NOVARTIS

Region AMAC CD&MA

QVA149A (indacaterol maleate/glycopyrronium bromide)

CQVA149A3405 / NCT02516592

A 12-week treatment, multi-center, randomized, double-blind, double-dummy, parallel group study to assess the efficacy and safety of switching from salmeterol/fluticasone to QVA149 (indacaterol maleate/glycopyrronium bromide) in symptomatic COPD patients

Authors:	[redacted]
Document type:	Amended protocol
EUDRACT number:	Not applicable
Version number:	v02
Development phase:	IIIb/IV
Release date:	17-Jun-2015

Clinical Trial Protocol Template Version 2.0, November, 2013

Table of contents

List of tables

List of figures

List of abbreviations

AE	Adverse Event
ATS	American Thoracic Society
BDI	Baseline Dyspnea Index
b.i.d.	twice a day
BMI	Body Mass Index
BPH	Benign Prostatic Hyperplasia
CAT	COPD Assessment Test
CFR	US Code of Federal Regulations
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
EOS	End Of Study
ER	Emergeny Room
ERS	European Respiratory Society
FAS	Full Analysis Set
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume in one second
FDC	Fixed Dose Combination
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
H_0	null hypotesis
Ha	alternative hypothesis
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 Response Technology
IUD	Intrauterine Device
IUS	Intrauterine System
LABA	Long-Acting Beta-2 Agonist
LAMA	Long-Acting Muscarinic Antagonist
LOCF	Last Observation Carried Forward
MDDPI	Multi-Dose Dry Powder Inhaler
MDI	Metered Dose Inhaler
MedDRA	Medical dictionary for regulatory activities
o.d.	once a day
p.o.	oral(ly)
PPS	Per-Protocol Set
QTcF	QT correction formula
RAN	randomized set
SABA	Short-Acting Beta-2 Agonist
SAE	Serious Adverse Event
SAMA	Short-Acting Muscarinic Antagonist
SDDPI	Single Dose Dry Powder Inhaler
SmPC	Summary of Products Characteristics
SNRI	Serotonin Noradrenaline Reuptake Inhibitors
SUSAR	Suspected Unexpected Serious Adverse Reactions
TDI	Transition Dyspnea Index
WHO	World Health Organization

Glossary of terms

Assessment	A procedure used to generate data required by the study
Control drug	Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the drug being tested in the trial
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product.”
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include protocol-specified concomitant background therapies when these are standard treatments in that indication
Medication number	A unique identifier on the label of each investigational/study drug package in studies that dispense medication using an IRT system
Period	A portion of the study which serves a specific purpose. Typical Periods are: screening/recruitment, wash-out, treatment, and follow-up
Premature subject/patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Protocol	A written account of all the procedures to be followed in a trial, which describes all the administrative, documentation, analytical and clinical processes used in the trial.
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
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
Subject Number	A number assigned to each patient who enrolls into the study
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study

Amendment 2

Amendment rationale

The purpose of this amendment is to update the eligibility criteria related to COPD exacerbations before the patients are screened, to clarify washout periods for parenteral or oral corticosteroids and intra-muscular depot corticosteroids before visit 1 and to revise the spirometry guidelines for the reversibility test at screening visit.

This amendment should be implemented prior to the start of enrollment.

Changes to the protocol

The following sections of the protocol were changed:

1. Protocol Summary, section Exclusion criteria, is revised to add exclusion criteria related to COPD exacerbation within 6 weeks before Visit 1 and to align with revised Protocol section 4.2.
2. Protocol section 4.2, Exclusion criteria number 14 is revised to ensure patients enrolled did not have COPD exacerbation within the 6 weeks before Visit 1.
3. Protocol section 5.5.8, Table 5-2, is revised to provide clarity on the wash-out period prior to visit 1 for parenteral or oral corticosteroids and intra-muscular depot corticosteroids.
4. Protocol section 6.5.1, Table 6-2-Spirometry schedule at Visit 1 (screening), pre-dose time point is revised from -15 minutes to -5 minutes and post-dose time point is revised from +15 minutes to +60 minutes. In addition, further guidance on the reversibility test is provided within the section.
5. Appendix 1: Spirometry guidelines, Reversibility section at Visit 1 (screening) is revised to align the time point of pre-dose and post-dose spirometry test as in Protocol section 6.5, Table 6-2. In addition, the wording is revised to provide more clarity.

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.

Summary of previous amendments

Amendment 1

Amendment rationale

The purpose of this amendment is to update eligibility criteria and to correct an inconsistency regarding the use of intramuscular corticosteroids for treating COPD exacerbations.

This amendment is provided prior to the start of enrollment.

Changes to the protocol

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.

Protocol summary and Section 4.1 Inclusion criteria

Inclusion criterion number 3 in the original protocol includes current or ex-smokers who have a smoking history of at least 10 pack years (e.g. 10 pack years = 1 pack/day x 10 years, or ½ pack/day x 20 years). An ex-smoker is defined as a patient who has not smoked for ≥ 6 months at visit 1.

The definition of pack years is revised to reflect the number of cigarettes in order to account for variations in pack size. The revision states that ten pack years are defined as 20 cigarettes a day for 10 years, or 10 cigarettes a day for 20 years.

Section 4.2 Exclusion criteria

Criterion number 4 in the original protocol, which excludes patients diagnosed with Type I or uncontrolled Type II diabetes, is removed. Where QVA149 currently has marketing authorization in more than 60 countries (including countries in the European Union, Asia, and the Middle East as well as Canada, Japan and Australia) diabetes is not a contraindication. Though this criterion was used in the development phase QVA149 studies, it has been excluded from post-approval protocols. In compliance with the exclusion criterion for "clinically significant co-morbidity that could interfere with the assessment of the safety and efficacy of the study medication", investigators should decide to exclude such patients.

Minor edits and corrections

- In Section 5.5.8 in Table 5-2 Prohibited COPD-related medications during the trial: intra-muscular depot corticosteroids were incorrectly footnoted to state that they are allowed for treating COPD exacerbations. The footnote reference is deleted.
- In Sections 5.1.2 and 5.5.6, and Appendix 1 an edit is made to clarify that salbutamol **or** albuterol is administered for reversibility testing. This was presented in the original protocol as salbutamol/albuterol which could be interpreted to mean salbutamol and albuterol.
- In the synopsis and Section 6.3, CAT score is corrected to "≥ 10".

- In Section 8.3, an edit is made to remove description that ECG data will be processed centrally since this could lead to an incorrect interpretation that ECG will have central readings. ECG results will not have a central reading, the reading and interpretation is only performed locally.
- In Table 6-2, "albuterol" is added to the footnote.

Implementation

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 summary

Protocol number	CQVA149A3405
Title	A 12-week treatment, multi-center, randomized, double-blind, double-dummy, parallel group study to assess the efficacy and safety of switching from salmeterol/fluticasone to QVA149 (indacaterol maleate/glycopyrronium bromide) in symptomatic COPD patients
Brief title	Efficacy and safety of switching from salmeterol/fluticasone to QVA149 in symptomatic COPD patients
Sponsor and Clinical Phase	Novartis Phase 3b/4
Investigation type	Drug
Study type	Interventional
Purpose and rationale	To investigate whether switching symptomatic COPD patients from a fixed-dose combination of salmeterol/fluticasone 50/500 µg b.i.d. to a fixed dose combination of QVA149 110/50 µg o.d. leads to improved lung function and airflow and to assess the effect on symptom burden, breathlessness, and use of rescue medication.
Primary Objective(s)	To demonstrate superiority of QVA149 110/50 µg o.d. compared to salmeterol/fluticasone 50/500 µg b.i.d. in trough pre-dose FEV_1 at week 12
Secondary Objectives	To evaluate the effect of QVA149 110/50 µg o.d. compared to salmeterol/fluticasone 50/500 µg b.i.d. on: • Total score of TDI at week 12 • FVC at week 12 • COPD symptoms at week 12 as measured by the COPD Assessment Test (CAT) • The mean number of puffs of rescue medication use, and percentage of days without rescue medication use over the 12 week treatment period • Safety and tolerability during the 12 week treatment period
Study design	This is a randomized, double-dummy, double-blind, parallel group study. Eligibility is assessed during a 2 week screening period, during which open-label salmeterol/fluticasone 50/500 µg b.i.d., is provided. At the baseline (randomization) visit, eligible patients are randomized to one of the two treatment arms: 1) QVA149 110/50 µg o.d. or 2) salmeterol/fluticasone 50/500 µg b.i.d., at a ratio of 1:1. Randomized patients enter a 12 week, double-blind, double dummy treatment period. Visits are scheduled at weeks 6 and 12 (i.e. end of study) to conduct safety and efficacy assessments (see Table 6-1). No interim analysis is planned.
Population	The study population consists of approximately 492 randomized male and female adults age ≥ 40 years, with a clinical diagnosis of COPD, a

	smoking history of at least 10 pack years, treated with salmeterol/fluticasone 50/500 µg b.i.d. for at least 3 months prior to study entry, who are symptomatic as defined by a CAT score $\geq$ 10, and with not more than one COPD exacerbation in the previous year.
Inclusion criteria	• Written informed consent must be obtained before any assessment is performed. • Male and female ≥ 40 years • Current or ex-smokers who have a smoking history of at least 10 pack years (ten pack years are defined as 20 cigarettes per day for 10 years or 10 cigarettes per day for 20 years). An ex-smoker is defined as a patient who has not smoked for ≥ 6 months at visit 1 • Confirmed diagnosis of COPD and post-bronchodilator FEV1 ≥ 30% and < 80% of the predicted normal value and post-bronchodilator $FEV_1/FVC < 0.70$ at visit 1 • Treated with salmeterol/fluticasone 50/500 µg b.i.d. for at least 3 months prior to visit 1 • Documented CAT score of ≥ 10 at Visit 1 and 2
Exclusion criteria	• Treatment with any LAMA in the 2 weeks prior to visit 1 • Presence of any contraindication, warning, precaution, hypersensitivity in the approved prescribing information for salmeterol/fluticasone • Prior or current diagnosis of asthma • More than one COPD exacerbation requiring treatment with antibiotics and/or systemic corticosteroids and/or hospitalization in the year prior to Visit 1 • Patients who developed a COPD exacerbation of any severity within the 6 weeks before the screening (Visit 1) or between screening (Visit 1) and start of treatment (Visit 2) will not be eligible but will be permitted to be re-screened after a minimum of 6 weeks after the resolution of the COPD exacerbation • Respiratory tract infection within 4 weeks prior to Visit 1 • Respiratory tract infection between Visit 1 and 2. Patients can be re-screened 4 weeks after resolution of the infection • Requiring oxygen therapy prescribed for >12 hours per day • Onset of respiratory symptoms, including a COPD diagnosis prior to age 40 years
Investigational and reference therapy	1. QVA149 110/50 µg o.d. capsules for inhalation, supplied in blisters via a single dose dry powder inhaler (SDDPI) 2. Salmeterol/fluticasone 50/500 µg b.i.d. dry inhalation powder delivered via Accuhaler®/ Diskus® device
Efficacy assessments	• Spirometry • Baseline dyspnea index/transitional dyspnea index (BDI/TDI) • COPD assessment test (CAT) • Use of rescue medication

