AstraZeneca

Clinical Study Protocol	
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A Randomised, Double-Blind, Double-Dummy, Multicentre, Parallel Group Study to Assess the Efficacy and Safety of Glycopyrronium/Formoterol Fumarate fixed-dose combination relative to Umeclidinium/Vilanterol fixed-dose combination over 24 Weeks in patients with Moderate to Very Severe Chronic Obstructive Pulmonary Disease (AERISTO)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

VERSION HISTORY

Version 1, 1 February 2017
Initial version.

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

CLINICAL STUDY PROTOCOL SYNOPSIS

A Randomised, Double-Blind, Double-Dummy, Multicentre, Parallel Group Study to Assess the Efficacy and Safety of Glycopyrronium/Formoterol Fumarate fixed-dose combination relative to Umeclidinium/Vilanterol fixed-dose combination over 24 Weeks in patients with Moderate to Very Severe Chronic Obstructive Pulmonary Disease (AERISTO)

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Study site(s) and number of patients planned

The study will be conducted at approximately 150 sites in 7 about countries in North America and Europe. Across these sites, it is planned that approximately 1400 patients will be screened and 1000 patients will be randomised into the study.

Phase of development
IIIb

Study design

This is a phase IIIb randomised, double-blind, double-dummy, multicentre, parallel group, 24 week study to assess the efficacy and safety of Glycopyrronium/Formoterol Fumarate (GFF) fixed-dose combination 7.2/4.8 µg 2 inhalations twice daily compared to Umeclidinium/Vilanterol (UV) 62.5/25 µg fixed-dose combination 1 inhalation once daily in patients with moderate to very severe COPD.

Objectives

Primary Objective:	**Outcome Measure:**
To assess the effects of GFF relative to UV on lung function as measured by trough FEV_1 in patients with moderate to very severe COPD	**Primary endpoint:** Change from baseline in morning pre-dose trough FEV_1 over 24 weeks

Secondary Objective:	Outcome Measure:
To further assess the effects of GFF relative to UV on lung function.	**Secondary endpoints:** • Onset of action on day 1; proportion of patients with increase of FEV_1 of ≥100 ml from baseline at 5 minutes • Change from baseline in Peak FEV_1 within 2 hours post-dosing over 24 weeks • Change from baseline in Peak Inspiratory Capacity (IC) within 2 hours post-dosing over 24 weeks
To assess the effects of GFF relative to UV on dyspnea	**Secondary endpoint:** Transition Dyspnea Index (TDI) focal score over 24 weeks
To assess the effects of GFF relative to UV on symptoms of COPD	**Secondary endpoint:** Change from baseline in Early Morning Symptoms COPD Instrument (EMSCI) over 24 weeks **Other endpoints:** • Change from baseline in Night Time Symptoms COPD Instrument (NiSCI) over 24 weeks • Change from baseline in daily rescue (albuterol/salbutamol MDI) use over 24 weeks
To assess the effects of GFF relative to UV on health-related quality of life	**Other endpoint:** Change from baseline in COPD Assessment Test (CAT) score over 24 weeks

Safety Objective:	Outcome Measure:
To assess the safety of GFF	Adverse events (AEs), serious adverse events (SAEs), adverse events leading to treatment discontinuation (DAEs)

Exploratory Objective:	Outcome Measure:
To assess health status for COPD patients treated with GFF	Change from baseline in EuroQol 5 Dimensions Questionnaire (EQ-5D-5L) over 24 weeks
To assess overall and COPD-specific Healthcare Resource Utilization and work productivity loss for GFF	Health Economics Questionnaire for healthcare resource utilization. Work Productivity and Activity Impairment - General Health (WPAI-GH)

Target patient population

Patients, 40-95 years of age, with moderate to very severe COPD.

Duration of treatment

Patients will be treated for 24 weeks.

Investigational product, dosage and mode of administration

Each patient will undergo a screening period of 1 to 4 weeks (-28 to -9 days). During the screening period, patients will be provided with ipratropium bromide MDI 2 inhalations QDS as COPD maintenance therapy. Albuterol/salbutamol MDI will be provided as rescue medication during the screening period and throughout the study.

Patients will be randomised in a 1:1 scheme. Approximately 500 patients will be randomised to the GFF and UV treatment groups, respectively. Patients will be stratified based on incoming COPD treatment at screening; rescue/maintenance monotherapy (LAMA, LABA or ICS only) vs. double maintenance therapy (LABA/LAMA or ICS/LABA).

The first dose of IP will be taken at Visit 3 (Day 1). During the 24 week double-blind treatment period, patients will take two inhalations in the morning and in the evening from the GFF inhaler (active or placebo) and one inhalation in the morning from the UV inhaler (active or placebo).

Statistical methods

The primary analysis will be conducted using the Per Protocol analysis set. Data following important protocol deviations or from visits where patients do not comply with required restrictions will be excluded from this analysis. Supportive analyses and superiority testing will be conducted in the full analysis set of all patients randomised and dosed, using all data obtained while on treatment.

The primary endpoint of change from baseline in morning pre-dose trough FEV_1 will be analysed using a linear mixed effects repeated measures approach. The model will include baseline FEV_1 and bronchodilator responsiveness as continuous covariates and stratification factors (prior treatment - rescue/maintenance monotherapy vs double maintenance therapy), region, visit, treatment, and treatment by visit, as categorical covariates. Patient will be considered a random effect.

The primary analysis will be based upon an estimate of the treatment difference over the entire 24-week treatment period, along with two-sided 95% confidence intervals. Non-inferiority will be concluded if the lower bound of this confidence interval is greater than the pre-specified margin of -50 mL. This is equivalent to a one-sided hypothesis test at the 2.5% significance level. 1-sided p-values will be produced for both non-inferiority and superiority hypothesis testing.

The secondary endpoints of peak change from baseline in FEV_1 within 2 hours post-dosing, peak change from baseline in IC within 2 hours post-dosing, TDI focal score and EMSCI symptom severity score will be analysed using a similar repeated measures model to the primary endpoint, including appropriate baselines in the model. Peak FEV_1 and IC will be referred to a non-inferiority margin of -50mL, while TDI and EMSCI will be referred to non-inferiority margins of -1.0 units and -0.1 units respectively.

A hierarchical testing strategy will be defined so as to control type I error across all non-inferiority hypothesis tests for secondary endpoints. If non-inferiority is demonstrated for an endpoint in the per protocol analysis set, then testing may proceed to the next endpoint in the hierarchy, and a superiority test of the endpoint will also be conducted in the full analysis set where relevant.

An exception to this sequential non-inferiority/superiority testing procedure is the secondary endpoint of onset of action (proportion of patients with increase in FEV_1 of $\geq$100 ml from baseline at 5 minutes on day 1). For this endpoint superiority testing will immediately be carried out using logistic regression without any prior non-inferiority testing.

Rescue medication use, CAT, NiSCI and other spirometry and symptom sub-scale endpoints will also be analysed using mixed effects repeated measures models.

Adverse events (AEs) and exploratory endpoints will be reported descriptively.

Approximately 500 patients per arm are to be randomised and it is expected that around 440 patients per arm will be included in the Per Protocol Analysis Set for the primary analysis. This sample size will provide around 94% power to demonstrate that the difference between GFF and UV in change from baseline in morning pre-dose trough FEV_1 over 24 weeks is greater than the non-inferiority margin of -50 mL, using a one-sided significance level of 0.025 and assuming an effective standard deviation of 167mL and a true difference of -10 mL.

TABLE OF CONTENTS PAGE

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AE	Adverse Event
ATS	American Thoracic Society
AZRand	AstraZeneca Global Randomisation system
BDI	Baseline Dyspnea Index
BD	Twice daily
BMI	Body Mass Index
CAT	COPD Assessment Test
COPD	Chronic Obstructive Pulmonary Disease
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CT	Computed Tomography
DAE	Adverse event leading to discontinuation of investigational product
DPI	Dry Powder Inhaler
DUS	Disease under study
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
eCRF	Case Report Form (electronic)
EQ-5D-5L	EuroQol 5 Dimensions Questionnaire
EMSCI	Early Morning Symptoms of COPD Instrument
ERS	European Respiratory Society
ePRO	Electronic Patient Reported Outcomes
FDA	U.S. Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FF	Formoterol Fumarate
FVC	Forced vital capacity
GCP	Good Clinical Practice
GFF	Glycopyrronium and Formoterol Fumarate

Abbreviation or special term	Explanation
GLI	Global Lung Function Initiative
GMP	Good Manufacturing Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	Glycopyrronium
HCRU	Healthcare resource utilization
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICS	Inhaled corticosteroids
IC	Inspiratory capacity
IP	Investigational Product
IWRS/IVRS	Interactive Web Response System/Interactive Voice Response System
LABA	Long-acting beta2-adrenergic agonist
LAMA	Long-acting muscarinic antagonist/inhaled anticholinergic
LPLV	Last Patient Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
MDI	Metered dose inhaler
NiSCI	Nighttime Symptoms of COPD Instrument
OAE	Other Significant Adverse Event
OD	Once daily
QDS	Four times daily
PI	Principal Investigator
PP	Per Protocol
Pre-BD	Pre-bronchodilator
PRN	As needed
Post-BD	Post-bronchodilator
SAE	Serious Adverse Event
SAMA	Short-acting muscarinic antagonist/ inhaled anticholinergics
SAP	Statistical Analysis Plan
SD	Standard Deviation
TDI	Transitional Dyspnea Index
UV	Umeclidinium/Vilanterol
VAS	Visual Analogue Scale

Abbreviation or special term	Explanation
WBDC	Web Based Data Capture
WPAI-GH	Work Productivity and Activity Impairment Questionnaire - General Health

1. INTRODUCTION

1.1 Background and rationale for conducting this study

Long-acting bronchodilators are central to the pharmacological management of chronic obstructive pulmonary disease (COPD) (GOLD 2017). However, many patients remain symptomatic despite the availability of effective long-acting monotherapies. In a real-world study (Dransfield et al 2011), patients receiving tiotropium, formoterol, or salmeterol as long-acting bronchodilator maintenance therapy continued to report dyspnea and high levels of supplemental rescue medication use, irrespective of the level of airflow limitation.

Glycopyrronium (GP) is a long-acting muscarinic antagonist (LAMA) which exerts its bronchodilatory effect via muscarinic receptors located on smooth muscle cells within the trachea and bronchi. GP is approved in many countries in multiple formulations for different indications, including for the treatment of COPD.

Formoterol fumarate (FF) is a selective long-acting β_2-agonist (LABA) approved worldwide for use in COPD. In addition, FF is also approved worldwide in combination with inhaled corticosteroids (ICS) such as budesonide (e.g., Symbicort® MDI, Symbicort® Turbuhaler® (TBH [AstraZeneca, LP]) for use in patients with asthma and COPD. When inhaled, FF acts locally in the lung as a bronchodilator. FF stimulates β2-adrenoreceptors in the airways, inducing airway smooth muscle relaxation and reducing or preventing bronchoconstriction.

Dual long-acting bronchodilator therapy represents an alternative to long-acting bronchodilator monotherapy (Cazzola et al 2010). Glycopyrronium/Formoterol Fumarate (GFF) is a fixed-dose combination of GP and FF in a metered dose inhaler (MDI). It is approved in the USA for maintenance treatment of COPD (at a dose of 7.2/4.8µg two inhalations twice daily (Bevespi Aerosphere™ prescribing information, 2016.). Dual bronchodilation with GFF has been shown to provide greater improvements in lung function than GP or FF alone, with similar or greater improvements in measures of dyspnea, rescue medication use, and health-related quality of life (Martinez et al 2016). However, a direct comparison between GFF and other inhaled LAMA/LABA combinations has not been performed

Umeclidinium/Vilanterol (UV) is a fixed-dose combination of the LAMA umeclidinium and the LABA vilanterol, which is approved in many countries for the treatment of COPD. UV is a dry powder inhaler (DPI) prescribed at a dose of 62.5 µg/25 µg once daily (Anoro™ Ellipta™ prescribing information, 2016.).

The rationale for a direct comparison between LAMA/LABA combinations is multi-fold. There are several LAMA/LABA combinations available, approved at once-daily or twice-daily dosing regimens (Duaklir® Genuair® Summary of Product Characteristics 2015; Anoro™ Ellipta™ prescribing information, 2016.;Utibron™ Neohaler® prescribing information 2016.;Stiolto® Respimat® prescribing information 2016). The mono-components of the LAMA/LABA combinations have different pharmacological properties which may

have an impact clinically on both lung function and symptoms. The symptomatic impact of COPD can vary over the course of the day and night, whereby different dosing regimens and differences in treatment effects may be important. It is a well-known fact that many COPD patients find the morning hours particularly burdensome, as they get up and start their day. Therefore, effective bronchodilation during the night and fast onset of effect in the morning have relevance for this patient group (Roche et al 2013). A direct comparison between two LAMA/LABAs will help elucidate the influence of their different dosing regimens and pharmacological properties on the treatment effects and evaluate the importance of these differences for patients' lung function, symptoms and health-related quality of life.

