stooping	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
g Walking <u>more than a kilometre</u>	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
h Walking <u>several hundred metres</u>	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
i Walking <u>one hundred metres</u>	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
j Bathing or dressing yourself	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the <u>amount of time</u> you spent on work or other activities.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
b <u>Accomplished less</u> than you would like	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
c Were limited in the <u>kind of</u> work or other activities	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
d Had <u>difficulty</u> performing the work or other activities (for example, it took extra effort)	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the <u>amount of time</u> you spent on work or other activities.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
b <u>Accomplished less</u> than you would like	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
c Did work or other activities <u>less carefully than usual</u>	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very severe
▼	▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
b Have you been very nervous?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
c Have you felt so down in the dumps that nothing could cheer you up?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
d Have you felt calm and peaceful?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
e Did you have a lot of energy?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
f Have you felt downhearted and depressed?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
g Did you feel worn out?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
h Have you been happy?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
i Did you feel tired?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
	▼	▼	▼	▼	▼
a I seem to get sick a little easier than other people	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
b I am as healthy as anybody I know	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
c I expect my health to get worse	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
d My health is excellent	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

Appendix 4: EQ-5D Questionnaire

By placing a check-mark in one box in each group below, please indicate which statements best describe your own state of health today.

Mobility

- I have no problems in walking about ☐
- I have some problems in walking about ☐
- I am confined to bed ☐

Self-Care

- I have no problems with self-care ☐
- I have some problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

Usual Activities (*e.g. work, study, housework, family or leisure activities*)

- I have no problems with performing my usual activities ☐
- I have some problems with performing my usual activities ☐
- I am unable to perform my usual activities ☐

Pain/Discomfort

- I have no pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have extreme pain or discomfort ☐

Anxiety/Depression

- I am not anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am extremely anxious or depressed ☐

To help people say how good or bad their state of health is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your state of health is today.

**Your own
state of health
today**