Safety assessments	• Adverse events and serious adverse events • Vital signs • ECG • COPD exacerbations
Other assessments	Not applicable
Data analysis	The analysis of the primary objective will be performed on the FAS. The PPS may be used for the supportive analysis of the primary variable. The FAS will be used for the analysis of all other efficacy variables. The safety set will be used in the analysis of all safety variables. The following null hypothesis (Ho) versus the alternative hypothesis (Ha) will be tested at a significance level of 0.05 in the FAS: Ho: There is no difference in mean trough pre-dose FEV_1 after 12 weeks of treatment between QVA149 110/50 µg o.d. and salmeterol/fluticasone 50/500 µg b.i.d. Ha: There is a significant difference in mean trough pre-dose FEV_1 after 12 weeks of treatment between QVA149 110/50 µg o.d. and salmeterol/fluticasone 50/500 µg b.i.d.
Key words	Chronic Obstructive Pulmonary Disease, COPD, Glycopyrronium bromide, Indacaterol maleate, salmeterol/fluticasone, COPD assessment test, baseline dyspnea index/transitional dyspnea index, spirometry

1 Introduction

1.1 Background

Chronic Obstructive Pulmonary Disease (COPD) is a disease of the lungs characterized by airflow limitation which is not fully reversible, and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Worldwide, COPD is projected to rank fifth in burden of disease and third with respect to mortality by 2020 (Buist AS et al 2007). 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 (GOLD 2014).

Current treatment guidelines for COPD recommend the use of bronchodilators for all severities, either on an as-required (pro re nata: prn) basis, or on a regular basis (GOLD 2014). Inhaled long-acting bronchodilators such as β2-adrenergic agonists (LABAs) and muscarinic antagonists (LAMAs) are recommended as a monotherapy or in combination (LABA+LAMA) (in GOLD B, C and D patients) for treatment of COPD patients.

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

GOLD 2014 COPD strategy document states that long term treatment with inhaled corticosteroids is recommended for patients with severe and very severe COPD and frequent exacerbations that are not adequately controlled by long-acting bronchodilators (Evidence A). It also suggests that long-term treatment containing inhaled corticosteroids should not be prescribed outside their indications, due to the risk of pneumonia and the possibility of an increased risk of fractures following long-term exposure (GOLD 2014).

QVA149 once daily provided significantly and clinically relevant improvements in lung function compared with salmeterol/fluticasone twice daily with significant symptomatic benefits in patients with moderate-to-severe COPD with no history of exacerbation in the last year (Vogelmeier et al 2013). This study confirmed the superiority of dual bronchodilator treatment to a Fixed Dose Combination (FDC) of ICS/LABA in this population.

Many COPD patients remain symptomatic despite their current standard of care treatment, which often includes LABA/ICS (Hersh 2010). While ILLUMINATE, a 26-week study, (Vogelmeier et al 2013) showed superiority of QVA149 versus ICS/LABA in a head to head randomized study, it is unclear if switching symptomatic, infrequently exacerbating patients from ICS/LABA treatment to QVA149, without a washout period (i.e. real-life scenario), will benefit the patient with regard to efficacy and safety.

1.2 Purpose

To investigate whether switching symptomatic COPD patients from a fixed-dose combination of salmeterol/fluticasone 50/500 µg b.i.d. to a fixed dose combination of QVA149 110/50 µg o.d. leads to improved lung function and airflow, and to assess the effect on symptom burden, breathlessness, and use of rescue medication.

2 Study objectives

2.1 Primary objective

To demonstrate superiority of QVA149 110/50 µg o.d. compared to salmeterol/fluticasone 50/500 µg b.i.d. in trough pre-dose FEV_1 at week 12.

2.2 Secondary objectives

To evaluate the effect of QVA149 110/50 µg o.d. compared to salmeterol/fluticasone 50/500 µg b.i.d. on:

- Total score of TDI at week 12
- FVC at week 12
- COPD symptoms at week 12 as measured by the COPD Assessment Test (CAT)
- The mean number of puffs per day of rescue medication use, and percentage of days without rescue medication use over the 12 week treatment period
- Safety and tolerability during the 12 week treatment period

3 Investigational plan

3.1 Study design

This is a randomized, double-dummy, double-blind, parallel group study. Eligibility is assessed during a 2 week screening period during which open-label salmeterol/fluticasone 50/500 µg b.i.d. is provided. At the baseline (randomization) visit, eligible patients are randomized to one of the two treatment arms: 1) QVA149 110/50 µg o.d. or 2) salmeterol/fluticasone 50/500 µg b.i.d., at a ratio of 1:1. Randomized patients enter a 12 week, double-blind, double dummy treatment period. Visits are scheduled at weeks 6 and 12 (i.e. end of study) to conduct safety and efficacy assessments (see Table 6-1). No interim analysis is planned.

Screening period – Visit 1

Visit 1 is the screening visit during which the investigator checks the patient's eligibility, detailed in Sections 4.1 and 4.2, and performs all assessments outlined in Table 6-1. The investigator must obtain written informed consent from the patient before conducting Visit 1. Informed consent may occur at a date prior to Visit 1.

The required assessments at Visit 1 include spirometry reversibility testing. Spirometry testing should only be performed if the last dose of salmeterol/fluticasone was taken ≥ 24 hours, last dose of any SABA was taken ≥ 6 hours and last dose of any SAMA was taken ≥ 8 hours prior to spirometry. **Visit 1 should only be conducted if the spirometry testing can be performed.** If not, this visit must be scheduled for a later date. An example follows: a patient presents for a routine visit, the investigator presents the study and the patient provides written informed consent to participate. The investigator determines that the patient had taken salmeterol/fluticasone within the last 3 hours. In this case, the investigator must schedule study Visit 1 to take place at a later time. After the patient has provided informed consent, the investigator should instruct the patient on the medication "wash-out" timing required for the spirometry testing. Refer to Appendix 1: Spirometry Guidance for detailed instructions. At Visit 1, after initial eligibility is determined, patients then begin the 2 week screening period. During the screening period, all patients are provided open-label salmeterol/fluticasone 50/500 µg b.i.d. multi-dose dry-powder inhaler (MDDPI) treatment. Patients are also provided with a SABA (salbutamol or albuterol) for use as a rescue inhaler on an "as needed" basis throughout the study; for more details on rescue medication please refer to Section 5.5.6.

Patients are also supplied with a paper diary (see Appendix 7) to collect information on study and rescue medication usage throughout the duration of the study. The diary is reviewed by the investigator at each study visit and is intended to help with assessing study medication compliance and use (i.e. quantity) of rescue medication. Patients should be resupplied with diary pages as needed.

Treatment period – Visits 2, 3 and 4

Visit 2 (Day 1) is the visit during which final eligibility is confirmed and patients who meet all criteria are randomized. This visit is to be conducted in the morning. It is recommended that the investigator phones the patient on the day prior to the visit to remind the patient that s/he should take the usual morning and evening doses on the day prior to the visit but must not take the morning dose on the day of the visit. This visit should occur 14 days after Visit 1.

At this visit patients complete the CAT questionnaire and eligibility is reviewed. After the CAT questionnaire is completed, the diary data is reviewed and all assessments per Table 6-1, including spirometry, are performed.

Patients who meet the eligibility criteria are randomized in a 1:1 ratio to one of the 2 treatment arms for the duration of the 12-week treatment period. Study treatment is dispensed (see Section 5.5.2) and instructions are given on the correct use of the inhalation device and study treatment.

Visit 3 (Day 42) is conducted 6 weeks after randomization (Day 1) and should take place in the morning. It is recommended that the investigator phones the patient on the day prior to the visit to remind the patient that s/he should take the usual morning and evening doses of the day prior to the visit but not the morning dose on the day of the visit. Study medication is dispensed during the visit after all pre-dose procedures and assessments are performed.

Visit 4 (Day 84) is conducted 12 weeks after randomization (Day 1) and should take place in the morning. This is the final end of study (EOS) visit. All EOS assessments are conducted as

outlined in Table 6-1. It is recommended that the investigator phones the patient on the day prior to the visit to remind the patient that s/he should take the usual morning and evening doses of the day prior to the visit but not the morning dose on the day of the visit.

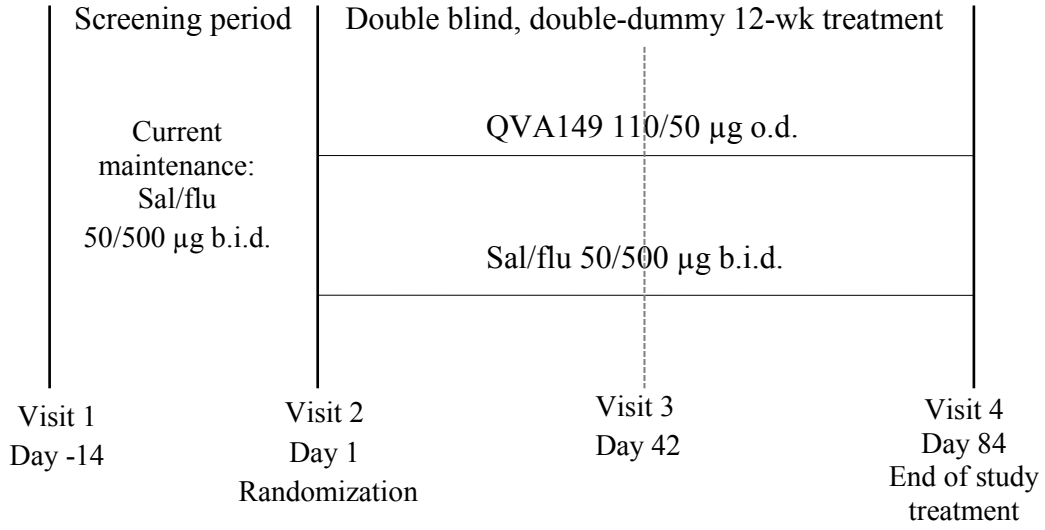
Patients should be seen for all visits on the designated day or as close as possible with an allowable visit window of +/- 3 days for Visits 2, 3 and 4.