This study will compare the efficacy of GFF to UV in patients with moderate to very severe COPD.

1.2 Rationale for study design, doses and control groups

This is a randomised, double-blind, active controlled, parallel group study of 24 weeks duration in patients with moderate to very severe COPD. The study design is commonly used in COPD and is consistent with regulatory guidelines. 24 weeks is sufficient duration to be able to observe improvements in airflow obstruction and symptom relief.

As described in Section 1.1, both GFF and UV are approved therapies for COPD in the USA, and while UV is already approved in several other major markets, GFF is expected to gain similar approvals by the time of completion of this study. Both treatments will be given in accordance with their labelled dosing regimens. A direct comparison of these two treatments will support the evidence base for the prescribing of GFF.

This study will recruit patients with moderate to very severe COPD; therefore, spirometry entry requirements are set according to the thresholds defined by GOLD grade 2 or above (GOLD 2017). These requirements are in line with the inclusion criteria used in the pivotal study programmes of both GFF and UV. In addition, patients are required to be symptomatic at baseline with a COPD Assessment Test (CAT) score of 10 or above. This threshold is specified in the current guidelines (GOLD 2017) as determining those in need of treatment for symptoms of COPD. In patients meeting these criteria, with severe or persistent breathlessness, treatment with dual bronchodilator therapy is recommended (GOLD 2017).

Randomisation and blinding minimise any potential for selection bias, or for bias in the assessment of study endpoints or the management of patients. This is especially important given the patient-reported endpoints collected in this study. As GFF is delivered in a metered dose inhaler (MDI) and UV in a dry powder inhaler (DPI), it is not possible to provide a single matched inhaler that could deliver either investigational treatment. Therefore, a double-dummy design will be used whereby matched placebo versions of each of the MDI and DPI will be used and patients will be randomised to receive one of the active inhalers to be taken alongside one of the placebo inhalers. Patients will also continue to use short-acting rescue medication when necessary (albuterol/salbutamol MDI inhaler). As the aim of this study is to directly assess the differences in lung function and symptoms attributable to the two LAMA/LABA combinations, patients should discontinue from inhaled corticosteroid (ICS)

treatment before being randomised. Given that multiple inhalers are involved in study treatment, there would also be concerns about treatment complexity and compliance if a fourth inhaler were used. Patients who are receiving a stable ICS/LABA combination at screening may enter the study if ICS treatment is withdrawn. The switch to LAMA/LABA treatment for these patients, particularly those with lower blood eosinophil counts, is justified since recent studies (Wedzicha et al 2016) have demonstrated the benefits of LAMA/LABA dual bronchodilation over ICS/LABA combination treatment in terms of reduction in exacerbation risk and improvements in lung function and symptoms.

Patients at high exacerbation risk who experience further exacerbations may need their treatment to be escalated (for example to triple therapy including ICS). Patients who experience ≥2 moderate exacerbations (requiring antibiotics or ≥3 days of systemic steroids) or ≥1 severe exacerbation (leading to hospitalisation) while on study will be withdrawn.

The primary endpoint in this study is morning pre-dose trough FEV_1. This is a recognised measure of pulmonary function and airflow obstruction and has been used as the primary endpoint in many regulatory studies in COPD, including the pivotal studies of both GFF and UV (Martinez et al 2016; Donohue et al 2013). Since trough FEV_1 measures lung function at the nadir of the effect of the randomised therapies and it is important to consider the entire dosing interval, peak FEV_1 is included as a secondary endpoint. Other secondary endpoints include recognised and validated measures of dyspnea, COPD symptoms and health-related quality of life. These are important factors to patients experiencing COPD in addition to measures of airflow obstruction.

As the comparator is an approved active therapy, the primary objective of the study will be to establish the non-inferiority of GFF to UV in improving lung function and symptoms. The potential for superiority over UV in maximum bronchodilation, inspiratory capacity (IC), early onset of effects and morning symptom control will also be assessed. No placebo arm is included, but as there is extensive experience of these therapies in terms of the endpoints used (in particular the primary endpoint and other spirometry assessments), there are no concerns about assay sensitivity in this study. Similar two-arm non-inferiority studies have been conducted with other products in COPD, including between dual bronchodilator combinations (Kalberg et al 2016; Buhl et al 2015).

The proposed non-inferiority margin of 50mL for trough FEV_1 is well established and based upon considerable experience in reproducible effects of long acting bronchodilators over placebo. It relates to half of the commonly recognised clinically important difference of 100mL (Donohue 2005) and has been used in several non-inferiority studies, both of dual and single long acting bronchodilators (Kalberg et al 2016; Chapman et al 2014; Volgelmeier et al 2010). The same margin will be applied to Peak FEV_1 and IC.

The non-inferiority margin for TDI is based upon the Minimum Clinically Important Difference (MCID) of 1 unit (Mahler et al 2005). Although there is less precedent for formal non-inferiority testing of TDI, a similar approach to using the MCID as a pre-specified margin has been used previously for SGRQ (Buhl et al 2015). There is less clinical experience with the use of EMSCI, but a non-inferiority margin of 0.1 units is proposed based upon the

difference observed between LAMA/LABA and LAMA only treated patients (D'Urzo et al 2014).

1.3 Benefit/risk and ethical assessment

GFF was approved by the US FDA for patients with COPD in April 2016 and launched in the US January 2017. Its two mono-components, GP and FF, are used as single therapy or in combination with other inhaled drugs in patients with COPD in many countries worldwide. The clinical development program for GFF included 4,602 patients with COPD. Overall, the program demonstrated that GFF was effective for long-term maintenance therapy in patients with COPD and provided additional efficacy benefits compared to its mono-components (as assessed by measures of lung function, COPD symptoms and disease-specific health status). GFF was well tolerated, with a safety profile comparable to the mono-components, and with no unexpected safety observations. Adverse drug reactions with ≥1% incidence were anxiety, headache, tremor, dry mouth, nausea, muscle spasms and chest pain. Less common adverse drug reactions were hyperglycaemia, agitation, restlessness, sleep disturbance, tachycardia, palpitations, atrial fibrillation, supraventricular tachycardia, extrasystoles, dizziness and hypersensitivity. In conclusion, these findings support a favourable benefit-risk profile for GFF in the treatment of patients with COPD.

UV was approved by the US FDA in 2013 and has since then been launched worldwide for patients with COPD. Adverse drug reactions with ≥1% incidence reported with UV are pharyngitis, sinusitis, lower respiratory tract infection, constipation, diarrhoea, pain in extremity, muscle spasms, neck pain and chest pain. Less common adverse drug reactions are productive cough, dry mouth, dyspepsia, abdominal pain, gastroesophageal reflux disease, vomiting, musculoskeletal chest pain, chest discomfort, asthenia, atrial fibrillation, ventricular extrasystoles, supraventricular extrasystoles, myocardial infarction, pruritus, rash, and conjunctivitis.

During screening, all patients will switch their COPD therapy to ipratropium bromide MDI four times daily (QDS) and albuterol/salbutamol MDI as needed (PRN). Although this regimen is expected to give adequate symptom relief for most patients, some of them (mainly those with previous LAMA/LABA combination treatment) may experience an increase in symptoms. Patients will be have a faster follow up than what they would experience in regular clinical settings and will be reminded to contact their physicians if they have significantly worsening symptoms. During the 24-week treatment period, all patients will be treated with a LAMA/LABA combination, and since patients on incoming triple therapy will not be eligible, no patients will be subjected to a step-down in therapy after randomisation compared to their regular maintenance therapy. Patients on incoming rescue treatment only or maintenance monotherapy will be eligible only if they are symptomatic (CAT score ≥10) at screening, i.e. a step-up in treatment for these patients will be based on clinical judgement and will offer a potential for improvement. Both arms will use approved doses and the study population represents the population for which these medications were approved.

Based on the safety profile of the investigational products (IPs), no new or specific risks beyond what has been described are anticipated with the doses and the dose regimens being

used in this trial. Investigators will ensure adequate medical care of the study participants at all times throughout the course of the study, and patients will be followed by clinic visits every 4-8 weeks.

The study requires documentation of a standard chest x-ray (as per local practice), or computed tomography (CT) scan of the chest/lungs, within 6 months of enrolment to rule out clinically significant abnormalities not associated with COPD. The requirement for chest x-ray introduces minimal radiation exposure and is a standard diagnostic test for COPD symptom worsening and pneumonia.

1.4 Study Design

This is a phase IIIb randomised, double-blind, double-dummy, multicentre, parallel group, 24 week study to assess the efficacy and safety of GFF 7.2/4.8 µg 2 inhalations twice daily (BD) compared to UV 62.5/25 µg 1 inhalation once daily (OD) in patients with moderate to very severe COPD.

The study will be conducted in approximately 150 sites. Across these sites, it is planned that approximately 1400 patients will be screened and 1000 randomised into the study.

Patients will be randomised in a 1:1 scheme. Approximately 500 patients each will be randomised to the GFF and UV treatment groups. Patients will be stratified based on incoming COPD treatment at screening: rescue only/maintenance monotherapy (LAMA or LABA or ICS only) vs. double maintenance therapy (LABA/LAMA or ICS/LABA).

The study will evaluate the benefit of GFF compared to UV in patients with moderate to very severe COPD. Patients on rescue medication only or maintenance monotherapy will be required to be symptomatic (CAT $\geq$10) at screening (Visit 1), whereas there will be no symptom requirement at screening for patients on double maintenance therapy (ICS/LABA or LAMA/LABA). All patients will be required to be symptomatic (CAT $\geq$10) at randomisation (Visit 3). Patients on triple maintenance therapy will not be eligible. A history of exacerbations in the previous year will be obtained to characterize the population but will not be included as an entry criterion. COPD severity, defined as post-bronchodilator forced expiratory volume in 1 second (FEV_1), must be <80% predicted normal value, calculated using the Global Lung Function Initiative (GLI) equations (Quanjer et al 2012), and the measured FEV_1 must also be $\geq$750 mL if FEV_1 less than 30 % of predicted normal value.

Post-bronchodilator FEV_1 (after inhalation of albuterol/salbutamol MDI) will be tested at screening (Visit 1 and Visit 2) to determine eligibility and COPD severity. Bronchodilator responsiveness to albuterol/salbutamol MDI will be tested at Visit 2.

Any treatment with ICS, LAMA, LABA and existing rescue medications will be stopped at the screening visit. During the screening period, patients will be treated with ipratropium bromide MDI 2 inhalations QDS and albuterol/salbutamol MDI as needed. Albuterol/salbutamol MDI will also be used as rescue medication throughout the 24-week treatment period.

Baseline assessments: vital signs, 12-lead electrocardiogram (ECG), clinical laboratory testing and pregnancy test will be performed to assess patients' eligibility.

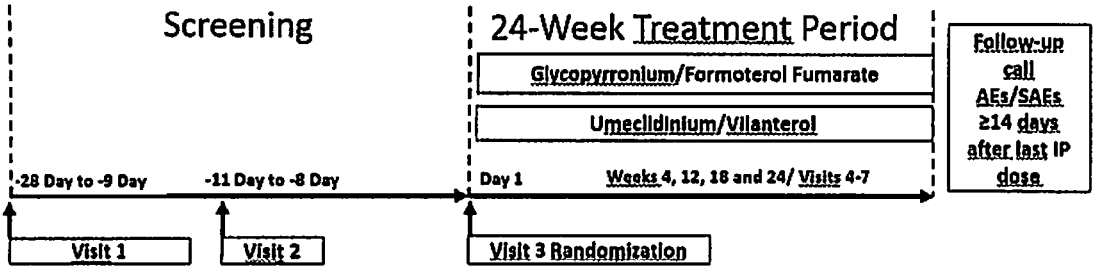
After the Randomisation Visit (Visit 3), patients will be evaluated at Visit 4 (Week 4), Visit 5 (Week 12), Visit 6 (Week 18) and Visit 7 (Week 24) using spirometry and patient reported outcome questionnaires. From Visit 2 onwards, patients will also enter data daily in an electronic Patient Reported Outcomes device (ePRO).

For patients who remain on treatment throughout the study (i.e., complete Visit 7), a follow-up telephone call will be performed approximately 14 days after the last IP dose.

Patients who discontinue study treatment prior to Week 24 (Visit 7) will complete a Treatment Discontinuation/Withdrawal Visit. These patients will be placed on appropriate maintenance COPD medications, as per the Investigator's judgement. Consideration should be given to maintaining patients on at least double therapy, while ensuring appropriate follow-up and further evaluation of the prescribed treatment.

A follow-up telephone call will be performed approximately 14 days after the last IP dose. No further data will be collected. In the event the Treatment Discontinuation/Withdrawal Visit is performed approximately14 days post last IP dosing, a follow-up TC will not be required.

Figure 1 Study flow chart



1.5 Study governance and oversight – Not Applicable

2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	Outcome Measure:
To assess the effects of GFF relative to UV on lung function as measured by trough FEV_1 in patients with moderate to very severe COPD	**Primary endpoint:** Change from baseline in morning pre-dose trough FEV_1 over 24 weeks

2.2 Secondary objectives

Secondary Objective:	Outcome Measure:
To further assess the effects of GFF relative to UV on lung function.	**Secondary endpoints:** • Onset of action on day 1; proportion of patients with increase of FEV_1 of ≥100 ml from baseline at 5 minutes • Change from baseline in Peak FEV_1 within 2 hours post-dosing over 24 weeks • Change from baseline in Peak Inspiratory Capacity (IC) within 2 hours post-dosing over 24 weeks
To assess the effects of GFF relative to UV on dyspnea	**Secondary endpoint:** Transition Dyspnea Index (TDI) focal score over 24 weeks
To assess the effects of GFF relative to UV on symptoms of COPD	**Secondary endpoint:** Change from baseline in Early Morning Symptoms COPD Instrument (EMSCI) over 24 weeks **Other endpoints:** • Change from baseline in Night Time Symptoms COPD Instrument (NiSCI) over 24 weeks • Change from baseline in daily rescue (albuterol/salbutamol MDI) use over 24 week
To assess the effects of GFF relative to UV on health-related quality of life	**Other endpoint:** Change from baseline in COPD Assessment Test (CAT) score over 24 weeks

2.3 Safety objectives

Safety Objective:	Outcome Measure:
To assess the safety of GFF	Adverse events (AEs), serious adverse events (SAEs), adverse events leading to treatment discontinuation (DAEs)

2.4 Exploratory objectives

Exploratory Objective:	Outcome Measure:
To assess health status for COPD patients treated with GFF	Change from baseline in EuroQol 5 Dimensions Questionnaire (EQ-5D-5L) over 24 weeks
To assess overall and COPD-specific Healthcare Resource Utilization and work productivity loss for GFF	Health Economics Questionnaire for healthcare resource utilization. Work Productivity and Activity Impairment - General Health (WPAI-GH)

3. PATIENT SELECTION, ENROLMENT, RANDOMISATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

3.1 Inclusion criteria

For inclusion in the study patients should fulfil the following criteria:

1. Provision of informed consent prior to any study specific procedures.

2. Female or male patients aged 40-95 years inclusive at the time of enrolment at Visit 1.

3. Tobacco Use: Current or former smoker with a history of at least 10 pack-years of cigarette smoking (1 pack year = 20 cigarettes smoked per day for 1 year).

4. A current clinical diagnosis of COPD, with COPD symptoms for more than 1 year prior to screening, as defined by GOLD criteria or other current guidelines.

5. COPD Severity defined as:

   - At Visit 1 and Visit 2, post-bronchodilator FEV_1/FVC ratio <0.70, FEV_1 <80% of predicted normal value, and $FEV_1 \geq 750$ mL if FEV_1 is <30% of predicted normal value.

- At Visit 3 (randomisation), FEV_1/FVC ratio <0.70 and FEV_1 <80% of predicted normal value in both pre-dose assessments.

6. COPD treatment with rescue medication only, or stable dose of maintenance monotherapy (LAMA, LABA or ICS), or stable dose of double maintenance therapy (LAMA/LABA or ICS/LABA), for one month prior to screening (Visit 1). Triple maintenance therapy (LAMA/LABA/ICS) is not allowed for one month prior to screening. Stepping-down from triple maintenance therapy before the month prior to screening must only be based on clinical symptoms in the opinion of the Investigator.

7. COPD symptom severity: CAT ≥10 at screening (Visit 1) for patients on rescue medication only or maintenance monotherapy. No symptom requirement at screening for patients on double maintenance therapy. CAT ≥10 at randomisation (Visit 3) for all patients.

8. Patient is willing and, in the opinion of the Investigator, able to adjust current COPD therapy as required by the protocol.

9. Documentation of a chest x-ray (as per local practice) or computed tomography (CT) within 6 months prior to Visit 1, with no clinically significant pulmonary abnormalities other than related to COPD.

   - Specific to countries with restrictive radiology assessment practice: if no documentation of chest x-ray or CT of the chest/lungs within 6 months prior to Visit 1 is available, an MRI may be used instead, as per local practice assessment, or the Investigator may follow local guidelines to have the chest x-ray or CT approved.

10. Ability and willingness to comply with all study procedures, including daily completion of ePRO.

3.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. Respiratory disease:

(a) Asthma: Patients that, in the opinion of the Investigator, have a current diagnosis of asthma.

(b) Alpha-1 Antitrypsin Deficiency: Patients who have alpha-1 antitrypsin deficiency as the cause of COPD.

(c) Other Respiratory Disorders: Patients who have other active pulmonary disease such as active tuberculosis, lung cancer, clinically significant bronchiectasis

disease, sarcoidosis, idiopathic interstitial pulmonary fibrosis (IPF), primary pulmonary hypertension, or uncontrolled sleep apnea.

(d) Lung Volume Reduction: Patients who have undergone lung volume reduction surgery, lobectomy or bronchoscopic lung volume reduction within 1 year of Visit 1.

(e) A severe COPD exacerbation (resulting in hospitalisation) that has not resolved within 8 weeks prior to Visit 1, or a moderate COPD exacerbation (requiring antibiotics or ≥3 days of systemic steroids) that has not resolved within 4 weeks prior to Visit 1, or a moderate or severe COPD exacerbation that occurs between Visit 1 and Visit 3 (randomisation).

(f) Pneumonia or lower respiratory tract infection: Patients who had pneumonia or lower respiratory tract infection that required antibiotics within 8 weeks prior to Visit 1 (screening) or during the screening period (Visit 1 to Visit 3).

(g) Risk factors for pneumonia: immune suppression (HIV), severe neurological disorders affecting control of the upper airway or other risk factors that in the opinion of the Investigator would put the patients at substantial risk of pneumonia.

(h) Oxygen: patients receiving long-term-oxygen therapy (LTOT) or nocturnal oxygen therapy required for greater than 12 hours per day.

(i) Patient use of any non-invasive positive pressure ventilation device. Note: Patients using continuous positive airway pressure or bi-level positive airway pressure for sleep apnea syndrome are allowed in the study if not used for ventilatory support.

(j) Pulmonary rehabilitation: Patients who have participated in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to Visit 1 (screening) or who will enter the acute phase of a pulmonary rehabilitation program during the screening period. Patients who are in the maintenance phase of a pulmonary rehabilitation program are not to be excluded.

2. Cardiac disease:

- Unstable angina/acute coronary syndrome, or Coronary Artery Bypass Grafting (CABG), Percutaneous Coronary Intervention (PCI) or myocardial infarction within the past 6 months.
- Congestive heart failure New York Heart Association (NYHA) class III/IV.
- Structural heart disease (hypertrophic cardiomyopathy, significant valvular disease).

- Paroxysmal (within the past 6 months) or symptomatic chronic cardiac tachyarrhythmia.
- Left bundle branch or high-degree AV block (second degree AV block type 2 and third degree AV block) unless the patient has a pacemaker.
- Sinus node dysfunction with pauses.
- Ventricular pre-excitation and/or Wolff-Parkinson-White syndrome.
- QTcF interval >470 msec (QT interval corrected using Fridericia's formula; $QTcF=QT/[RR^{1/3}]$).
- Any other ECG abnormality deemed clinically significant by the Investigator.
- Bradycardia with ventricular rate < 45 bpm.
- Uncontrolled hypertension (> 165/95 mmHg).

3. Renal disease: Patients with a calculated eGFR <30 mL/minute using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (Levey, 2009).

4. Cancer: Patients who have cancer that has not been in complete remission for at least 5 years. Note: Patients with squamous cell carcinoma of the skin, basal cell carcinoma of the skin, or localized prostate cancer are eligible if, in the opinion of the Investigator, the condition has been adequately worked up, is clinically controlled and the patient's participation in the study would not represent a safety concern.

5. Glaucoma: Patients with a diagnosis of narrow-angle glaucoma that, in the opinion of the Investigator, has not been adequately treated. All medications approved for control of intraocular pressures are allowed including topical ophthalmic non-selective beta-blockers (such as betaxolol, carteolol, levobunolol, metipranolol, timolol) and prostaglandin analogues.

6. Patients with symptomatic prostatic hypertrophy or bladder neck obstruction/urinary retention that is clinically significant in the opinion of the Investigator.

7. Significant diseases or conditions other than COPD which, in the opinion of the Investigator, may put the patient at risk because of participation in the study or may influence either the results of the study or the patient's ability to participate in the study.

8. Any clinically relevant abnormal findings in physical examination, clinical chemistry, haematology, urinalyses, vital signs or ECG, which in the opinion of the Investigator, may put the patient at risk because of his/her participation in the study.

9. Women who are pregnant or lactating, or are planning to become pregnant during the course of the study, or women of childbearing potential who are not using an acceptable method of contraception, as judged by the Investigator. Female patients who are not post-menopausal or surgically sterile must have a negative pregnancy test prior to randomisation and must comply with contraception methods.

10. Drug allergy: Patients who have a history of hypersensitivity to β2 agonists, GP or other muscarinic anticholinergics, or any component of the MDI or DPI.

11. Substance abuse: Patients who in the opinion of the Investigator abuse alcohol or drugs.

12. Medication prior to spirometry: Patients who are medically unable to withhold their short-acting bronchodilators for the 6-hour period required prior to spirometry testing at study visits.

13. Prohibited medications: Patients who, in the opinion of the Investigator, would be unable to abstain from protocol-defined prohibited medications during the screening period and treatment phases of this study (see Table 3).

14. Non-compliance: Patients unable to comply with study procedures during screening, including non-compliance with ePRO completion (i.e., <70% patient completion of ePRO assessments).

15. Affiliations with Investigator site: Study Investigators, sub-Investigators, study coordinators, employees of a participating Investigator or immediate family members of the aforementioned are excluded from participation.

16. Questionable validity of consent: Patients with a history of psychiatric disease, intellectual deficiency, poor motivation, substance abuse (including drug and alcohol), or other conditions that will limit the validity of informed consent to participate in the study as judged by Investigator.

17. Investigational drugs or devices: Treatment with IP or device in another clinical study within the last 30 days or 5 half-lives prior to Visit 1 (screening), whichever is longer. Note: Patient participation in observational studies (i.e., studies that do not require change to medication or an additional intervention) is not exclusionary.

18. Patients who have needed additions or alterations to their usual maintenance therapy for COPD due to worsening symptoms within 1 month prior to Visit 1 and up to Visit 3.

19. Treatment with depot corticosteroids within 6 weeks, and other systemic corticosteroids within 4 weeks, prior to Visit 1. Exception: Patients who are steroid dependent, and maintained on an equivalent of 5 mg prednisone per day, or 10 mg every other day, for at least 3 months prior to Visit 1, are eligible for enrolment providing the dose of oral steroids remains stable during the screening period.

20. Any monoclonal or polyclonal antibody therapy taken for any reason within 6 months prior to Visit 1.

21. Planned hospitalisation or significant surgical procedure during the study.

22. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

23. Previous randomisation in the present study.

Procedures for withdrawal of incorrectly enrolled patients see Section 3.4.

3.3 Patient enrolment and randomisation

The Investigator should keep a record, the Patient Screening Log, of patients who entered pre-study screening.

The Investigator will:

1. Obtain signed informed consent from the patient before any study-specific procedures are performed.

2. Assign the patient a unique enrolment number, beginning with 'E#' (using the Interactive Web Response System [IWRS/IVRS]).

3. Determine patient eligibility (see Section 3.1 and 3.2).

4. Randomise the patient using IWRS/IVRS (randomisation code will be blinded).

If a patient withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused. Only the enrolment number will be used for patient identification in the eCRF.

3.4 Procedures for handling incorrectly enrolled or randomised patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Patients who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomised or initiated on treatment and must be withdrawn from the study.

Where a patient does not meet all the eligibility criteria but is randomised in error, or incorrectly started on treatment, the Investigator should inform the AstraZeneca study physician immediately, and a discussion should occur between the AstraZeneca study physician and the Investigator regarding whether to continue or discontinue the patient from treatment. Treatment must be discontinued in all cases where continued treatment is deemed to pose a safety risk to the patient. The AstraZeneca study physician must ensure all decisions including the rationale for continuing or discontinuing treatment are appropriately documented.

3.5 Methods for assigning treatment groups

The randomisation codes will be computer-generated using the AstraZeneca Global Randomisation system (AZRand) and loaded into the IWRS/IVRS database. The randomisation codes will be generated in blocks to ensure approximate balance (1:1) between the two treatment groups. Patients will be stratified based on incoming COPD treatment; rescue or maintenance monotherapy (LAMA, LABA or ICS only) at screening vs. double maintenance therapy (LABA/LAMA or ICS/LABA).

3.6 Methods for ensuring blinding

Patients, study site personnel, and AZ personnel will not know which medication the patient is receiving.

Since there are two different devices, a double-dummy technique will be applied to ensure the double-blinding of the study. Matched placebo to GFF and UV will be present with the same external appearance. There will be no differences between active and placebo formulations with regards to appearance, odour or colour that could unmask the blinded design.