The investigator should instruct the patient to notify the study site about any new medications s/he takes after the start of the study. All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts the study must be listed on the concomitant medications of the electronic Case Report Form (eCRF).

Patients who discontinue study treatment early should complete the end of study assessments per Table 6-1.

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

Figure 3-1 Study design



3.2 Rationale of study design

The randomized double-blind, double-dummy, parallel-group design provides the most robust methodology, with the least amount of bias, to evaluate the effect of switching from salmeterol/fluticasone to QVA149 in symptomatic COPD patients.

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

QVA149 110/50 µg o.d. is the registered dose for the COPD indication and for some participating countries this study is conducted in the post-approval phase. The 12-week duration is considered appropriate in order to show the impact of the treatment switch in terms of safety and efficacy.

3.4 Rationale for choice of comparator

Salmeterol/fluticasone is widely used as maintenance therapy for COPD, and for many countries 50/500 µg b.i.d. is the only registered regimen indicated for COPD.

3.5 Purpose and timing of interim analyses/design adaptations

Not applicable

3.6 Risks and benefits

The risk to subjects in this trial will be minimized by compliance with all of the eligibility criteria and by close clinical monitoring. Although altering the current COPD medication regimen carries a potential risk, this population is defined as not optimally controlled by their current medication and therefore needs treatment adaptation/adjustment and according to guidelines, switching to a LABA/LAMA combination is recommended as one of the 2nd treatment choices, therefore switching patients to QVA149 is an expected benefit. The treatment duration of 12 weeks is a reasonable duration to detect any measurable change in lung function by any inhaled medication. Furthermore, patients will be allowed to use rescue medication (SABA) as needed during the screening and blinded treatment periods, thus mitigating these risks. The short duration of the trial (14 weeks including screening) and the provision of rescue medication (SABA) for both treatment arms provides sufficient risk mitigation for changing the treatment (QVA149 treatment arm) as well as keeping sub optimally-treated patients on their current treatment (salmeterol/ fluticasone treatment arm).

Similarly, repetitive lung function measurement maneuvers during the study can lead to cough, shortness of breath, dizziness, or exhaustion. Since the patient only carries out forced maneuvers during clinic visits (not at home), these are performed under medical supervision to ensure availability of immediate aid if required. The assessments are infrequent and part of the regular medical assessments of this patient population.

The risks of side effects from the study medication are those known for the compounds QVA149, QAB149 and NVA237. The most frequently reported side effects in the development of QVA149 to date are nasopharyngitis, upper respiratory tract infection, cough, and headache. Further information can be obtained from the QVA149 Investigator's Brochure. For QAB149 and NVA237, please refer to the QAB149 and NVA237 sections of the QVA149 Investigator's Brochure.

The risk of side effects for the active comparator (salmeterol/fluticasone 50/500 µg b.i.d.) are those known for salmeterol and fluticasone, such as tremor, headache, palpitations, pneumonia, bronchitis, hypokalemia, nasopharyngitis, throat irritation, sinusitis, muscle

cramps, traumatic fractures, hoarseness and candidiasis in the mouth and throat. Further information can be obtained from the SmPC of Seretide®.

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

Indacaterol, which is one part of the study medication QVA149, is a LABA. However, indacaterol is not indicated to treat asthma and there have not been studies done that show whether or not indacaterol has the same risks as salmeterol when given to patients with asthma. There is also currently no data that show whether or not there is the same risk when given to patients with COPD. Per the eligibility criteria in Section 4.2, patients with a prior or current asthma diagnosis are excluded.

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

4 Population

The study population consists of approximately 492 male and female adults age ≥ 40 years, with a clinical diagnosis of COPD, a smoking history of at least 10 pack years, treated with salmeterol/fluticasone 50/500 µg b.i.d. for at least 3 months prior to study entry, who are symptomatic as defined by a CAT score ≥ 10, and with not more than one COPD exacerbation in the previous year.

It is anticipated that approximately 492 patients will be randomized in order to end the study with 418 completed patients (considering a 15% drop-out rate). Drop-outs will not be replaced. The study will be multinational.

4.1 Inclusion criteria

Patients eligible for inclusion in this study must fulfill all of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Male and female ≥ 40 years
3. Current or ex-smokers who have a smoking history of at least 10 pack years (Ten pack years is defined as 20 cigarettes per day for 10 years or 10 cigarettes per day for 20 years). An ex-smoker is defined as a patient who has not smoked for ≥ 6 months at visit 1
4. Confirmed diagnosis of COPD and post-bronchodilator FEV_1 ≥ 30% and < 80% of the predicted normal value and post-bronchodilator $FEV_1/FVC < 0.70$ at visit 1
5. Treated with salmeterol/fluticasone 50/500 µg b.i.d. for at least 3 months prior to visit 1*
6. Documented CAT score of ≥ 10 at Visit 1 and 2

*Salmeterol/fluticasone 50/500 µg b.i.d. treatment has been decided by the patient's primary physician who has full discretion of the appropriateness of this treatment. This treatment

decision has been taken outside the context of study and prior to the patient's consideration for participating 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. Treatment with any LAMA in the 2 weeks prior to visit 1
2. Presence of any contraindication, warning, precaution, hypersensitivity in the approved prescribing information for salmeterol/fluticasone
3. Prior or current diagnosis of asthma
4. History or current diagnosis of clinically significant ECG abnormalities including:
    a. Concomitant clinically significant cardiac arrhythmias, e.g. sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker
    b. History of familial long QT syndrome or known family history of Torsades de Pointes
5. Resting QTcF (Fridericia preferred) ≥ 450 msec (male) or ≥ 460 msec (female) during screening (Visit 1 or 2)
6. Concomitant use of medication known to significantly prolong the QT interval unless it can be permanently discontinued for the duration of the study
7. Clinically significant co-morbidity that could interfere with the assessment of the safety and efficacy of the study medication
8. Paroxysmal (e.g. intermittent) atrial fibrillation; patients with persistent atrial fibrillation as defined by continuous atrial fibrillation for at least 6 months and controlled with a rate control strategy (i.e., beta blocker, calcium channel blocker, pacemaker placement, digoxin or ablation therapy), for at least 6 months, may be considered for inclusion. In such patients, atrial fibrillation must be present at Visit 1 and 2, with a resting ventricular rate < 100/min.
9. Contraindications or hypersensitivity to
    a. Anticholinergic agents
    b. Long and short-acting β2-agonists
    c. Sympathomimetic amines
    d. Lactose or any other excipient of the study medication or to drugs of similar chemical classes
10. Any malignancy within the past 5 years except localized basal cell carcinoma of the skin

11. Narrow-angle glaucoma, symptomatic benign prostatic hyperplasia (BPH) or bladder-neck obstruction or moderate to severe renal impairment or urinary retention. Asymptomatic BPH patients are not excluded.
12. Not achieved acceptable spirometry results at visit 1 or 2 in accordance with the American Thoracic Society (ATS) or European Respiratory Society (ERS) criteria for acceptability. One retest may be performed for patients not meeting the acceptability criteria.
13. More than one COPD exacerbation requiring treatment with antibiotics and/or systemic corticosteroids and/or hospitalization in the year prior to Visit 1
14. Patients who developed a COPD exacerbation of any severity within the 6 weeks before the screening (Visit 1) or between screening (Visit 1) and start of treatment (Visit 2) will not be eligible but will be permitted to be re-screened after a minimum of 6 weeks after the resolution of the COPD exacerbation
15. Respiratory tract infection within 4 weeks prior to Visit 1
16. Respiratory tract infection between Visit 1 and 2. Patients can be re-screened 4 weeks after resolution of the infection
17. Requiring oxygen therapy prescribed for >12 hours per day
18. Onset of respiratory symptoms, including a COPD diagnosis prior to age 40 years
19. Intermittent treatment with a H_1-antagonist or intra-nasal corticosteroids for allergic rhinitis (treatment with a stable dose/regimen is permitted).
20. Concomitant pulmonary disease (e.g. lung fibrosis, sarcoidosis, interstitial lung disease, pulmonary hypertension, clinically significant bronchiectasis)
21. Diagnosed with α-1 anti-trypsin deficiency
22. Active pulmonary tuberculosis, unless confirmed by imaging, within the past year, to be no longer active unless there is a documented record of appropriate treatment and a chest radiograph suggesting that the disease is no longer active
23. Pulmonary lobectomy or lung volume reduction surgery or lung transplantation
24. Participating in or planning to participate in the active phase of a supervised pulmonary rehabilitation program during the study (maintenance program is permitted)
25. Receiving any medication in the classes listed in Table 5-1
26. Receiving medications in the classes listed in Table 5-3 should be excluded unless the medication has been stable for the specified period and the stated conditions are met
27. Use of investigational drugs/devices (approved or unapproved) at the time of enrollment, or within 30 days or 5 half-lives of Visit 1, whichever is longer.
28. Unable to use a dry powder inhaler device, Metered Dose Inhaler (MDI) or a pressurized MDI (rescue medication) or comply with the study regimen.
29. 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 urine test.

30. 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 defined as surgical hysterectomy, bilateral oophorectomy, or tubal ligation at least six weeks before taking the study treatment (Single oophorectomy does not meet the definition of female sterilization).
    - Male sterilization (at least 6 months 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

- QVA149 110/50 µg o.d. capsules for inhalation, supplied in blisters via a single dose dry powder inhaler (SDDPI)
- Salmeterol/fluticasone 50/500 µg b.i.d. dry inhalation powder delivered via Accuhaler®/Diskus® device

5.1.2 Additional study treatment

At Visit 1 all patients are administered ipratropium bromide for the purpose of reversibility testing. Ipratropium bromide is supplied to the investigator site by Novartis or provided by the study center and reimbursed by Novartis.

At Visit 1 all patients are administered inhaled SABA (salbutamol or albuterol) for reversibility testing. All patients entering the screening period are asked to retain the SABA inhalers to use as rescue medication on an "as needed" basis throughout the study, and are resupplied as needed. Salbutamol or albuterol must not to be administered within 6 hours prior to Visit 2 and 3. If use is unavoidable, the visit must be rescheduled.

Salbutamol (100µg) or albuterol (90µg) is supplied to the investigator sites by Novartis or provided by the study center and reimbursed by Novartis.

At Visit 1 all patients are provided open-label salmeterol/fluticasone 50/500 µg b.i.d. MDDPI medication to take during the 2 week screening period.

Please refer to Section 5.5.6 for more details regarding rescue medication.

5.2 Treatment arms

Patients are assigned to one of the following 2 double-blind treatment arms in a ratio of 1:1:

1. QVA149 110/50 µg o.d. and placebo for salmeterol/fluticasone
2. Salmeterol/fluticasone 50 /500µg b.i.d. and placebo for QVA149

5.3 Treatment assignment, randomization

At Visit 2 all eligible patients are randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate contacts the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT assigns a randomization number to the patient, which is used to link the patient to a treatment arm and specifies a unique medication number for the first package of study treatment to be dispensed to the patient. The randomization number is not to be communicated to the caller.

The randomization number is generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list is produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list is produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

Randomization is not stratified.

5.4 Treatment blinding

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

(1) Randomization data are kept strictly confidential until the time of unblinding, and are not accessible by anyone else involved in the study.

(2) The identity of the treatments is concealed by the use of study treatment that are all identical in packaging, labeling, schedule of administration, appearance, taste and odor.

A double-dummy design is used because the identity of the study treatment cannot be disguised, as the drug products are visibly different. In other words the two treatments (i.e. salmeterol/fluticasone and QVA149) cannot be made to look identical. To employ the double dummy blinding method each patient receives active drug and an indistinguishable placebo.

5.5 Treating the patient

5.5.1 Patient numbering

Each patient is uniquely identified in the study by a combination of his/her center number and patient number. The center number is assigned by Novartis to the investigative site. Upon signing the informed consent form, the patient is assigned a patient number by the investigator. At each site, the first patient is assigned patient number 1, and subsequent patients are assigned consecutive numbers (e.g. the second patient is assigned patient number 2, the third patient is assigned patient number 3). The investigator or his/her staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. For studies using eCRFs, only the assigned patient number should be entered in the field labeled "Patient ID" on the EDC data entry screen (e.g. enter '1', '2', etc.). Once assigned to a patient, the patient number will not be reused. If the patient fails to be randomized for any reason, the IRT must be notified within 2 days that the patient was not randomized. The reason for not being randomized will be entered on the Screening Log, and the Demography eCRF should also be completed.

5.5.2 Dispensing the investigational treatment

Screening Period: Open label salmeterol/fluticasone 50/500 µg b.i.d. MDDPI is supplied by Novartis. The medication is dispensed at Visit 1 for treatment during the screening period.

Treatment period: Each study site is supplied by Novartis with study treatment in packaging of identical appearance. Each patient receives medication kits at each dispensing visit, containing QVA149 active or placebo and salmeterol/fluticasone active or placebo. Medication kits are dispensed at Visits 2 and 3 to cover the treatment period between patient visits and to allow for late visits and other unforeseen events.

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

Initial training kits will be provided to study sites following registration of the center by study site personnel after site initiation and prior to the first patient at that center attending for Visit 1. Training kits will contain blister strips with placebo capsules to QVA149, SDDPI devices and Accuhaler®/Diskus® placebo devices for training use only.

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

At randomization - Visit 2

Investigator staff contacts the IRT to randomize the patient and obtain the assigned study treatment kit number. QVA149/placebo and fluticasone/salmeterol/placebo kits are dispensed at this visit.

Visits 3 and 4

The patient's study treatment supplies should be checked at each visit and the drug accountability log completed appropriately.

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

All devices and associated blister kits must be returned to the site at Visits 3 and 4 (or for patients who withdraw from the study prematurely).

5.5.3 Handling of study treatment

5.5.3.1 Handling of investigational treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all study treatment should be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Pharma Organization (CPO) Quality Assurance.

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

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

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

5.5.3.2 Handling of other study treatment

Rescue medication (salbutamol or albuterol) and ipratropium bromide for reversibility testing must be provided 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. All study treatment must be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CPO Quality Assurance.

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

5.5.4 Instructions for prescribing and taking study treatment

Patients are instructed on how to use the study treatment SDDPIs and Accuhaler®/Diskus® devices. Additional kits are provided with SDDPI and blisters with placebo capsules, and Accuhaler®/Diskus® placebo devices for training and demonstration purposes (see Appendix 2 and Appendix 3 for the patient instructions on how to use the study inhalers).

Patients are instructed to come to the clinic in time to complete pre-dosing assessments and to allow investigation treatment to be taken in the morning between 08:00 and 11:00 am. Patients are instructed to withhold the use of SABA (rescue medication) for at least 6 hours prior to all clinic visits, unless the use is absolutely necessary. If use of rescue medication is unavoidable then the visit must be rescheduled. It is recommended that the investigator phones the patient on the day prior to the visit to provide these reminders to the patient.

Patients are instructed to take one capsule, each day, in the morning between 08:00 and 11:00 from each of their medication kits in the following order;

Morning (08:00-11:00): one inhalation from the QVA149 SDDPI followed by one inhalation from fluticasone/salmeterol Accuhaler®/Diskus® device.

Afternoon (approximately 12 hours after their AM dose +/- 30 minutes): one inhalation from fluticasone/salmeterol Accuhaler®/Diskus® device.

All used and unused study medication must be returned by the patient at each study visit. The date and time of dose administration at each visit is recorded on the Dosage Administration Record eCRF.

All kits of study treatment assigned by the IRT are recorded in the IRT.

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 s/he is unable for any reason to take the study treatment as prescribed.

5.5.5 Permitted dose adjustments and interruptions of study treatment

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

5.5.6 Rescue medication

All patients are provided with a SABA (salbutamol or albuterol) which they are instructed to use throughout the trial as rescue medication. Nebulized salbutamol or albuterol is not allowed as rescue medication. Salbutamol (100µg) or albuterol (90µg) will either be supplied to the investigator sites locally by a Novartis designee or provided by the study center and reimbursed by Novartis. During the treatment period salbutamol or albuterol should be taken for rescue (when required) purposes only. No other rescue treatment is permitted.

In order to standardize measurements, patients are instructed to abstain from taking rescue medication (salbutamol or albuterol) within 6 hours prior to each visit when spirometry is scheduled. If rescue medication is taken within 6 hours prior to a visit, the visit should be rescheduled to the next day, if possible. The investigator must use their judgment when deciding how many times a visit for an individual patient should be rescheduled.

Use of rescue medication (number of puffs taken in the previous 12 hours) is recorded (once in the morning and once in the evening) by the patient, in the patient diary. At each study visit, the investigator should review the patient diary to assess the use of rescue medication.

Use of rescue medication must be recorded on the Rescue Medication CRF.

5.5.7 Concomitant treatment

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

5.5.8 Prohibited Treatment

Use of treatments displayed listed in Table 5-1 and Table 5-2 are NOT allowed after the patient enters screening.

Patients requiring the treatments in Table 5-1 are considering ineligible for study participation (see Section 4). Patients who have discontinued these medications according to the minimum cessation period are eligible. **Washout of the prohibited medications, for the purpose of study participation, should not be done.**

Table 5-1 Prohibited treatment

Class of Medication[1]	Minimum cessation period prior to Visit 1
Non-potassium sparing diuretics (unless administered as a fixed-dose combination with a potassium conserving drug)	7 days
Non-selective systemic beta-blocking agents[2]	7 days
Other drugs with potential to significantly prolong the	14 days or 5 half-lives, whichever is

Class of Medication[1]	Minimum cessation period prior to Visit 1
QT interval	longer
Antibiotics[3]	30 days
Systemic Mast cell stabilizers (e.g., cromoglycate, nedocromil, ketotifen)	7 days
Systemic anticholinergics	7 days
IgE inhibitors (e.g, Xolair)	6 months
Leukotriene antagonists and leukotriene synthesis inhibitors	7 days

[1]This table is not considered all-inclusive. Medications should be assessed for adherence to the indication and other inclusion/exclusion criteria.
[2] Selective β_1 blocking agents are permitted.
[3]If antibiotics were taken to treat a COPD exacerbation in the 6 weeks prior to Visit 1 the patient should be excluded; please refer to exclusion criteria (Section 4.2) for more details. Antibiotics are permitted to treat a COPD exacerbation from V2 until the end of the study.

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

Class of Medication[1]	Minimum cessation period prior to Visit 1
Long-acting muscarinic antagonist (LAMA) (except combination of LABA/LAMA as study medication)	Two weeks
Short-acting β_2 agonists (SABA) (except rescue medication see section 5.5.6)	6 hours
Short-acting muscarinic antagonist (SAMA)	8 hours
Fixed combinations of short-acting β_2 agonists and short-acting muscarinic antagonist (SABA/SAMA)	8 hours
Long-acting β_2 agonists (LABA) (except combination of LABA/ICS or LABA/LAMA as study medication)	24 hours
Oral Phosphodiesterase-IV inhibitor	Not applicable
Xanthines (any formulation)	Not applicable
Parenteral or oral corticosteroids[2]	30 days
Intra-muscular depot corticosteroids	90 days

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

Table 5-3 Medication allowed under specific conditions

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

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

5.5.9 Discontinuation of study treatment

Patients may voluntarily discontinue study treatment for any reason at any time.

The investigator should discontinue study treatment for a given patient if, on balance, s/he believes that continuation would be detrimental to the patient's well-being.

Study treatment must be discontinued under the following circumstances:

- Withdrawal of informed consent (See Section 5.5.10)
- Adverse events for which continued use of study treatment would be detrimental to the patient
- Abnormal test procedure results indicating risk for the patient to continue study treatment
- Pregnancy
- Need to treat a COPD exacerbation with intra-muscular depot corticosteroids (e.g. Depo-Medrone®).
- Any protocol deviation that results in a significant risk to the patient's safety

If premature discontinuation of study treatment occurs, the patient should return for the EOS visit, as soon as possible, and complete the assessments per Table 6-1. The investigator must determine the primary reason for the patient's premature discontinuation of study treatment and record this information on the Dosage Administration eCRF. At a minimum, the investigator should make every effort to obtain information regarding serious adverse events. The appropriate personnel from the site and Novartis will assess whether investigational treatment should be discontinued for any patient whose treatment code has been broken inadvertently for any reason.