3.7 Methods for unblinding

Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the Investigator or pharmacists from the IWRS/IVRS. Routines for this will be described in the IWRS/IVRS user manual that will be provided to each site.

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomisation. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to patient to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IP and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

3.8 Restrictions

The following is restricted during the study:

- Donation of blood is not allowed throughout the study.
- Patient should keep regular night/day shifts.
- The activities that should be avoided in the morning prior to lung function testing are :
  - Smoking within at least 1 hour of testing.
  - Consuming alcohol within 4 hours of testing.
  - Performing vigorous exercise within 30 minutes of testing.
  - Wearing clothing that substantially restricts full chest and abdominal expansion.
  - Eating a large meal within 2 hours of testing.
  - Using albuterol/salbutamol MDI within approximately 6 hours of testing.
  - Using ipratropium bromide MDI within approximately 6 hours of testing at Visit 2.
  - Using IP in the morning before visits 4-7.
- Restrictions regarding concomitant medication are described in Section 7.

Any event likely to interfere with the objectives of the study will be communicated to the Investigator and reported without delay to AstraZeneca.

3.9 Discontinuation of IP

Patients may be discontinued from IP in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment.
- AEs that, in the opinion of the Investigator, contraindicates further IP treatment.
- Severe non-compliance with the Clinical Study Protocol as judged by the Investigator or AstraZeneca. The study physician should be consulted before IP is discontinued based on this criterion.

- In the opinion of the Investigator, patient requires additional treatment or care beyond what is provided by the study, including treatment with prohibited COPD medications (see Table 8).
- Eligibility requirement found not to be fulfilled.
- A severe COPD exacerbation (requiring hospitalisation) or more than one moderate exacerbation (requiring antibiotics or ≥3 days of systemic steroids).
- Pregnancy.

3.9.1 Procedures for discontinuation of a patient from investigational product

At any time, patients are free to discontinue IP or withdraw from the study (i.e., IP and assessments – see Section 3.10), without prejudice to further treatment. A patient that decides to discontinue IP will always be asked about the reason(s) and the presence of any AEs.

If possible, patients who discontinue IP prematurely will be seen and assessed by the Investigator at an Early Discontinuation/Withdrawal Visit which should be performed at the earliest possibility. Patients will return to appropriate COPD maintenance medications, per the Investigator's discretion. Consideration should be given to maintaining patients on at least double therapy, while ensuring appropriate follow-up and further evaluation of the prescribed treatment. AEs will be followed up (see Section 6) and rescue medication, ePRO and all IPs should be returned by the patient. The reason and date for premature discontinuation of IP will be documented in the source documentation and in the eCRF.

A follow-up telephone call will be performed approximately 14 days after the last IP dose for follow-up of any AEs. After the follow-up telephone call, patients will be withdrawn and no further data will be collected. In the event the Early Discontinuation/Withdrawal Visit is performed approximately 14 days post last IP dosing, a follow-up contact will not be required. If a patient is withdrawn from study (see Section 3.10).

3.10 Criteria for withdrawal

If a patient withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused. Withdrawn patients will not be replaced.

3.10.1 Screen failures

Screening failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be randomised. These patients should have the reason for study withdrawal recorded as 'Screen failure'. (This reason for study withdrawal is only valid for the patients who have not been randomised.)

3.10.2 Discontinuation of investigational product

Patients who discontinue IP will be withdrawn from the study (see Section 3.9.1).

3.10.3 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time without prejudice to further treatment (IP and assessments).

A patient who withdraws consent should always be asked about the reason(s) and whether any AEs are present; to ensure patient safety in such cases, the Investigator should follow up AEs outside of the clinical study period based on clinical judgement. The patient will return electronic PRO (ePRO) devices to the study site.

Withdrawal of consent should be documented by the Investigator in the eCRF and medical records. If possible, the patient should complete the Early Discontinuation/Withdrawal Visit at the time of withdrawal of consent.

3.11 Discontinuation of the study

The study may be stopped if, in the judgment of AstraZeneca, study patients are placed at undue risk because of clinically significant findings that:

- are assessed as causally related to IP and
- are not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the CRF.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests and wellbeing.

4. STUDY PLAN AND TIMING OF PROCEDURES

Table 1 Study plan detailing the procedures

Visit[a]	**1** Screening	**2**	**3** Randomisation	**4**	**5**	**6**	**7**	**Early Discontinuation/ Withdrawal Visit**	**Follow-Up call**	**For details see Section**
Week			**0**	**4**	**12**	**18**	**24**			**Section**
Day	**-28 to -9**	**-11 to -8**	**1**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**-**	**14 days Post-Dose**	
Obtain Informed Consent	X									4
IWRS/IVRS call/record	X	X	X	X	X	X	X	X	X	3.3 4
Review Inclusion /Exclusion Criteria	X	X	X							3.1 3.2 4
Bronchodilator responsiveness		X								4
Demographics & Medical/Surgical History	X									4.1.1
Physical Examination	X									4.1.1 5.2.2
Smoking Status	X									4.1.1
Prior/Concomitant Medications[b]	X	X	X	X	X	X	X	X	X	7.7
Vital Signs	X									4.1.1
12-Lead ECG	X									4.1.1

Visit[a]	1 Screening	2	3 Randomisation	4	5	6	7	Early Discontinuation/ Withdrawal Visit	Follow-Up call	For details see Section
Week			0	4	12	18	24			Section
Day	-28 to -9	-11 to -8	1	±3 days	±3 days	±3 days	±3 days	-	14 days Post-Dose	
Pregnancy Test	X		X		X		X	X		4
Clinical Laboratory Testing	X									5.2.1
Chest Image or CT	X									4.1.1
Inspiratory Capacity			X	X	X	X	X	X[d]		4
Spirometry (FEV_1 and FVC)[c]	X	X	X	X	X	X	X	X[d]		4 5.1.1
Adjust COPD Medications	X						X	X		4.1.1
COPD Exacerbation history	X									4.1.1
Adverse Events		X	X	X	X	X	X	X	X	6
HCRU			X	X	X	X	X	X		4 5.3.1.3
ePRO Training	X	X								4 5.1.2
ePRO Dispense/Collect	X[e]	X					X	X		4
BDI/TDI			X	X	X	X	X	X[d]		4 5.1.2.1 Appendix F

Visit[a]	**1** **Screening**	**2**	**3** **Randomisation**	**4**	**5**	**6**	**7**	**Early Discontinuation/ Withdrawal Visit**	**Follow-Up call**	**For details see Section**
Week			**0**	**4**	**12**	**18**	**24**			**Section**
Day	**-28 to -9**	**-11 to -8**	**1**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**-**	**14 days Post-Dose**	
CAT[f]	X		X	X	X	X	X	X[d]		4 5.1.2.2 Appendix B
EQ-5D-5L			X				X	X		4 5.3.1.1 Appendix C
WPAI-GH			X	X	X	X	X	X		4 5.3.1.2 Appendix D
Review of ePRO			X	X	X	X	X	X		4
Training of inhalation technique and device cleaning	X	X	X	X	X	X				4
Rescue medication Dispensing/Collection (dispensing via IWRS/IVRS)	X		X	X	X	X	X	X		4 7
Screening period maintenance treatment dispensing/collection (dispensing via IWRS/IVRS)	X		X							4

Visit[a]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Early Discontinuation/ Withdrawal Visit**	**Follow-Up call**	**For details see Section**
	Screening		**Randomisation**							
Week			**0**	**4**	**12**	**18**	**24**			**Section**
Day	**-28 to -9**	**-11 to -8**	**1**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**-**	**14 days Post-Dose**	
IP Dispensing/Collection			X	X	X	X	X	X		47
IP Administration[g]			X	X	X	X	X			4
Telephone contact in the morning of the day before a visit (recommended)		X	X	X	X	X	X			4

[a] Sites should make every effort to maintain patients within the scheduled visit window. Patients who fall outside the visit window will be placed in the appropriate visit window at the next scheduled visit.

[b] At all visits beyond Visit 1, note time of last dose of short-acting bronchodilator and other COPD medications (if less than approximately 6 hours, the visit should be rescheduled).

[c] Spirometry to be performed at specific time points as specified in Table 2.

[d] Spirometry, TDI, CAT, to be performed at the Early Discontinuation/Withdrawal Visit only if patient is still taking IP (last dose of IP taken on a day before visit or at Early Discontinuation/Withdrawal Visit).

[e] At Visit 1 patient should only complete CAT questionnaire using ePRO, and leave it at the site. The ePRO device will only be dispensed at Visit 2 for the use at home.

[f] CAT score will be used as inclusion criterion as well as endpoint.

[g] After Visit 3, note time of IP intake the previous day (and consider rescheduling of the visit as outlined in Section 7.7.1.2).

Table 2 Timed Assessments at Each Treatment Visit (Visit 3 to Visit 7)

Clinical Variable	Pre-dosing			Dosing		Post-dosing				For details see Section
	Before -60 minutes	-60 minutes	-30 minutes	0 minutes	5 minutes	15 minutes	30 minutes	1 hour	2 hours	
BDI/TDI	X									5.1.2.1 Appendix F
CAT	X									5.1.2.2 Appendix B
EQ-5D-5L[a]	X									4, 5.3.1.1 Appendix C
WPAI-GH	X									5.3.1.2 Appendix D
Review of ePRO[b]	X									4
IP Collection	X									4
Inspiratory Capacity		X[c]	X[c]					X	X	4
Spirometry (FEV_1 and FVC)		X	X		X[d]	X	X	X	X	4 5.1.1
IP Administration				X						4 7

BDI/TDI=Baseline Dyspnea Index/Transition Dyspnea Index; ECG=electrocardiogram;

FEV_1=forced expiratory volume in 1 second; FVC=Forced vital capacity;

Note: When data collection time points are concurrent, it is recommended that variables be collected in the following order: BDI/TDI, CAT, EQ-5D-5L Questionnaire and spirometry.

[a] EQ-5D-5L ONLY at Visit 3 and Visit 7 and Early Discontinuation/Withdrawal Visit
[b] This is not a timed assessment. Sites should plan to perform these activities so as not to interfere with collection of timed assessments such as spirometry
[c] -60 and -30 min pre-dosing IC assessment ONLY at Visit 3
[d] 5-minute spirometry assessment post-dose ONLY at Visit 3

4.1 Screening/Enrolment period

At screening, consenting patients are assessed to ensure that they meet eligibility criteria. Patients who do not meet these criteria must not be enrolled in the study.

The screening period will start at Visit 1 with the signature of the ICF, followed by Visit 2, and will end at the randomisation visit (Visit 3).

The minimum length of screening period will be 9 days (one day for Visit 2, and a minimum of 7 full days of ePRO assessments in the patient's home to establish baseline data for the ePRO instruments); maximum will be 4 weeks.

4.1.1 Visit 1 (day -28 to -9)

The screening visit will be scheduled in the morning, preferably at a time similar to future study visits (as outlined in Section 4.2 and 5.1.1.2). The following assessments and processes will be performed during Visit 1:

- Obtaining signed informed consent before any study-related procedures
- Assignment of an E-code in IWRS/IVRS to the patient
  - Any patient signing the ICF should be recorded in IWRS/IVRS and should be assigned an E-code
- Review of medical/surgical history, demographic, COPD history (date of COPD diagnosis, diagnosis of chronic bronchitis or emphysema, number of COPD exacerbations during last year and date of last COPD exacerbation and if hospitalization) and smoking information (i.e., date of smoking initiation, current smoker or former smoker, date of smoking cessation and total-pack years)
- ePRO Training (for CAT questionnaire)
- CAT questionnaire
  - Completed by patient in the ePRO
  - Patient will be trained how to use ePRO and will be asked to complete CAT questionnaire in the ePRO (ePRO device will be dispensed at Visit 2)
- Prior/Concomitant Medications
  - All medications the patient is currently taking and has taken during the month prior to signing of the ICF should be collected
- Physical examination including body weight (in light indoor clothes, without shoes) and height measurement

  - BMI will be calculated automatically by eCRF system

- Vital signs

  - Body temperature will be measured by an appropriate method according to local practice and standards. Systolic and diastolic pressure (in mmHg) and pulse will be measured after at least 5 minutes resting and before taking any blood sample and conducting any spirometry. Measurements will be carried out as per local practice.

- 12-Lead ECG

  - Standard 12-lead ECG evaluations will be recorded after approximately 5 minutes resting in supine position before any blood sampling and spirometry test.

- Pregnancy Test when appropriate

  - Urine pregnancy test

- Clinical Laboratory Test (non-fasting)

  - Blood sampling performed in the local laboratory for haematology and biochemistry

  - Urinalysis

- Chest Image or CT

  - New chest x-ray should be obtained if chest x-ray or CT performed within the last 6 months prior to Visit 1 is not available

- Spirometry

  - Post-bronchodilator forced manoeuvre test (FEV_1 and FVC measurement): Administer 4 inhalations of inhaled albuterol/salbutamol MDI with or without a spacer device. After 20 to 30 minutes perform 1 set of Spirometry Forced manoeuvre.