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

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 Withdrawal of consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. In case of study withdrawal, data collected up to that point is processed and analyzed.

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

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

5.5.11 Loss to follow-up

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

5.5.12 Emergency breaking of assigned treatment code

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

It is the investigator’s responsibility to ensure that there is a procedure in place to allow access to the IRT in case of emergency. The investigator will inform the patient how to contact his/her backup in cases of emergency when s/he is unavailable. The investigator will provide protocol number, study treatment name if available, patient number, and instructions for contacting the local Novartis Country Pharma Organization (CPO) (or any entity to which it has delegated responsibility for emergency code breaks) to the patient in case an emergency treatment code break is required at a time when the investigator and backup are unavailable.

In case of a treatment code break, the patient must be discontinued from the study.

5.5.13 Study completion and post-study treatment

Completion of the study for an individual patient is when s/he has completed the 12 week treatment period. When the patient has completed all scheduled assessments the investigator must call IRT to record patient completion.

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

5.5.14 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, 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 the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

6 Visit schedule and assessments

Table 6-1 lists all of the assessments and indicates with an "x" the visits during which the assessments are performed. All data obtained from these assessments must be supported in the patient's source documentation.

The following assessments are scheduled to be performed in order as follows: COPD Assessment Test (CAT), BDI/TDI, followed by spirometry. Whenever other assessments are scheduled at the same time-point, spirometry must take precedence such that it occurs as near as possible to the scheduled time point.

Patients who discontinue from the study or are withdrawn from study treatment should return for the EOS visit assessments per Table 6-1 as soon as possible.

Table 6-1 Assessment schedule

Period	Screening	Treatment		
Visit number	**1**	**2**	**3**	**4**
Day	**-14**	**1**	**42**	**84 End of study (EOS)**
Information & Informed consent	x[1]			
Inclusion/Exclusion criteria	x	x		
Medical history, smoking history, demographics	x			
COPD exacerbation history/events	x	x	x	x
Vital signs	x	x	x	x
Height and weight	x			x
Physical exam	S		S	S
ECG	x	x		x
Prior and current medications	x	x	x	x
Pregnancy test (urine)[2]	x			x
Spirometry	x	x	x	x
BDI		x		
TDI			x	x
CAT	x	x	x	x
Issue & instruct on paper diary	x			
Review diary; provide as needed		x	x	x
Record study treatment compliance		x	x	x
Record rescue medication use		x	x	x
Contact IRT	x	x	x	x
Randomization via IRT		x		
Dispense sal/flu for screening period	x			
Inhalation device training	x	x		
Dispense double-blind, double dummy study medication		x	x	
Dispense rescue medication	x	x	x	
Adverse events (AE/SAE)	x	x	x	x

[1]On or before Visit 1
[2]Only women of child-bearing potential
S = source documentation only

6.1.1 Timing of assessments

Assessments must be conducted in the following order (see Figure 6-1):

Visit 1: CAT → ECG → Vital signs → Spirometry

Visit 2: CAT → BDI → ECG → Vital signs → Spirometry

Visit 3: CAT → TDI → Vital signs → Spirometry

Visit 4: CAT → TDI → ECG → Vital signs → Spirometry

Figure 6-1 Order of assessments

6.2 Information to be collected on screening failures

All patients who have signed informed consent but not entered into the next period will have the study completion page for the screening period, demographics, inclusion/exclusion, and adverse events/serious adverse event data collected. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

6.3 Patient demographics/other baseline characteristics

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

- Date of birth
- Sex
- Race and ethnicity
- Height and weight
- Date of COPD diagnosis
- COPD exacerbation history
- Relevant medical history / current medical condition present before signing informed consent
- Smoking history and status
- Prior (taken within the 1 year prior to study entry) and concomitant medications
- Pre- and post-bronchodilator spirometry (screening spirometry)
- COPD related symptoms as defined by a CAT score ≥ 10
- Baseline physical examination (only relevant co-morbidities recorded as medical history)
- Vital signs

6.4 Treatment exposure and compliance

Study treatment compliance is assessed by the investigator at all visits. The Investigator or designee collects, from the patient, the used / unused investigational medication and packaging (morning and evening capsules / blister strips and SDDPIs) at all dispensing visits. Study drug compliance is assessed from the capsule count and from information provided by the patient and/or caregiver. The investigator should also review the patient diary to help assess study drug compliance. This information should be captured in the source documentation.

The time of study treatment administration at each visit is collected on the eCRF. For assessments where spirometry is performed, the time of dosing is to be taken from the spirometer.

The date of any dosing interruptions/missed doses is entered in the eCRF.

6.5 Efficacy

6.5.1 Spirometry

Table 6-2 provides the scheduled timing for spirometry measurements. All study visits take place in the morning. It is recommended that the investigator phones the patient on the day prior to the visit to remind the patient that s/he should take the usual morning and evening doses on the day prior to the visit but must not take the morning dose on the day of the visit. Study medication is administered on the day of the visit after all required assessments are performed. If patients have taken salmeterol/fluticasone on the day of Visit 1 then spirometry should be rescheduled for the following day or as soon as possible. Visit 1 should only take place if spirometry testing can be performed (see Section 3.1). A central reading is performed for spirometry and the results are usually available within 48 hours.

Table 6-2 Spirometry schedule

	Time point	FEV_1 and FVC
Visit 1 (Screening)[1]	-5 min	x
	+60 min	x
Visit 2 (Day 1)[2]	-45 min	x
	-15 min	x
Visit 3 (Day 42)[2]	-45 min	x
	-15 min	x
Visit 4 (Day 84)[2]	-45 min	x
	-15 min	x

[1]Time point is relative to administration of ipratropium and salbutamol or albuterol.

[2]Time point is relative to the morning dose of the visit day

At Visit 1, reversibility testing is conducted in order to evaluate a patient's eligibility (see inclusion criteria).

The reversibility test should be performed in the morning as follows:

• Perform pre-bronchodilator spirometry and record FEV_1 and FVC.

• Administer 84 µg (or equivalent dose) of ipratropium bromide. The administration of ipratropium bromide should be within 5 minutes of pre-bronchodilator spirometry.
• Administer 400 µg of salbutamol (or 360 µg albuterol) a few minutes after the administration of ipratropium bromide.
• Perform post-bronchodilator spirometry and record FEV_1 and FVC 1 hour after the administration of salbutamol/albuterol.

At Visits 2, 3 and 4, FEV_1 and FVC measurements are performed.

Please refer to the detailed instructions provided in Appendix 1: Spirometry guidance.

6.5.2 Baseline Dyspnea Index and Transitional Dyspnea Index (BDI/TDI)

Patients must be interviewed by an assessor experienced in the use of such questionnaires.

The assessor will grade the degree of impairment due to dyspnea at Visit 2 (BDI only), at Visit 3 and at Visit 4, or at the time of discontinuation for patients who discontinue prematurely (TDI only). Every attempt should be made to ensure it is the same assessor that completes all the BDI/TDI assessments for an individual patient.

An example of the BDI and TDI (Mahler & Wells 1988) is provided in Appendix 4.

6.5.3 COPD Assessment Test (CAT)

The COPD assessment test (CAT) is a short instrument used to quantify the symptom burden of COPD and is used to assess the health status of patients in this study (Jones et al 2009, Jones et al 2012). It is completed by the patient at the beginning of the study visit before any other assessment to avoid influencing the responses. The CAT is completed by the patient at the investigator's site at Visits 1, 2, 3 and 4 or at the time of discontinuation for patients who prematurely withdraw from the study. It consists of eight items, each presented as a semantic 6-point differential scale, providing a total score out of 40. A higher score indicates a worse health status. The result is immediately available without the need for any calculation, apart from summing the scores on individual items. Scores of 0 - 10, 11 - 20, 21 - 30 and 31 - 40 represent a mild, moderate, severe or very severe clinical impact of COPD upon the patient.

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

6.5.4 Rescue medication

Use of rescue medication (number of puffs taken in the previous 12 hours) is recorded morning and evening, by the patient, in the paper diary. The use of rescue medication is entered in the eCRF.

6.5.5 Appropriateness of efficacy assessments

The efficacy assessments planned for this study: trough pre-dose FEV_1, FVC, rescue medication usage and patient symptoms (BDI/TDI and CAT) are standard for COPD clinical trials.

6.6 Safety

6.6.1 Physical examination

A physical examination will be performed at Visits 1, 3 and 4; please refer to Table 6-1. It will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams are performed.

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

6.6.2 Vital signs

Vital signs include radial pulse rate (measured for 60 seconds) and systolic and diastolic blood pressure. Pulse rate and blood pressure is assessed after the patient has rested in the sitting/supine position for at least 5 minutes. If an automated blood pressure device is used, it should be calibrated according to the manufacturer's guidelines. Clinically notable vital signs are defined in Appendix 6. Vital signs will be obtained at each visit described in Table 6-1.

6.6.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) is measured at Visit 1. Weight is recorded again at Visit 4.

6.6.4 Laboratory evaluations

Not applicable

6.6.5 Electrocardiogram (ECG)

A standard single 12 lead ECG is collected at Visit 1, 2 and 4. ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and spirometry. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

The original ECGs appropriately signed, should be collected and archived at the study site. Each ECG tracing should be labeled with study number, subject initials, subject number, date and time, and filed in the study site source documents. For any ECGs with subject safety concerns, two additional ECGs should be performed to confirm the safety finding. Clinically significant ECG findings at baseline must be discussed with the sponsor before administration with investigational treatment.

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

Only local reading/interpretation of ECGs is performed. The ECG equipment provides an immediate computer-generated interpretation but no central reading performed.

6.6.6 Pregnancy and assessments of fertility

A urine pregnancy test is performed in pre-menopausal women who are not surgically sterile per Assessment Schedule Table 6-1. A positive pregnancy test at Visit 1 or at any time during the study requires the patient to be discontinued from the study treatment. Refer to Section 5.5.9 for more details.

Women of child-bearing potential should be instructed to notify the investigator staff immediately if the woman becomes pregnant at any time during the study. The patient must be discontinued from the study treatment.

6.6.7 Pneumonia

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

6.6.8 COPD exacerbations

COPD exacerbation is defined as:

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

- dyspnea
- sputum volume
- sputum purulence

OR

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

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

A COPD exacerbation is considered of **moderate severity** if treatment with systemic corticosteroids or antibiotics or both was required and **severe,** if hospitalization was required. An emergency room (ER) visit of longer than 24 hours will be considered a hospitalization.