- Review of inclusion/exclusion criteria

Only patients who meet all inclusion/exclusion criteria at this point will be allowed to continue (patient meets COPD definition following spirometry assessments). See Section 4.4 for rescreening procedures. Otherwise, screening failure will be recorded in the IWRS/IVRS and eCRF. When patients fulfil inclusion/exclusion criteria, the following will occur:

- Screening period maintenance treatment (ipratropium bromide MDI) and rescue medication (albuterol/salbutamol MDI) dispensing using IWRS/IVRS
  - Adjustment of COPD Medications
  - Stop prohibited COPD medications and change COPD medications (i.e., to sponsor provided ipratropium bromide MDI 2 inhalations QDS and albuterol/salbutamol MDI PRN).
- Training of inhalation technique and device cleaning
  - Training devices will be available at each study site for instructional purposes
- Scheduling of Visit 2. Patient will be reminded to avoid the intake of ipratropium bromide MDI and albuterol/salbutamol MDI for at least approximately 6 hours before attending Visit 2, and to bring back the rescue and wash-out medications
- It is recommended that the time of Visit 2 is scheduled according to instructions outlined in Section 4.2 and Section 5.1.1.2.

4.1.2 Visit 2 (Day -11 to -8)

- Telephone Contact - **(in the morning of day before the visit)** - It is recommended that sites call the patient in the morning of the day before a scheduled visit to remind the patient of the expectations for the upcoming visit:
  - Withhold albuterol/salbutamol MDI and ipratropium bromide MDI for at least approximately 6 hours prior to start of the spirometry procedures
  - Follow other restrictions related to spirometry
  - Bring all study medications to the visit
- Review of inclusion/exclusion criteria
- Prior/Concomitant Medications review
  - Confirm that no prohibited medication was taken during the washout period and that the appropriate withholds have been made, if required.
- AEs
- Site will be provided with Albuterol/salbutamol MDI for Bronchodilator responsiveness test and spirometry for all patients
- Spirometry Forced manoeuvre test (FEV_1 and FVC measurement): 1 set of tests will be performed.

- Bronchodilator responsiveness test
  - Administer 4 inhalations of inhaled albuterol/salbutamol MDI with or without a spacer device 30 ± 15 minutes after previous spirometry test. After waiting another 20 to 30 minutes, perform again 1 set of Spirometry Forced manoeuvre.
- Training of inhalation technique and device cleaning
- ePRO will be dispensed
  - Patient should be trained how to use ePRO and reminded to complete it every morning and evening until day of Visit 3. Any rescue medication and ipratropium bromide MDI use should also be recorded in the ePRO.
- - Calling IWRS/IVRS to register the visit
- Scheduling of Visit 3. Patient will be reminded to avoid the intake of albuterol/salbutamol MDI and ipratropium bromide MDI for at least approximately 6 hours before attending Visit 3, and to bring back the rescue and wash-out medications
- It is important that the time of Visit 3 is scheduled according to instructions outlined in Section 4.2 and Section 5.1.1.2

4.2 Treatment period

4.2.1 Visit 3, Randomisation Visit (Day 1)

The following assessments will be performed pre-randomisation and pre-morning IP dose:

- Telephone Contact (in the morning of day before the visit) - It is recommended that sites call the patient in the morning of the day before a scheduled visit to remind the patient of the expectations for the upcoming visit:
  - Withhold albuterol/salbutamol MDI and ipratropium bromide MDI for at least approximately 6 hours prior to start of the spirometry procedures
  - Follow other restrictions related to spirometry
  - Bring all study medications and ePRO to the visit

A <u>Pre-dose assessments:</u>

- Review of ePRO
  - Review of ePRO should be performed by site personnel before the visit

  - Check compliance with the ePRO (a minimum of 70% of entries of the morning questionnaires is required for eligibility, i.e. at least 5 out of the 7 days before randomisation)

- Before proceeding with any visit procedures, patient should be asked if pre-visit restrictions have been followed

  - Check appropriate medication wash-outs before visit (at least 6h since last intake of ipratropium bromide MDI and albuterol/salbutamol MDI).

- BDI

  - BDI interview should be completed in the ePRO by a trained interviewer unaware of current status of the patients based on other assessments. . BDI/TDI should be collected first, followed immediately by the CAT, EQ-5D-5L and WPAI-GH Questionnaire. The BDI, CAT, EQ-5D-5L and WPAI-GH Questionnaire should be completed prior to any other visit procedures.

- CAT questionnaire

  - Completed by patient in the ePRO

- EQ-5D-5L Questionnaire

  - Completed by patient in the ePRO

- WPAI-GH questionnaire

  - Completed by patient in the ePRO

- Pregnancy Test when appropriate

  - Urine pregnancy test

- AEs

- Prior/Concomitant Medications

- HCRU, including exacerbations of COPD

  - Completed by the Investigator

- Confirmation of inclusion/exclusion criteria

- Spirometry

- Spirometry (slow manoeuvre for IC assessment followed by forced manoeuvre for FEV_1 and FVC): 2 sets will be performed during the hour preceding the scheduled morning IP dose (-60 minutes and -30 minutes), allowing 30 min between them.

- If the average of the -60 and -30 minute FEV_1 is >20% or >200 ml different from the pre-dose FEV_1 at visit 2, the investigator will be alerted to contact the study physician for a discussion about patient eligibility.

Only patients who meet all inclusion/exclusion criteria at this point will be allowed to continue. See Section 4.4 for re-screening procedures. Otherwise the screening failure will be recorded in the IWRS/IVRS and eCRF.

When patient fulfils inclusion/exclusion criteria, the following assessments will be performed:

B Randomisation

- Randomise the patient via IWRS/IVRS, and obtain kits number assignment. Document the randomisation date on the medical notes. Stratification factors entered into IWRS/IVRS should be consistent with prior medications recorded at screening.

C Morning IP administration

- Dispense the kit numbers assigned by IWRS/IVRS and record the kits numbers dispensed on the medical records

- Training of inhalation technique and device cleaning

  - The technique for inhalation from an MDI (GFF) is different from the technique used with a DPI (UV). **It is important to ensure that patients apply correct inhalation technique for both types of inhalers.** Training devices will be available at each study site for instructional purposes.

- IP Administration

  - Dosing of IP in the clinic should be planned to occur at approximately the same time the patient prefers to administer IP in the mornings between the visits. The patient should then be advised that subsequent morning IP administration should happen at approximately this time, and that evening dosing should occur as close as possible to 12 hours from this. It is recommended that dosing in the clinic occurs before approximately 10:00 AM. If it is unavoidable that IP administration in the clinic is at a later time of day than the patient normally administers IP at home (for example due to the travelling time to site), then patients should be strongly advised that on the day prior to the next clinic visit,

the time of IP administration should be adjusted to be approximately 24 hours and 12 hours prior to the planned dosing at the clinic. **Sites should make every effort to ensure that dosing in the clinic occurs as close as possible to 24 and 12 hours after the patient's IP intake the previous day.**

- IP is administered by inhalation of 2 inhalations from the GFF/placebo inhaler followed by 1 inhalation from the UV /placebo inhaler. **Site personnel should check that the patient uses the inhalers correctly.**

- Record the date and time of the IP administration in the medical notes and in the spirometry equipment, Masterscope®CT. In clinic dosing time is recorded as the time of the second inhalation.

D Post-dose assessments

- Post-dose spirometry:

    - FEV_1 and FVC at +5 min, +15 min, +30 min, +1h and +2h

    - IC at +1h and +2h. The slow manoeuvre for IC assessment is always conducted prior to the forced manoeuvre for FEV_1 and FVC.

- Spirometry assessments need to be conducted within ±15 minutes of specified time prior to IP administration (see Table 2); ±5 minutes of specified time point for the first 60 minutes post IP administration; ±15 minutes of the 2h assessment.

The following procedures will be performed at any time after post-morning IP dose:

- Dispense IP kits to the patient

- Remind the patient to inhale 2 inhalations from the GFF/placebo inhaler and 1 inhalation from the UV/placebo inhaler every morning and 2 inhalations from the GFF/placebo inhaler every evening until the last evening before next visit. Remind the patient to use the GFF/placebo device right before the UV/placebo device, and to come to next visit with the medication kits to assess the drug accountability.

- Rescue medication (albuterol/salbutamol MDI) will be dispensed, using IWRS/IVRS

    - Containers dispensed during the Visit 1 should be collected and new rescue medication (albuterol/salbutamol MDI) should be dispensed

- The ePRO will be re-dispensed

    - Remind the patient to complete ePRO:

- NiSCI and EMSCI: every morning, preferably between 7 AM and 11 AM and approximately 1 hour or later after taking IP. The NiSCI and EMSCI will not be recorded on Visit days
- IP administration every morning and evening
- Rescue medications use every morning and evening

- Next protocol visit will be scheduled according to instructions above and in Section 5.1.1.2. Patient will be reminded to hold the morning IP dose that day, avoid the intake of rescue medication for at least approximately 6 hours before attending the next visit, and to bring the IP kits, rescue medication inhaler and ePRO to the clinic. The patient should be strongly advised to take morning and evening IP doses on the day prior to a clinic visit at approximately 24 and 12 hours prior to the anticipated time of dosing in the clinic. (For example at 9am and 9pm on the day prior to a clinic visit if they are expected to be dosed at 9am in the clinic).

4.2.2 Visit 4 – Visit 6 (Week 4, Week 12, Week 18 ±3 days)

The following assessments will be performed:

- Telephone Contact (in the morning of day before the visit) - It is recommended that sites call the patient in the morning of the day before a scheduled visit to remind the patient of the expectations for the upcoming visit:
  - **Take morning and evening IP doses approximately 24 and 12 hours prior to the anticipated time of dosing in the clinic.** (For example at 9am and 9pm on the day prior to a clinic visit if they are expected to be dosed at 9am in the clinic).
  - Withhold IP dosing the morning of the scheduled visit
  - Withhold rescue albuterol/salbutamol MDI for at least approximately 6 hours prior to start of the spirometry procedures
  - Follow other restrictions related to spirometry
  - Bring all study medications and ePRO to the visit

A <u>Pre-dose assessments</u>

- Before proceeding with any visit procedures, the dosing of IP on the day prior to the visit should be reviewed in the patient's ePRO, and the patient should be asked if pre-visit restrictions have been followed.

  - Check IP dosing the previous day as well as time interval since last IP intake (within approximately 12±1 hours and approximately 24±1 hours before the planned dosing at the visit, and no IP intake the same morning)

  - Check appropriate rescue medication wash-out (at least 6h since last intake)

- TDI

  - TDI interview should be completed in the ePRO by a trained interviewer unaware of current status of the patients based on other assessments. TDI should be collected first, followed immediately by the CAT and WPAI-GH Questionnaire. The TDI, CAT and WPAI-GH Questionnaire should be completed prior to any other visit procedures.

- CAT questionnaire

  - Completed by patient in the ePRO

- WPAI-GH questionnaire

  - Completed by patient in the ePRO

- ePRO review

- HCRU, including exacerbations of COPD

  - Completed by the Investigator

- AEs

- Concomitant medication review since last visit

- Site personnel should collect empty containers

- Site personnel should check IP compliance and retrain patient if required

- Spirometry (forced manoeuvre for FEV_1 and FVC): 2 sets will be performed during the hour preceding the scheduled morning IP dose (-60 minutes and -30 minutes), allowing 30 min between them. While spirometry assessments should be performed within approximately ±1 hour of the time of the spirometry assessments on Visit 3 (randomisation), priority should be given to the dosing of IP approximately 24 and 12 hours after the patient's IP intake the previous day.

- Urine pregnancy test – **only at Visit 5/week 12**

B Morning IP administration

- Dispense the kit numbers assigned by IWRS/IVRS and record the kits numbers dispensed on the medical records

- Re-training of inhalation technique and device cleaning

  - The technique for inhalation from an MDI (GFF) is different from the technique used with a DPI (UV). **It is important to ensure that patients apply correct inhalation technique for both types of inhalers.** Training devices will be available at each study site for instructional purposes.

- IP Administration

  - Dispense new IP kits (assigned by IWRS/IVRS) to the patient

  - Administration of the IPs (new kits assigned) at approximately the same time as Visit 3. It is recommended that dosing occurs before approximately 10:00 AM. Patients should be strongly advised that on the day prior to the visit, IP should be administered approximately 24 hours and 12 hours prior to the planned dosing in the clinic. **Sites should make every effort to ensure that dosing in the clinic occurs as close as possible to 24 and 12 hours after the patient's IP intake the previous day.** If it is not possible to keep these time intervals within approximately 24 ±1 hours and 12 ±1 hours, it is strongly recommended that the visit is rescheduled. If any IP intake the previous day was missed, or if IP was not taken as directed, rescheduling of the visit is required (see Section 7.7.1.2).

  - IP is administered by 2 inhalations from the GFF/placebo inhaler and 1 inhalation from the UV/placebo inhaler. **The site personnel should check that the patient uses the inhalers correctly.**

  - Record the date and time of the IP administration in the medical notes and in the spirometry equipment, Masterscope CT. In clinic dosing time is recorded as the time of the second inhalation.

C Post-dose assessments

- Post-dose spirometry:

  - FEV_1 and FVC at +15 min, +30 min, +1h, and +2h.

  - IC at + 1h and + 2h. The slow manoeuvre for IC assessment is always performed prior to the forced manoeuvre for FEV_1 and FVC.

- Spirometry assessments need to be conducted within ±15 minutes of specified time prior to IP administration (see Table 2); ±5 minutes of specified time point for the first 60 minutes post IP administration; ±15 minutes of the 2h assessment.

The following procedures will be performed at any time after post-morning IP dose:

- Remind the patient to inhale 2 inhalations from the GFF/placebo inhaler and 1 inhalation from the UV /placebo inhaler every morning and 2 inhalations from the GFF/placebo inhaler every evening until the last evening before next visit. Remind the patient to use the GFF/placebo device right before the UV /placebo DPI device, and to come to next visit with the medication kits to assess the drug accountability

- Rescue medication (albuterol/salbutamol MDI) will be dispensed, using IWRS/IVRS

  - Containers dispensed during the previous visit should be collected and new rescue medication (albuterol/salbutamol MDI) should be dispensed

- The ePRO will be re-dispensed

  - Remind the patient to complete ePRO:

    - NiSCI and EMSCI: every morning, preferably between 7 AM and 11 AM, and approximately 1 hour or later after taking IP. The NiSCI and EMSCI will not be recorded on Visit days

    - IP administration every morning and evening

    - Rescue medications use every morning and evening

- Next protocol visit will be scheduled. The start of Visits 4-7 should be scheduled according to instructions above and in Section 5.1.1.2. Patient will be reminded to hold the morning IP dose that day, avoid the intake of rescue medication for at least approximately 6 hours before attending the next visit, and to bring the IP kits, rescue medication inhaler and ePRO to the clinic. The patient should be strongly advised to take morning and evening IP doses on the day prior to a clinic visit approximately 24 and 12 hours prior to the anticipated time of dosing in the clinic. (For example at 9am and 9pm on the day prior to a clinic visit if they are expected to be dosed at 9am in the clinic).

4.2.3 Visit 7 (Week 24 ±3days)

The following assessments will be performed:

- Telephone Contact (in the morning of day before the visit) - It is recommended that sites call the patient in the morning of the day before a scheduled visit to remind the patient of the expectations for the upcoming visit:

  - **Take morning and evening IP doses approximately 24 and 12 hours prior to the anticipated time of dosing in the clinic.** (For example at 9am and 9pm on the day prior to a clinic visit if they are expected to be dosed at 9am in the clinic).

  - Withhold IP dosing the morning of the scheduled visit

  - Withhold rescue albuterol/salbutamol MDI for at least approximately 6 hours prior to start of the spirometry procedures

  - Follow other restrictions related to spirometry

  - Bring all study medications and ePRO to the visit

A <u>Pre-dose assessments</u>

- Before proceeding with any visit procedures, the dosing of IP on the day prior to the visit should be reviewed in the patient's ePRO, and the patient should be asked if pre-visit restrictions have been followed.

  - Check IP dosing the previous day as well as time interval since last IP intake (within approximately 12±1 hours and approximately 24±1 hours before the planned dosing at the visit, and no IP intake the same morning)

  - Check appropriate rescue medication wash-out (at least 6h since last intake)

- TDI

  - TDI interview should be completed in the ePRO by a trained interviewer unaware of current status of the patients based on other assessments. TDI should be collected first, followed immediately by the CAT, EQ-5D-5L and WPAI-GH Questionnaire. The TDI, CAT, EQ-5D-5L and WPAI-GH Questionnaire should be completed prior to any other visit procedures.

- CAT questionnaire

  - Completed by patient in the ePRO

- EQ-5D-5L Questionnaire

  - Completed by patient in the ePRO

- WPAI-GH
  - Completed by patient in the ePRO
- ePRO review
- HCRU, including exacerbations of COPD
  - Completed by the Investigator
- AEs
- Concomitant medication review since last visit
- Site personnel should check IP compliance
- Spirometry (forced manoeuvre for FEV_1 and FVC): 2 sets will be performed during the hour preceding the scheduled morning IP dose (-60 minutes and -30 minutes), allowing 30 min between them. While spirometry assessments should be performed within approximately ±1 hour of the time of the spirometry assessments on Visit 3 (randomisation), priority should be given to the dosing of IP approximately 24 and 12 hours after the patient's IP intake the previous day.
- Urine pregnancy test

B Morning IP administration

- IP Administration – **using kits assigned on the previous visit - Visit 6 Week 18**
  - Administration of the IPs (new kits assigned) at approximately the same time as Visit 3. Sites should make every effort to ensure that dosing occurs before approximately 10:00 AM. It is recommended that dosing occurs before approximately 10:00 AM. Patients should be strongly advised that on the day prior to the visit, IP should be administered approximately 24 hours and 12 hours prior to the planned dosing in the clinic. **Sites should make every effort to ensure that dosing in the clinic occurs as close as possible to 24 and 12 hours after the patient's IP intake the previous day.** If it is not possible to keep these time intervals within approximately 24 ±1 hours and 12 ±1 hours, it is strongly recommended that the visit is rescheduled. If any IP intake the previous day was missed, or if IP was not taken as directed, rescheduling of the visit is required (see Section 7.7.1.2).
  - IP is administered by 2 inhalations from the GFF/placebo inhaler and 1 inhalation from the UV/placebo inhaler. The site personnel should check that the patient correctly uses the inhalers.

- Record the date and time of the IP administration in the medical notes and in the spirometry equipment, Masterscope CT. In clinic dosing time is recorded as the time of the second inhalation.

C Post-dose assessments

- Post-dose spirometry:
    - FEV_1 and FVC at +15 min, +30 min, +1h, and +2h.
    - IC at + 1h and + 2h. The slow manoeuvre for IC assessment is always performed prior to the forced manoeuvre for FEV_1 and FVC.
- Spirometry assessments need to be conducted within ±15 minutes of specified time prior to IP administration (see Table 2); ±5 minutes of specified time point for the first 60 minutes post IP administration; ±15 minutes of the 2h assessment.

The following procedures will be performed at any time after post-morning IP dose:

- Site personnel should collect empty containers
- Retrieval of rescue medication
- Patient will be instructed by study personnel to resume the COPD medication taken before study start, or any other appropriate inhaled maintenance for COPD according to medical judgement. Consideration should be given to maintaining patients on at least double therapy, while ensuring appropriate follow-up and further evaluation of the prescribed treatment.
- The ePRO will be collected
- IWRS/IVRS Completion call should be recorded in the system

4.2.4 Early Discontinuation/Withdrawal Visit

- Before proceeding with any visit procedures, the dosing of IP on the day prior to the visit should be reviewed in the patient's ePRO, and the patient should be asked if pre-visit restrictions have been followed.
    - Check IP dosing the previous day as well as time interval since last IP intake (within approximately 12±1 hours and approximately 24±1 hours before the planned dosing at the visit, and no IP intake the same morning)
    - Check appropriate rescue medication wash-out (at least 6h since last intake)

If IP has already been discontinued and was not administered according to protocol on the day before the visit, the following assessments will not be performed at the early discontinuation visit:

- TDI
- CAT Questionnaire
- Spirometry

With the above exceptions, the following procedures will be performed:

- TDI
  - TDI interview should be completed in the ePRO by a trained interviewer unaware of current status of the patients based on other assessments. TDI should be collected first, followed immediately by the CAT and EQ-5D-5L Questionnaire. The TDI, CAT and EQ-5D-5L Questionnaire and WPAI-GH Questionnaire should be completed prior to any other visit procedures.
- CAT Questionnaire
- EQ-5D-5L Questionnaire
- WPAI-GH
  - Completed by patient in the ePRO
- HCRU, including exacerbations of COPD
  - Completed by the Investigator
- AEs
- Concomitant medication review since last visit
- Urine pregnancy test (when appropriate)
- Spirometry

<u>If last dose of IP was taken on the day before the Visit (evening dose):</u>

- Spirometry (forced manoeuvre for FEV_1 and FVC): 2 sets will be performed

If last dose of IP will be taken at Early Discontinuation/Withdrawal Visit:

- Spirometry (forced manoeuvre for FEV_1 and FVC): 2 sets will be performed during the hour preceding the scheduled morning IP dose (-60 minutes and -30 minutes), allowing 30 min between them. While spirometry assessments should be performed within approximately ±1 hour of the time of the spirometry assessments on Visit 3 (randomisation), priority should be given to the dosing of IP approximately 24 and 12 hours after the patient's IP intake the previous day.

- Administration of the IPs (**using kits assigned on the previous visit**) at approximately the same time as Visit 3. It is recommended that dosing occurs before approximately 10:00 AM. Patients should be strongly advised that on the day prior to the visit, IP should be administered approximately 24 hours and 12 hours prior to the planned dosing in the clinic. **Sites should make every effort to ensure that dosing in the clinic occurs as close as possible to 24 and 12 hours after the patient's IP intake the previous day.**

- IP is administered by 2 inhalations from the GFF/placebo inhaler and 1 inhalation from the UV/placebo inhaler. The site personnel should check that the patient correctly uses the inhalers.

- Record the date and time of the IP administration in the medical notes and in the spirometry equipment, Masterscope CT. In clinic dosing time is recorded as the time of the second inhalation.

- Post-dose spirometry:

  - FEV_1 and FVC at +15 min, +30 min, +1h, and +2h.

  - IC at + 1h and + 2h. The slow manoeuvre for IC assessment is always performed prior to the forced manoeuvre for FEV_1 and FVC.

  - Spirometry assessments need to be conducted within ±15 minutes of specified time prior to IP administration (see Table 2); ±5 minutes of specified time point for the first 60 minutes post IP administration; ±15 minutes of the 2h assessment.

- ePRO review
- The ePRO will be collected
- Site personnel should collect empty containers
- Site personnel should check IP compliance

- Retrieval of rescue medication

- Patient will be instructed by study personnel to resume the COPD medication taken before study start, or any other appropriate inhaled maintenance for COPD according to medical judgement. Consideration should be given to maintaining patients on at least double therapy, while ensuring appropriate follow-up and further evaluation of the prescribed treatment.

- IWRS/IVRS Withdrawal call should be recorded in the system

4.3 Follow-up period

4.3.1 Follow-up call

A follow-up call should be performed approximately 14 days after last IP dose intake for patients completing the treatment or discontinuing IP prematurely, in order to assess new or ongoing AE (as well as any concomitant medication administered to treat the mentioned AE) and COPD exacerbations. IWRS/IVRS Follow-up call "Study completion" should be recorded in the system. Follow-up call will not be performed if Early Discontinuation/Withdrawal visit was done 14 or more days since the last dose of IP.

4.4 Rescreening and rescheduling of visits.

4.4.1 Rescreening

Patients with an event, such as a COPD exacerbation or pneumonia, occurring within the exclusion criteria specified time requirements prior to Visit 1, should not be screened; if this is done in error, these patients should be screen failed. Patients who experience an event during the screening period, which is specified in the exclusion criteria, should also be screen failed. Screen-failed patients may be re-screened observing timelines described in the exclusion criteria.

Other instances where rescreening is being considered should be discussed with the AZ study physician.

Re-screening is only allowed once per patient.

If a patient is re-screened, a new informed consent form is to be signed, and re-screening Visit 1 procedures must be initiated within 3 working days from the date of the new ICF. Rescreened patient keeps an originally assigned enrolment number.

4.4.2 Rescheduling of visits

Rescheduling of a visit will be allowed within the specified visit window for reasons such as incorrect dosing/time of dosing of IP the day prior to a visit, intake of disallowed medication or other disallowed events related to spirometry, or technical issues with spirometry or ePRO. If rescheduling is not possible within the specified visit window, the rescheduled visit should occur as soon as possible. If a visit needs to be rescheduled, no assessments will be performed,

or if already partly done they will need to be repeated at the rescheduled visit. An important note regarding spirometry: during screening, for the spirometer technical reasons, each visit can be rescheduled only once and only if spirometry was not yet started at the original visit. During treatment, spirometry cannot be repeated when rescheduled using the same visit, and then an unscheduled visit would need to be used.

5. STUDY ASSESSMENTS

The Rave Web Based Data Capture (WBDC) system will be used for data collection and query handling. The Investigator will ensure that data are recorded on the electronic Case Report Forms as specified in the Clinical Study Protocol and in accordance with the instructions provided.

The Investigator will ensure the accuracy, completeness and timeliness of the data recorded as well as provision of answers to data queries according to the Clinical Study Agreement. The Investigator will sign the completed electronic Case Report Forms. A copy of the completed electronic Case Report Forms will be archived at the study site.