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

All moderate or severe COPD exacerbations (as per definition above) should be recorded on the COPD exacerbation eCRF.

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

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

Patients who develop a COPD exacerbation between Visits 1 and 2 are discontinued but are permitted to be re-screened after a minimum of 6 weeks after the resolution of the COPD exacerbation (see exclusion criteria).

If systemic corticosteroids are taken for a COPD exacerbation within 7 days prior to any study visit, the visit must be rescheduled to allow a washout of 7 days (Patient should be discontinued if treated with Depo-Medrone® as discussed in (Section 5.5.9). Scheduled spirometry should not be performed during an exacerbation until it has completely resolved. Any spirometry data collected during an exacerbation will not be used in the data analysis if the systemic corticosteroids to treat the exacerbation were administered within 7 days of the spirometry assessment.

Following treatment for the exacerbation, the patient will be expected to continue in the study provided the investigator considers that the patient can safely return to their pre-exacerbation medications. No spirometry assessments should be taken until after the exacerbation has resolved.

6.6.9 Appropriateness of safety measurements

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

6.7 Other assessments

No additional tests are performed on patients entered into this study.

7 Safety monitoring

7.1 Adverse events

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

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

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

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

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

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

All adverse events should be treated appropriately. Treatment may include one or more of the following:

- no action taken (i.e. further observation only)

- study treatment dosage adjusted/temporarily interrupted
- study treatment permanently discontinued due to this adverse event
- concomitant medication given
- non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged

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

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

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

7.2 Serious adverse events

7.2.1 Definition of SAE

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

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition

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

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

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe (see Annex IV, ICH-E2D Guideline).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (see Annex IV, ICH-E2D Guideline).

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

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

7.2.2 SAE reporting

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

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

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

Follow-up information should be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE.

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

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study 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 study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

7.3 Liver safety monitoring

Not Applicable

7.4 Renal safety monitoring

Not Applicable

7.5 Pregnancy reporting

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

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

In addition to the pregnancy form, all pregnancies must be reported on the AE CRF. Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE report form and AE CRF.

7.6 Prospective suicidality assessment

Not Applicable

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative (or designated CRO representative) will review the protocol and CRFs with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of entries on the (e)CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by centralized Novartis (or CRO) study personnel. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

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

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

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the eCRF using fully validated software that conforms to US CFR 21Part 11 requirements. Designated investigator site staff will not be given access to the electronic data collection (EDC) system until they have been trained.

Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the CRO working on behalf of Novartis. The Investigator must certify that the data entered into the eCRFs are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

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

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

ECG results will be sent electronically to Novartis (or a designated CRO).

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

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

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

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

8.4 Data Monitoring Committee

Not required

8.5 Adjudication Committee

Not required

9 Data analysis

9.1 Analysis sets

The randomized set (RAN) will include all randomized patients, regardless of whether or not they actually received randomized study medication. Patients in the RAN will be analyzed according to the treatment they were randomized to.

The full analysis set (FAS) will include all randomized patients who received at least one dose of randomized study medication. Following the intent-to-treat principle, patients will be analyzed according to the treatment they were assigned to at randomization.

The per-protocol set (PPS) will include all patients in the FAS without any major protocol deviations. Major protocol deviations will be defined prior to database lock and the un-blinding of the study. Patients will be analyzed according to the randomized treatment.

The safety set will include all patients who received at least one dose of randomized study treatment. Patients will be analyzed according to the treatment they received during the randomized treatment period. If a patient took both treatments the patient will be analyzed according to the randomized treatment.

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

Note that the FAS and safety sets will contain the same patients except that the safety set allows the inclusion of non-randomized patients who receive randomized study treatment in error.

9.2 Patient demographics and other baseline characteristics

Demographic and baseline characteristics including age, sex, race, ethnicity, height, weight, body mass index (BMI), severity and duration of COPD, smoking history and estimated number of pack years, COPD exacerbation history, other relevant medical history, concomitant medications (COPD related and non-COPD related) discontinued prior to start of randomized study drug, results from CAT score, and results of screening and baseline spirometry will be summarized by treatment in the FAS. Baseline ECG and vital signs results will be summarized for the safety set.

Demographic data and SAEs of screening failures will be listed only.

9.3 Treatments

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

Concomitant medications will be summarized by treatment in the safety set. Concomitant COPD related medications will be summarized by pre-specified categories, route of administration and preferred term. Concomitant medications not related to COPD will be summarized by preferred term.

Treatment compliance will be summarized by treatment for the safety set according to percentage of days compliant.

9.4 Analysis of the primary variable(s)

The primary objective of this study is to demonstrate the superiority of QVA149 110/50 µg o.d. compared to salmeterol/fluticasone 50/500 µg b.i.d. in mean trough pre-dose FEV_1 at Week 12.

9.4.1 Variable(s)

Mean trough pre-dose FEV_1 at Week 12 is defined as the average of the measurements taken -45min and -15min pre study medication dose in the clinic after 12 weeks of treatment (Day 84). The baseline measurement is defined as the average of the scheduled FEV_1 values prior to first intake of randomized study drug at Day 1 (Visit 2).

Trough pre-dose for QVA corresponds to 24 hours after the last QVA dose (i.e. last dose prior to the FEV_1 measurement) and 12 hours after the last dose of salmeterol/fluticasone. Spirometry is performed in the morning prior to the administration of the morning dose of study medication.

9.4.2 Statistical model, hypothesis, and method of analysis

The following null hypothesis (Ho) versus the alternative hypothesis (Ha) will be tested at a significance level of 0.05 in the FAS:

> Ho: There is no difference in mean trough pre-dose FEV_1 after 12 weeks of treatment between QVA149 100/50 µg o.d. and salmeterol/fluticasone 50/500 µg b.i.d.
>
> Ha: There is a significant difference in mean trough pre-dose FEV_1 after 12 weeks of treatment between QVA149 100/50 µg o.d. and salmeterol/fluticasone 50/500 µg b.i.d.

The treatment difference between QVA149 110/50 µg o.d. and salmeterol/fluticasone 50/500 µg b.i.d. in terms of mean trough pre-dose FEV_1 after 12 weeks of treatment will be estimated using ANCOVA for repeated measures. The model will include terms of treatment, baseline FEV_1, smoking status at baseline, region, visit, treatment*visit interaction, baseline FEV_1*visit interaction and an unstructured variance-covariance structure assuming normal distribution of the FEV_1 data, where visit will be treated as a categorical variable. Center nested within region may be added as random effect depending on model convergence. Missing values of mean pre-dose FEV_1 at Day 42 and Day 84 will not be imputed.

The estimated treatment difference of QVA149 110/50 µg o.d. – salmeterol/fluticasone 50/500 µg b.i.d. will be displayed along with the associated 95% confidence interval and p-value. Superiority of QVA149 110/50 µg o.d. to salmeterol/ fluticasone 50/500 µg b.i.d. will be demonstrated if the p-value is less than 0.05 and the 95% confidence interval lies entirely to the right of 0 L.

9.4.3 Handling of missing values/censoring/discontinuations

If any of the values contributing to trough pre-dose FEV_1 or baseline FEV_1 are collected within 6 hours of rescue medication or less than 7 days after systemic corticosteroid use then the individual FEV_1 value will be set to missing. Also if a value is taken post-dose instead of pre-dose it will not be used for calculation of trough pre-dose or baseline values. Since dosing times are only recorded in the diary for the days prior to scheduled visits no further time window will be applied for deriving pre-dose values. For the primary analysis, values will not be carried forward since ANCOVA for repeated measures will be applied. If all values contributing to the baseline FEV_1 are missing (or are not confirmed to be pre-dose), then the pre-bronchodilator measurements taken at Screening will be used as the baseline.

9.4.4 Supportive analyses

The following supportive analyses may be conducted for mean pre-dose FEV_1 at Week 12:

(1) Imputation of missing Week 12 data by Last Observation Carried Forward (LOCF), i.e., using the value from Day 42. A linear mixed model including the terms of treatment, baseline FEV_1, smoking status at baseline, and region as fixed effects and center nested within region as random effect will be applied.

(2) Analysis based on pattern mixture model:

An additional method for handling missing data will be implemented to explore the sensitivity to the Missing At Random (MAR) assumption. A pattern-mixture model based on non-ignorable missing, i.e., Missing Not At Random (MNAR) will be used, where all drop-outs are assumed to switch back to salmeterol/fluticasone 50/500 µg b.i.d. treatment. This approach will be implemented by multiple imputations, where missing values are repeatedly replaced by sampling from the Bayesian posterior predictive distribution based on the switching model. Each of the completed datasets is then analyzed using the primary analysis, and then the estimates are combined to get the final inference.

(3) Applying the ANCOVA for repeated measurements using the PPS.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

TDI

The TDI focal score at Week 6 and Week 12 will be analyzed using ANCOVA for repeated measures. The model will be similar to the model of the primary analysis with the baseline BDI instead of baseline FEV_1 included in the model.

Additionally the percentage of patients with a clinically significant improvement after 12 weeks of treatment in TDI (of >=1 change from baseline) will be analyzed using a logistic regression model which includes the same terms as used for the analysis of the TDI focal score.

Mean pre-dose FVC

The same analyses as for mean trough pre-dose FEV_1 will be done for mean pre-dose FVC with the baseline FVC instead of baseline FEV_1 included in the model.

FEV_1 at individual post-baseline time points

A similar method as for the primary endpoint will be applied for the analysis of FEV_1 at Week 6 (Visit 3) and Week 12 (EOS/Visit 4), i.e., separate ANCOVA for repeated measures will be performed for each time point using visit as repeated variable.

FVC at individual post-baseline time points

The same analyses as for FEV_1 at Week 6 (Visit 3) and Week 12 (EOS/Visit 4) will be done for FVC.

CAT

A similar method as for the primary endpoint will be applied for the analysis of CAT with the baseline CAT result instead of baseline FEV_1 included in the model. Additionally the proportions of patients with different levels of clinical impact, i.e., total CAT scores of 0-10 (mild), 11-20 (moderate), 21-30 (severe) and 31-40 (very severe), will be summarized descriptively by treatment for each visit.

Daily use of rescue medication (number of puffs)

The mean daily number of puffs will be calculated for each patient over 12 weeks. Mean daily number of puffs during the screening period will be used to calculate the baseline. The mean daily number of puffs will be analyzed using a linear mixed model. The model will contain treatment, baseline mean daily number of puffs, smoking status at baseline, and region as fixed effects with center nested within region as a random effect.

Percentage of days without rescue medication usage over 12 weeks

The percentage of days without rescue medication usage will be calculated for each patient over the 12 week treatment period. This endpoint will be analyzed using a similar model as for rescue medication use, but with baseline percentage of days without rescue medication usage instead of baseline mean number of puffs included in the model.

9.5.2 Safety variables

Adverse events

All adverse events including COPD exacerbations, coded using MedDRA, will be listed. Treatment emergent adverse events are defined as those events starting on or after the time of the first administration of randomized study drug but not later than 7 days (30 days in the case of serious adverse events) after the last administration of study medication.

Summaries of treatment emergent adverse events will be produced, overall by system organ class and preferred term for the following types of adverse events:

- all adverse events,
- all adverse events by maximum severity,
- adverse events suspected to be study drug related,

- adverse events leading to permanent discontinuation of study treatment,
- adverse events leading to interruption of study treatment,
- adverse events leading to adjustment (dose increase or decrease) of study treatment,
- adverse events requiring significant additional therapy,
- serious adverse events (SAEs),
- fatal adverse events.

COPD exacerbations during the 12 week treatment period

COPD exacerbations will be included in all adverse event analyses described above. In addition, COPD exacerbations reported during the 12 week treatment period will be summarized descriptively by severity.

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

Vital signs and ECG

Vital signs (blood pressure, pulse rate, and body weight) and ECG data will be summarized by treatment and scheduled visit including changes from baseline. The baseline value will be the pre-dose measurement at Visit 2. Data measured more than 7 days after last inhalation of study drug are regarded as post-treatment data and will not be summarized, only listed.

The analyses will include maximum and minimum vital signs data and maximum QTc and ventricular rate during randomized treatment (up to 7 days after end of treatment).

In addition, frequencies of notable vital signs and Fridericia's QTc (QTcF) will be summarized by treatment. Notable values are defined as follows:

Clinical notable criteria for vital signs

Vital sign parameter (unit)	Lower bound of clinically notable range	Upper bound of clinically notable range
Notable value considering newly occurring or worsening cases		
Systolic blood pressure (mmHg)	< 75	> 200
Diastolic blood pressure (mmHg)	< 40	> 115
Pulse rate (bpm)	< 40	> 130
Notable change from baseline		
Systolic blood pressure (mmHg)	≤ 90 and decrease from baseline by ≥ 20	≥ 180 and increase from baseline by ≥ 20
Diastolic blood pressure (mmHg)	≤ 50 and decrease from baseline by ≥ 15	≥ 105 and increase from baseline by ≥ 15
Pulse rate (bpm)	≤ 50 and decrease from baseline by ≥ 15	≥ 120 and increase from baseline by ≥ 15
Weight (kg)	Decrease ≥ 7% from baseline	Increase ≥ 7% from baseline

The following table shows the clinical notable criteria for QTcF.

Clinical notable criteria for QTcF (Fridericia's formula)

ECG parameter (unit)	Clinically notable range
Notable value considering newly occurring or worsening cases	
QTc (ms)	> 450 (both male and female)
QTc (ms)	> 480
QTc (ms)	> 500
Notable change from baseline	
QTc	30 – 60
QTc	> 60

9.5.3 Resource utilization

Not Applicable

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

No interim analysis is planned.

9.7 Sample size calculation

For the endpoint trough pre-dose FEV_1 change from baseline, a SD of 220mL was used based on a review of the results of Novartis phase III COPD studies. Discontinuation rate = 15% was assumed.

Sample size calculation for trough pre-dose FEV_1 change

alpha=0.05, 2-sided			
Power(%)	90	90	90
Difference to detect	65	70	75
SD	220	220	220
n per arm	242	209	182
with 15% drop-out rate	285	246	215
Total	570	492	430

Based on these calculations, a sample size of 418 completed patients is selected in order to detect a trough pre-dose FEV_1 change of 70mL with 90% power. Assuming a 15% drop out rate, 492 patients will be randomized.

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative(s) of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, s/he 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

Before initiating a trial, the investigator/institution should obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

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

11 Protocol adherence

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

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

11.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented immediately provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 Safety Monitoring should be followed.

12 References

Bateman ED, Ferguson GT, Barnes N, Gallagher N, Green Y, Henley M, Banerji D (2013) Dual bronchodilation with QVA149 versus single bronchodilator therapy: the SHINE study. Eur Respir J 42(6):1484-94.

Buist AS, McBurnie MA, Vollmer WM, et al. (2007) International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. Lancet 370(9589):741-50.

Dahl R, Chapman KR, Rudolf M, et al (2013) Safety and efficacy of dual bronchodilation with QVA149 in COPD patients: The ENLIGHTEN study. Respir Med 107(10):1558-67.

Global Initiative for Chronic Obstructive Lung Disease [GOLD] (2014) Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. Available from www.goldcopd.com

Hersh CP (2010) Pharmacogenetics of chronic obstructive pulmonary disease: challenges and opportunities. Pharmacogenomics 11(2): 237-247.

Jones PW, et al (2012) (on behalf of the CAT Development Steering Group) The COPD Assessment Test healthcare professional user guide: expert guidance on frequently asked questions. Issue 3: February 2012.

Jones PW, et al (2009). Development and first validation of the COPD Assessment Test. Eur Respir J 34(3):648-54.

Mahler D and Wells CK (1988) Evaluation of clinical methods for rating dyspnea. Chest 93:580-586.

Mahler DA, Decramer M, D'Urzo, A et al. (2014) Dual bronchodilation with QVA149 reduces patient-reported dyspnoea in COPD: the BLAZE study. Eur Respir J 43(6): 1599-609.

Vogelmeier CF, Bateman ED, Pallante J, et al. (2013) Efficacy and safety of once-daily QVA149 compared with twice-daily salmeterol-fluticasone in patients with chronic obstructive pulmonary disease (ILLUMINATE): a randomised, double-blind, parallel group study. Lancet Respir Med 1(1):51-60.

Appendix 1: Spirometry guidelines

Equipment

Spirometers must meet the specifications and performance criteria recommended in the American Thoracic Society (ATS)/European Respiratory Society (ERS) Standardization of Spirometry[1]. Spirometers must have the capacity to print FVC tracings. All spirometry values should be reported at BTPS by the method established by the manufacturer.

Calibration

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

Preparing the test subject

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

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

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

Performing Spirometry

The subject's age, height and gender will be entered into the spirometer. It is important that the height is measured accurately at the study site. Spirometry, an effort-dependent test, requires careful instruction and cooperation of the subject. The technician should ensure a good seal around the mouthpiece, and confirm that the subject's posture is correct. The subject should be instructed to perform a maximal inspiration, followed by maximum forced expiration until no more air can be exhaled or for at least 6 seconds. Expiration must be rapid with exertion of maximal effort. The results of spirometry should meet the ATS/ERS criteria for acceptability and repeatability. Acceptability criteria should be applied before repeatability is determined.

Number of trials

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

Acceptability

An acceptable maneuver has the following characteristics:

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

Repeatability

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

Recording of data

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

Predicted normal

For subjects greater than 18 years of age, this study will utilize the spirometric predication equation standards for the European Community for Coal and Steel [2] or Nhanes[3].

Reversibility (Visit 1 only)

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

- 6 h for short-acting β_2-agonists
- 8 h short-acting anticholinergics
- 24 h for long-acting β_2-agonist
- 7 days long-acting anticholinergics
- 3 days indacaterol

Administer 84 µg (or equivalent dose) of ipratropium bromide within 5 minutes of pre-bronchodilator spirometry, followed by the administration of 400 µg of salbutamol (or 360 µg albuterol) a few minutes later.

Post-bronchodilator spirometry is performed 1h after the administration of salbutamol/albuterol

Reversibility is calculated as:

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

Following the reversibility testing assessment for post-bronchodilator FEV_1, if lung function has deteriorated (i.e. there is a decrease in post bronchodilator FEV_1 compared to pre-bronchodilator FEV_1 *as opposed to an increase*) after administration of ipratropium and salbutamol or albuterol, then the patient should be screen failed. Patients with COPD demonstrating significant reversibility (i.e. 20%) may require further clinical evaluation by the investigator to rule out a diagnosis of asthma.

References

[1] Miller MR et al, Standardization of Spirometry. Eur Resp J 2005;26:319-338.

[2] Quanjer PH at al. Lung volumes and forced ventilatory flows, Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory society. Eur Resp J 1993;6: Suppl. 16, 5-40.

[3] Hankinson JL, Odencrantz JR, Fedan KB (1999) Spirometric reference values from a sample of the general US population. Am J Respir Crit Care Med 159:179–187.

Appendix 2: Instructions for use of the SDDPI

How to use the SDDPI

Instructions for using inhaler and capsules.

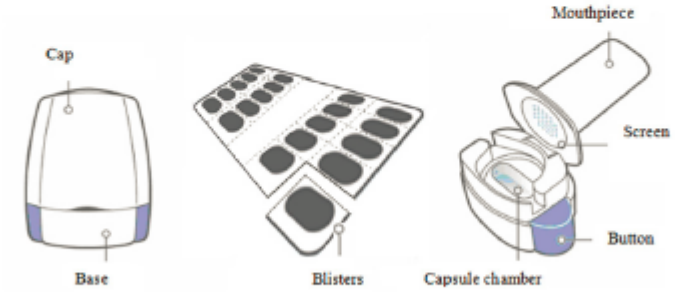
Do not swallow capsules.

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

Your inhaler and capsules

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

- Capsules are supplied in blisters.
- Inhaler consists of a cap, mouthpiece and a base.



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

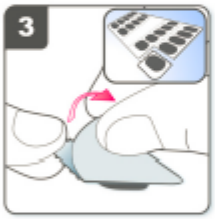
Do not use the study medication capsules with any other capsule inhaler, and do not use the

inhaler to take any other capsule medicine.

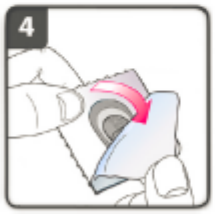
How to use your inhaler

Pull off cap.

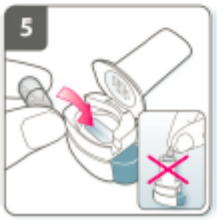
Open inhaler:
Hold the base of the inhaler firmly and tilt back the mouthpiece. This opens the inhaler.