5.1 Efficacy assessments

5.1.1 Spirometry Assessments at Clinic Visits

5.1.1.1 General requirements

Lung function (IC, FEV_1 and FVC) will be measured by spirometry using equipment provided by a central vendor. Spirometry will be performed by the Investigator or authorized delegate according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines (Miller et al 2005).

The central spirometry vendor is responsible for assuring that the spirometer meets ATS/ERS recommendations and that the study site personnel who will be performing the testing are properly certified. Spirometry calibration will be detailed in a separate spirometry procedures manual.

Important!

Patients should be instructed not to use their IP in the morning before site visits, as this will affect the spirometry results; IP will be taken at the site. For the same reason patients should not use their rescue albuterol/salbutamol MDI or their screening period ipratropium bromide MDI within approximately 6 hours of a scheduled site visit spirometry.

Options for handling patients who have inadvertently taken their COPD medication within the restricted window are described in Section 7.7.1.2.

N.B. There are no restrictions regarding medications taken prior to Visit 1, as spirometry at this visit will only measure lung function values following maximal bronchodilation.

5.1.1.2 Time of day for scheduled site visit spirometry

Spirometry testing should be done according to the schedule provided in Table 1 and Table 2. It is recommended to start spirometry testing in the morning between 6 and 9AM. Following randomisation, the spirometry assessment should be performed within approximately ±1 hour of the time at which spirometry was tested on Visit 3 (Randomisation). It is understood that this will not always be possible for patients or Investigators. The priority should be on performing spirometry 12 hours after evening dose and 24 hours after morning dose of IP.

The time for the spirometry assessments depends on the time chosen for IP administration, which should be planned to occur at approximately the same time the patient prefers to administer IP in the mornings between the visits (for further details on the timing of IP administration, please see Section 4.2). For example, if the patient prefers to administer IP at 9 AM (and 9 PM), then the pre-dose randomisation spirometry would be planned to start at 8 AM (so as to be 60 minutes prior to IP dosing), and all subsequent pre-dose spirometry testing should be initiated between 7 AM and 9 AM.

5.1.1.3 Spirometry technique

Patients should avoid engaging in strenuous exertion for at least 30 minutes prior to spirometry measurements. Patients should also avoid eating a large meal for at least 2 hours prior to spirometry measurements. Smoking should be avoided for at least 1 hour, and consuming alcohol for 4 hours.

For information about the slow manoeuvre technique used for IC assessment, please see Section 5.1.1.5.

Forced expiratory manoeuvres should be performed with the patient seated in an upright position. If this is not comfortable for the patient, standing is permitted. The same position should be used by the patient for each forced expiratory manoeuvre from enrolment throughout the study. The head must not be tilted during manoeuvres and the thorax should be able to move freely; hence tight clothing should be loosened. A nose-clip should be used for the manoeuvre. The patient from enrolment throughout the study should use mouthpieces of the same dimension and shape.

The forced expiratory manoeuvre (FEV_1 and FVC) should start with a maximal inspiration and then followed by a fast and forceful expiration that should last for at least 6 seconds. It is important to encourage the patient to continue the expiration to be fast and forceful throughout the manoeuvre. Ensure that none of the following has occurred: coughing during the first second, glottis closure, leak or obstruction of the mouthpiece (by the tongue).

Multiple forced expiratory efforts (at least 3 but no more than 8) will be performed for each site spirometry session and the 2 best efforts that meet the ATS/ERS acceptability and reproducibility criteria will be recorded. The best efforts will be based on the highest FEV_1.

The absolute measurement (for FEV_1 and FVC), and the percentage of predicted normal value (Quanjer et al 2012) will be recorded. The highest FVC will also be reported regardless of the effort in which it occurred (even if the effort did not result in the highest FEV_1).

5.1.1.4 Post-bronchodilator spirometry

Post-BD spirometry following maximal bronchodilation will be performed at Visit 1 (with no pre-BD spirometry) to confirm COPD diagnosis and disease severity, and at Visit 2 (after pre-BD spirometry) to assess BD responsiveness.

Maximal bronchodilation will be induced using 4 inhalations of albuterol (90 µg metered dose) or salbutamol (100 µg metered dose) with or without a spacer device. At visit 2, this will occur within 30 minutes ± 15 minutes of the final pre-BD spirometry measurement. Post-BD spirometry will be performed 20-30 minutes after administration of albuterol/salbutamol MDI. If a patient cannot tolerate 4 inhalations of beta agonist, a lower number of inhalations may be considered at the Investigator's clinical judgment (minimum 2 inhalations). BD responsiveness at Visit 2 will be a comparison of the average of the best FEV_1 effort obtained at 60 minute and 30 minute pre-BD to the best FEV_1 effort obtained at 30 minutes post-BD.

5.1.1.5 Inspiratory Capacity

IC assessments will be conducted at Visits 3, 4, 5 and 7. Pre-dose assessments will be at 60 minutes and 30 minutes prior to IP administration at Visit 3 only. Post-dose assessments will be 1 and 2 hours after administration of IP. The average of the two pre-dose assessments at Visit 3 will be used to establish the baseline IC. IC assessments are always performed prior to any other spirometry assessments.

All patients will be instructed on the performance of the slow manoeuvre technique used for IC assessment. Patients must be tested in the seated position wearing a nose clip with no air leaks between the mouth and mouthpiece. Patients should be relaxed with shoulders down and asked to breathe regularly for several breaths until the end-expiratory lung volume is stable (this usually requires at least five tidal manoeuvres). They are then urged to take a deep breath to total lung capacity with no hesitation. From at least three acceptable studies, the two largest IC measurements should agree within 5% or 100 mL. Both of these IC values will be captured.

5.1.1.6 Record keeping

A signed and dated copy of the pre- and post- BD printout must be kept at the study site for source data verification. The printout must be marked with the study code, enrolment code, date and time of measurement, visit number.

5.1.1.7 Spirometry references

The Global Lung Function Initiative (GLI) equations will be used to determine the patients predicted normal (PN) values and will be pre-programmed into the spirometer (Quanjer et al 2012).

FEV_1 expressed as percent of the PN value will be calculated as follows: FEV_1% of PN = FEV_1 measured/ FEV_1PN x 100.

5.1.2 Patient Reported Outcomes

Patients will complete PRO assessments at the study site and at home using a handheld electronic device (ePRO). PRO assessments must be collected in a systematic way to ensure data integrity. The following best practice guidelines should be followed when collecting PRO data at the site or at home via an ePRO device:

For PRO instruments administered during site visits using ePRO device

- Administer before other procedures
  - Always administer PRO instruments before other study procedures. For details how to activate them, refer to the ePRO materials.
- Provide the right environment
  - Provide a quiet and private location to complete the instrument.
- No right or wrong answers
  - Remind patients that there are no right or wrong answers and that we are asking them to complete these questionnaires because we're interested in hearing directly from them on how they feel.
- Help with procedural questions
  - Make sure the patient understands how to complete the instrument. Instrument instructions are usually self-explanatory but staff may answer questions about procedural issues like what it means to "tick a box".
- Avoid bias: do not clarify the meaning of questions or responses
  - Sometimes patients will ask site staff to clarify the meaning of a question or response. To avoid introducing any bias, politely tell the patient that you cannot clarify items. Remind them that there are no right or wrong answers. Tell them that they should select the response that best answers the question as they understand it.
- No time limits. Although most instruments require only a few minutes to complete the patient should be given as much time as is needed.
- Review for completeness

- Prompt review of the questionnaire for completeness will minimize missing data and data queries.

For PRO instruments captured at home using an ePRO device.

- Guidelines similar to PRO completion at the visits
  - Same principles apply for ePRO for home based assessments as assessment at site. Remind patients that there are no right or wrong answers, avoid bias by not clarifying items, remind patients that they should complete the ePRO questions in a quiet and private location without help from others.
- Train the patient on ePRO device usage
  - Train the patient on how to use the ePRO device using the materials and training provided by the ePRO vendor.
  - Provide guidance on whom the patient should call if they have problems
- Monitor compliance
  - Minimizing missing data is a key aspect of study success. Compliance must be checked at each study visit and should be checked more frequently to identify problems early. If compliance drops below 80% a check-in call from the site to ask the patient if they are having difficulties is highly recommended.

5.1.2.1 Baseline/Transitional Dyspnea Index (BDI/TDI)

The BDI/TDI is an instrument developed to provide a multidimensional measure of dyspnea in relation to activities of daily living (Mahler et al 1984). The Baseline Dyspnea Index (BDI) provides a measure of dyspnea at a single state, the baseline, and the Transitional Dyspnea Index (TDI) evaluates changes in dyspnea from the baseline state. The instrument consists of three components: functional impairment, magnitude of task, and magnitude of effort. For the BDI, each of these three components are rated in five grades from 0 (severe) to 4 (unimpaired), and are summed to form a baseline total score from 0 to 12. For the TDI, changes in dyspnea are rated for each component by seven grades from -3 (major deterioration) to +3 (major improvement), and are added to form a total TDI score from -9 to +9. Positive scores indicate an improvement, and a change from the BDI or a difference between treatments of 1 point has been estimated to constitute the minimum clinically important difference (MCID) (Mahler et al 2005).

The BDI/TDI is completed by a trained interviewer, who asks the respondent various questions as part of a medical history, and selects a grade (score) using specific criteria for each of the three components. The same interviewer will complete the BDI and the TDI for an individual patient. The questionnaires should be completed in a quiet area, and the patient should be allowed to ask questions. Site personnel should take care not to influence the patient's responses. The interviewer must be blinded to other assessments evaluated for the

patient on the day the BDI/TDI is administered except for assessments obtained after the BDI/TDI has been completed. Patients are not allowed to review their previous responses. BDI/TDI will be recorded in the ePRO, provided by the ePRO vendor in relevant local language. BDI will be completed at Visit 3, and TDI at Visit 4, Visit 5, Visit 6, Visit 7 and Early Discontinuation/Withdrawal Visit.

5.1.2.2 COPD Assessment Test (CAT)

The CAT is an 8-item PRO developed to measure the impact of COPD on health status (Jones et al 2009). The instrument uses semantic differential six-point response scales which are defined by contrasting adjectives to capture the impact of COPD. Content includes items related to cough, phlegm, chest tightness, breathlessness going up hills/stairs, activity limitation at home, confidence leaving home, sleep and energy. A CAT total score is the sum of item responses. Scores range from 0-40 with higher scores indicative of greater COPD impact on health status. CAT will be recorded by the patient in the ePRO, provided by the ePRO vendor in relevant local language, at Visit 1, Visit 3, Visit 4, Visit 5, Visit 6, Visit 7 and Early Discontinuation/Withdrawal Visit.

5.1.2.3 Night-time and Early morning symptoms of COPD instrument (NiSCI and EMSCI)

The questionnaire is made up of two parts. The first part covering "last night" symptoms (time elapsed from the time patient went to bed until woke up and got out of bed to start his/her day) and the second part covering "this morning" symptoms (time elapsed since patient got out of bed to start the day).

The EMSCI was developed to collect data about the frequency and severity of early morning symptoms and the impact of COPD symptoms on early morning activity in patients with COPD.

The NiSCI was developed to collect data about the frequency and severity of night-time symptoms and the impact of COPD symptoms on night-time awakenings in patients with COPD.

The data collected can be used to generate the following scores:

1. The six-Item Symptom Severity score is derived by averaging the responses from a patient on the six item-level symptom scores and can be used to quantify the severity of early morning and night-time symptoms.
2. The Overall COPD Symptom Severity score is comprised of a single item asking about overall COPD symptom severity in the early morning and at night.
3. The Early Morning Activity score obtains information on the reduction in early morning activity limitation due to COPD symptoms. The Night-time Awakenings score can be used to obtain information on the number (or proportion) of days without night-time awakening due to COPD symptoms.

The NiSCI and EMSCI (see Appendix E) will be recorded by the patient in the ePRO, provided by the ePRO vendor in relevant local language, every morning approximately between 7 AM and 11 AM, preferably approximately 1 hour or later after taking IP. The questionnaire will be collected from the day after Visit 2 (Screening) and up to Visit 7. The NiSCI and EMSCI will not be recorded on Visit days.

5.1.3 Investigational Product Use

Administration of IP taken will be recorded by the patient in the ePRO twice daily (morning and evening), from Visit 3 to the end of the study.

5.1.4 Rescue Medication Use

The number of inhalations of rescue medication taken will be recorded by the patient in the ePRO twice daily (morning and evening), from Visit 2 to the end of the study. Patients will report nighttime use (since last evening when completing the ePRO) in the morning, and daytime use in the evening.

5.2 Safety assessments

5.2.1 Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be taken at Visit 1. Fasting is not required.