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

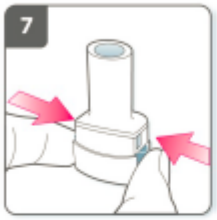


Remove a capsule:
Peel away the foil and remove the capsule from the blister.



Insert capsule:
Place the capsule into the capsule chamber.
Never place a capsule directly into the mouthpiece.

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



Pierce the capsule:

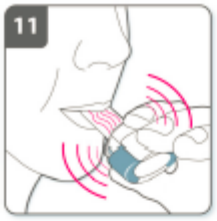
- Hold the inhaler upright with the mouthpiece pointing up.
- Pierce the capsule by firmly pressing together both side buttons at the same time. **Do this only once.**
- You should hear a "click" as the capsule is being pierced.

Release the side buttons fully.

Breathe out:
Before placing the mouthpiece in your mouth, breathe out fully.
Do not blow into the mouthpiece.

Inhale the medicine
To breathe the medicine deeply into your airways:

- Hold the inhaler as shown in the picture. The side buttons should be facing left and right. Do not press the side buttons.
- Place the mouthpiece in your mouth and close your lips firmly around it.
- Breathe in rapidly but steadily and as deeply as you can.



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

Additional information
Occasionally, very small pieces of the capsule can get past the screen and enter your mouth. If this happens, you may be able to feel these pieces on your tongue. It is not harmful if these pieces are swallowed. The chances of the capsule breakage will be increased if the capsule is accidentally pierced more than once (step 7). Therefore it is recommended that you follow the storage directions, remove the capsule from the blister immediately before use and pierce each capsule only once.

If you do not hear a whirring noise:
The capsule may be stuck in the capsule chamber. If this happens:

- Open the inhaler and carefully loosen the capsule by tapping the base of the inhaler. Do not press the side buttons.
- Inhale the medicine again by repeating steps 9 to 11.

Hold breath:
After you have inhaled the medicine:

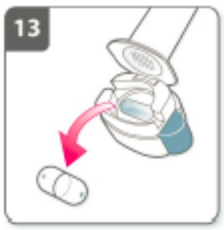
- Hold your breath for at least 5-10 seconds or as long as you comfortably can while taking the inhaler out of your mouth.
- Then breathe out.
- Open the inhaler to see if any powder is left in the capsule.

If there is powder left in the capsule:

- Close the inhaler.
- Repeat steps 9, 10, 11 and 12.

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

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



After you have finished taking your medicine:

- You may be directed by your physician to rinse mouth with water and spit it out; do not swallow the water.
- Open the mouthpiece again, and remove the empty capsule by tipping it out of the capsule chamber. Put the empty capsule in your household waste.
- Close the inhaler and replace the cap.

Do not store the capsules in the inhaler.

REMEMBER:

- Do not swallow capsules.
- Only use the inhaler contained in this pack.
- Capsules must always be stored in the blister, and only removed immediately before use.
- Never place a capsule directly into the mouthpiece of the inhaler.
- Do not press the side buttons more than once.
- Never blow into the mouthpiece of the inhaler.
- Always release the push buttons before inhalation.
- Never wash the inhaler with water. Keep it dry. See "How to clean your inhaler".
- Never take the inhaler apart.
- Always use the new inhaler that comes with your new medication pack. Dispose of each inhaler after the number of uses identified by your physician.
- Do not store the capsules in the inhaler.
- Always keep the inhaler and capsules in a dry place, and avoid very hot or cold temperatures.

How to clean your inhaler

- Clean your inhaler once a week.
- Wipe the mouthpiece inside and outside to remove any powder with a clean, dry lint-free cloth.
- Do not wash your inhaler with water. Keep it dry.
- Do not take the inhaler apart.

Manufactured by:

Novartis Pharma AG, Switzerland

CE

Appendix 3: Instructions for use of the Accuhaler®/Diskus®

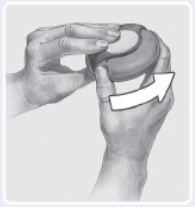
How to use the Accuhaler®/Diskus®

Instructions for use

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

Using your inhaler

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



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

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

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

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

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

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

How to clean your inhaler

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

Appendix 4: Baseline dyspnea index/transitional dyspnea index (BDI/TDI)

(Samples for illustrative purposes only)

BASELINE DYSPNEA INDEX (BDI)

Baseline 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	Subject has changed jobs and/or has abandoned at least one usual activity due to shortness of breath.
____Grade 1	Severe Impairment	Subject 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	Subject 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.

Baseline 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	Subject'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.

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	Subject'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.

TRANSITION DYSPNEA INDEX (TDI)

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	Subject 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.

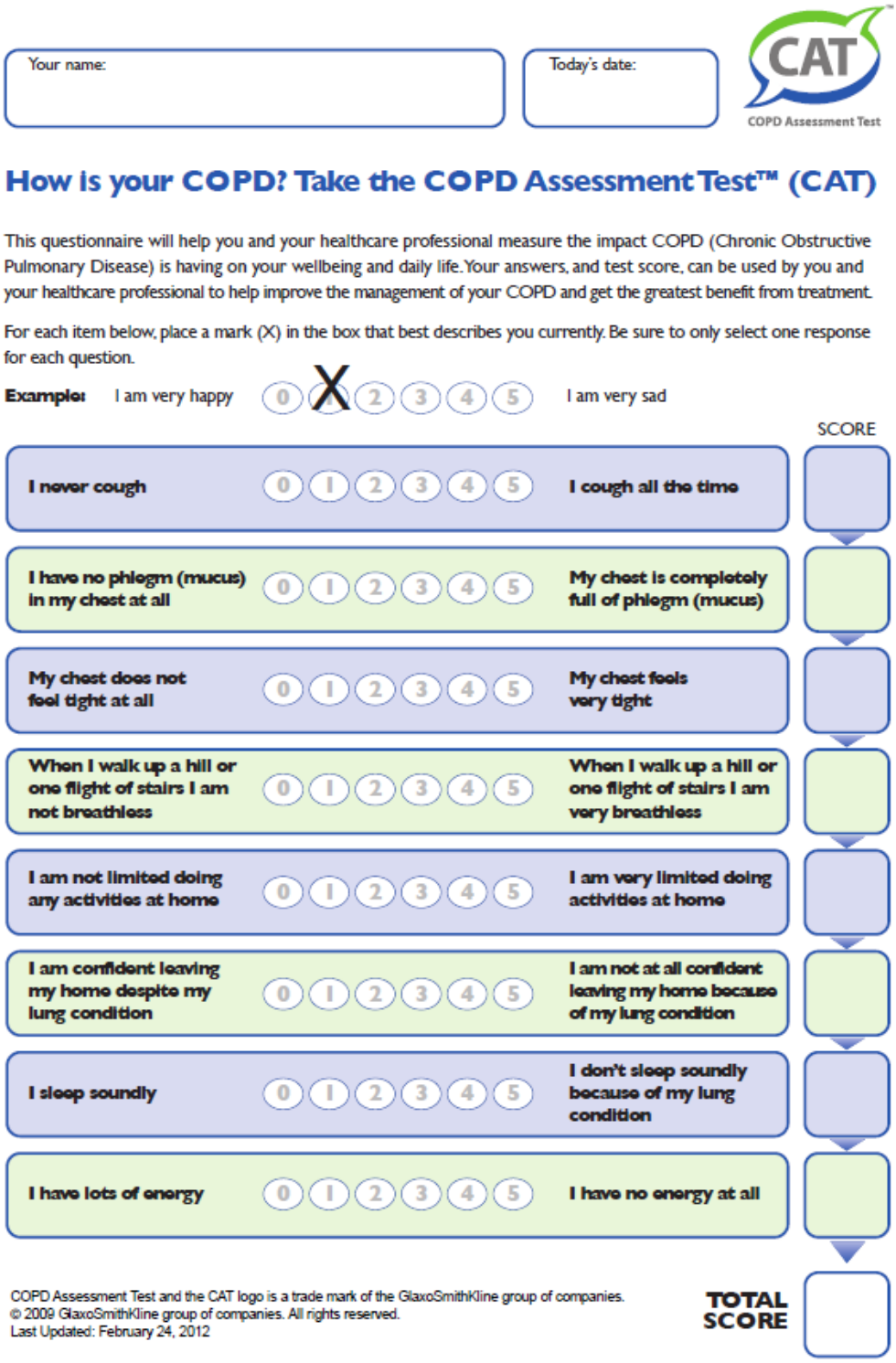
Change in Magnitude of Task

____-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. Subject 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. Subject 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	Subject has reduced exertion capacity, but not related to shortness of breath. For example, musculoskeletal problem or chest pain.

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	Subject has reduced exertional capacity, but not related to shortness of breath. For example, musculoskeletal problem or chest pain.

Appendix 5: COPD Assessment Test (CAT)



Your name:

Today's date:

CAT
COPD Assessment Test

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

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

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

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

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

Appendix 6: Clinically notable vital signs

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

Systolic blood pressure

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

Diastolic blood pressure

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

Pulse rate

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

Appendix 7: Patient diary (example)

PATIENT COPD TREATMENT DIARY

Instructions:

1. Please use this diary to record the time when you take your COPD medication each morning and evening. Please (√) check if you missed the dose.
2. Each morning and evening record the number of puffs of reliever medication taken during the past 12 hours.

Date	IN THE MORNING		IN THE EVENING	
	Morning time of study medication	Number of puffs of reliever medication taken in the past 12 hours	Evening time of study medication	Number of puffs of reliever medication taken in the past 12 hours
___ /___ /20_ _ (day) / (month)	_____:_____ ☐ missed	_______ puffs	_____:_____ ☐ missed	_______ puffs
___ /___ /20_ _ (day) / (month)	_____:_____ ☐ missed	_______ puffs	_____:_____ ☐ missed	_______ puffs
___ /___ /20_ _ (day) / (month)	_____:_____ ☐ missed	_______ puffs	_____:_____ ☐ missed	_______ puffs
___ /___ /20_ _ (day) / (month)	_____:_____ ☐ missed	_______ puffs	_____:_____ ☐ missed	_______ puffs
___ /___ /20_ _ (day) / (month)	_____:_____ ☐ missed	_______ puffs	_____:_____ ☐ missed	_______ puffs
___ /___ /20_ _ (day) / (month)	_____:_____ ☐ missed	_______ puffs	_____:_____ ☐ missed	_______ puffs
___ /___ /20_ _ (day) / (month)	_____:_____ ☐ missed	_______ puffs	_____:_____ ☐ missed	_______ puffs