The clinical chemistry, haematology and urinalysis will be performed at a local laboratory at or near to the Investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

The following laboratory variables will be measured:

Table 3 Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)
B-Haemoglobin (Hb)	S/P-Creatinine
B-Leukocyte count	S/P-Bilirubin, total
B-Leukocyte differential count (absolute count)	S/P-Alkaline phosphatise (ALP)
B-Platelet count	S/P-Aspartate transaminase (AST)
	S/P-Alanine transaminase (ALT)
Urinalysis (dipstick)	S/P-Albumin
U-Hb/Erythrocytes/Blood	S/P-Potassium
U-Protein/Albumin	S/P-Calcium, total
U-Glucose	S/P-Sodium
	S/P-Gamma-GT (gammaglutamyl

transpeptidase)

S/P-Glucose

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at site as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.3

Note: In case a patient shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥2xULN please refer to Section 6.3.7, for further instructions.

5.2.1.1 Pregnancy Test

Urine HCG test will be performed in female patients (when appropriate) using a urine dipstick. The test should be performed at the study site at Visit 1, and before IP administration at Visit 3, Visit 5, Visit 7 and at an Early Discontinuation/Withdrawal Visit.

5.2.2 Physical examination

A complete physical examination will be performed at Visit 1 and include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen. According to the Investigator's judgement, assessment will also include skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, abdomen, musculo-skeletal (including spine and extremities) and neurological systems.

Only relevant findings, detected at Screening Visit, will be recorded in the Medical History/Physical examination at the eCRF. Body weight and height will be measured only at Visit 1 (screening) (allowing calculation of Body Mass Index done automatically by the eCRF system) which will be recorded on the MasterScope CT. Patients should be in light indoor clothes without shoes.

5.3 Other assessments

5.3.1 Clinical Outcome Assessments/Patient Reported Outcomes

5.3.1.1 EQ-5D-5L EuroQol 5 Dimensions Questionnaire

The EQ-5D-5L questionnaire assesses 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 response options (no problems, slight problems, moderate problems, severe problems, and extreme problems) that reflect increasing levels of difficulty.

The patient will be asked to indicate his/her current health state by selecting the most appropriate level in each of the 5 dimensions. The questionnaire also includes a visual analogue scale, where the patient will be asked to rate current health status on a scale of 0-100, with 0 being the worst imaginable health state.

The EQ-5D-5L will be completed at randomisation Visit 3 at visit 7 and Early Discontinuation/Withdrawal Visit using the ePRO device.

5.3.1.2 Work Productivity and Activity Impairment Questionnaire - General Health (WPAI - GH)

The WPAI-GH will be used to measure self-reported productivity loss and consists of questions on COPD impact on patient's general health, ability to work and perform regular activities in daily living within the previous 7 days.

The questionnaire will initially be completed at the study site on Visit 3 (Day 1) on the ePRO device. Patients will then be prompted to complete the WPAI-GH on the ePRO device at Visit 4, Visit 5, Visit 6, Visit 7 and Early Discontinuation/Withdrawal Visit.

5.3.1.3 Healthcare Resource Utilization

Broad-based COPD-related health care resource utilization event information will be collected by the Investigator/authorized delegate in accordance with the schedule provided in Table 1 and recorded in the appropriate eCRF module.

At Visit 3, COPD-related Healthcare Resource Utilization information will be collected with a one year recall period. All the subsequent visits will collect COPD related Healthcare Resource Utilization and COPD exacerbation information with a recall period of 'since last scheduled visit'.

Note: Cases of hospitalization must also be reported as an SAE (see Section 6.2 and 6.4).

5.4 Pharmacokinetics – Not Applicable

5.5 Pharmacodynamics – Not Applicable

5.6 Genetics – Not Applicable

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

6.1 Definition of adverse events

An adverse event is the development of any untoward medical occurrence in a patient or clinical study patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including screening or washout periods, even if no study treatment has been administered.

6.2 Definitions of serious adverse event

A serious adverse event (SAE) is an AE occurring during any study phase (ie, screening, treatment, or follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in- patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix A to the Clinical Study Protocol.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

AEs and SAEs will be collected from time of signature of informed consent throughout the treatment period and until the follow-up telephone call.

6.3.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the time of the follow-up telephone call are followed up by the Investigator for as long as medically indicated, but without further recording in the CRF. AstraZeneca retains the right to request additional information for any patient with ongoing AEs/SAEs at the end of the study, if judged necessary.

6.3.3 Variables

The following variables will be collected for each AE;

- AE (verbatim)
- The date and time when the AE started and stopped
- Severity

  - Maximum intensity

  - The Investigator must categorize the severity of each AE according to the following guidelines:

1 mild (awareness of sign or symptom, but easily tolerated)

2 moderate (discomfort sufficient to cause interference with normal activities)

3 severe (incapacitating, with inability to perform normal activities)

- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to IP
- AE caused patient's withdrawal from study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- Reason that the AE is serious

  If the following two seriousness criteria, collect the following variables:

  Hospitalization

  - Date of hospital admission
  - Date of discharge

  Death

  - Probable cause of death
  - Date of death
  - Autopsy results
  - Causality assessment in relation to Study procedure(s)
- Causality assessment to other medication
- Causality assessment to additional study drug
- Description of AE.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2.

6.3.4 Causality collection

The Investigator will assess causal relationship between IP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the IP?'

For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix A to the Clinical Study Protocol.

6.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study site personnel: *'Have you had any health problems since the previous visit?'*, or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) rather than recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.3.6 Adverse events based on examinations and tests

The Clinical Study Protocol mandates laboratory testing, physical examination, and assessment of vital signs at screening only. Further testing may however be performed by the Investigator during the course of the trial. If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Values and/or vital signs that fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the IP should be reported. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations should be reported as AEs. Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE,unless the finding is associated with a medical condition reported as an AE.

6.3.7 Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3xULN together with total bilirubin ≥ 2xULN may need to be reported as SAEs. Please contact the AstraZeneca study physician for further instruction on cases of increases in liver biochemistry and evaluation of a potential Hy's Law case. Investigators should be vigilant for potential Hy's Law cases from ad hoc laboratory tests or AEs.

6.3.8 Disease under Study (DUS)

COPD symptoms or signs, such as bronchitis, cough, phlegm, sputum increased, dyspnea and wheeze, will be recorded as AEs when:

- the sign or symptom is serious according to definitions, see Section 6.2 and/or
- the patient discontinues the study due to the sign or symptom and/or
- the sign or symptom is new to the patient or not consistent with the patient's preexisting COPD history (defined as within 1 year of Visit 1) as judged by the Investigator

6.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the IP, or to the study procedures. All SAEs will be recorded in the CRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within one day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the Investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study site personnel how to proceed.

The reference document for definition of expectedness/listedness is the Investigator's Brochure for the AstraZeneca drug and the EU Summary of Product Characteristics for the active comparator product.

6.5 Overdose

This refers to the administration of a quantity of a medicinal product given per administration or cumulatively, which is above the maximum recommended dose according to the authorised product information. Clinical judgement should always be applied.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.
- An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose of an AstraZeneca IP occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 6.4. For other overdoses, reporting must occur within 30 days.

6.6 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca.

6.6.1 Maternal exposure

If a patient becomes pregnant during the course of the study the IP should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

6.7 Management of IP related toxicities - Not Applicable

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

Table 4 Identification of investigational product(s)

Investigational product	Dosage form and strength	Manufacturer
GFF	Metered dose inhaler (MDI), contains glycopyrronium/formoterol fumarate fixed-dose combination 7.2/4.8 µg per actuation	AstraZeneca
Anoro Ellipta (UV)	Dry powder inhaler (DPI), Each metered dose contains umeclidinium/vilanterol 62.5/ 25µg fixed-dose combination per inhalation	GlaxoSmithKline
Placebo	MDI, Formulation does not contain active ingredient	AstraZeneca
Placebo	DPI, Formulation does not contain active ingredient	GlaxoSmithKline

Open-label supplies include albuterol/salbutamol MDI 90 µg ex-actuator and ipratropium bromide MDI 17 µg ex-actuator. For both albuterol/salbutamol MDI and ipratropium bromide MDI, it is preferred that these be US-sourced products (Ventolin inhalation aerosol and Atrovent, respectively). In cases where it is not possible for the US-sourced product to be used, a locally available product may be provided by the Sponsor.

7.2 Dose and treatment regimens

Each patient will undergo a screening period of 1 to 4 weeks (-28 to -9 days). Patients will be provided albuterol/salbutamol MDI to be taken as needed (rescue medication) during the

screening period and throughout the study. Patients will be provided ipratropium bromide MDI taken as 2 inhalations QDS for use as COPD maintenance therapy during the screening period.

The first dose of IP will be taken at Visit 3 (Day 1). During the 24 week double-blind treatment period, patients will take two inhalations in the morning and in the evening from the GFF inhaler (active or placebo) and one inhalation in the morning from the UV inhaler (active or placebo).

Patients will be trained on how to use both IP inhalers at Visit 1 through Visit 6.

7.3 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

For blinded GFF/placebo supplies, each inhaler will be labelled with a single label. The actuator will be labeled with a single label. The foil pouch will be labeled with a single label.

For blinded UV/placebo supplies, each inhaler will be labelled with a single label. The foil pouch will be labeled with a single label.

Open-label albuterol/salbutamol MDI and ipratropium bromide MDI will be provided as individually labeled MDIs. Each MDI will contain a single label. The MDI actuator will be labeled with a single label.

Both single and two-part labels will be printed with black ink.

The label may include the following information:

Packaging Lot Trace ID #	Dosing Instructions
Space for entry of screening #	Storage Conditions
Component ID #	Compound ID - Protocol #
Space for entry of randomisation #	Country regulatory requirements
Fill Count & Dosage Form	Sponsor address (If applicable)
Space for entry of Interval ID (Visit # only)	Translation Key (If applicable)
Re-evaluation/Expiration date (if applicable)	

Blinded IP inhalers and open-label albuterol/salbutamol MDI and ipratropium bromide MDI supplies will be packaged in individual boxes. Each box will be labeled with a two-part label printed with black ink and may include the following text:

Packaging Lot ID #	Dosing Instructions (if applicable)
Space for entry of screening #	Storage Conditions
Component ID #	Compound ID - Protocol #
Space for entry of randomisation #	Country regulatory requirements
Kit Contents (1 MDI)	Sponsor address (If applicable)
Space for entry of Interval ID	Translation Key (If applicable)
Re-evaluation/Expiration date (if applicable)	

Individual GFF and Placebo inhaler, UV and Placebo inhaler will be packaged in a foil pouch and contained in an individual visit treatment box. Both the visit treatment box and the foil overwrap will have a label with a component ID number. Confirm that the identifier given by IWRS/IVRS and the component ID number written on the label are the same. The visit treatment box is labeled with a two part label. Write the patient number and treatment visit number on each of the two-part labels. The 'tear-off' part of the label is to be placed onto the medical records.

Each open-label albuterol/salbutamol MDI and ipratropium bromide MDI will be contained in an individual visit treatment box. The visit treatment box will have a label with a component ID number. Confirm that the identifier given by IWRS/IVRS and the component ID number written on the label are the same. The visit treatment box is labeled with a two part label. Write the patient number and treatment visit number on each of the two-part labels. The 'tear-off' part of the label is to be placed onto the medical records.

7.4 Storage

All study medications should be kept in a secure place under appropriate storage conditions. The IP label on the IP inhalers and boxes specifies the appropriate storage.

The clinical supplies storage area at the site must be monitored by the site personnel for temperature consistency with the acceptable storage temperature range specified in accordance with the product label. Documentation of temperature monitoring should be maintained.

7.5 Compliance

The technique for inhalation from an MDI (GFF) is different from the technique used with a DPI (UV). **It is important to ensure that patients apply correct inhalation technique for both types of inhalers.** Training devices will be available at each study site for instructional purposes, as well as for patients to practice the correct inhalation technique. Instruction and practice should occur prior to dispensing study medication, and review of patients' inhalation technique should be done at each visit.

The administration of all study medications (including IPs) should be recorded in the appropriate sections of the Case Report Form.

Administration of study medication will be recorded twice daily in the patient's ePRO. If IP use drops below 80%, or if IP use is not recorded on two consecutive days, an e-mail alert will be sent to the investigator; the patient should be contacted and the compliance problems investigated. Furthermore, site personnel will check study medication compliance in the ePRO at each visit, and any issues identified will be documented in the appropriate study files. If appropriate, site personnel will retrain the patient on the proper use of the IP inhalers. In case of repeated compliance alerts and/or if IP compliance drops below 50%, withdrawal of the patient should be considered. Before withdrawal of a patient due to low compliance, a discussion with the study physician is mandated.

7.6 Accountability

The study medications provided for this study will be used only as directed in the Clinical Study Protocol.

The study site personnel will account for all study medication, including IP, dispensed to and returned from the patient.

The supplies that are returned and accounted for or have never been used, shall be destroyed as applicable in a given country. Study site personnel or AZ monitor will account for all IPs received at the site, unused IPs and for appropriate destruction. Certificates of delivery, destruction and return should be signed.

7.7 Concomitant and other treatments

For permitted medications during the study, see Table 5, Table 6, Table 7and Table 10. For prohibited medications during the study, see Table 8 and Table 9.

Table 5 Permitted medications

Allowed Medication/Class of drug
Antitussives PRN not containing ephedrine or other bronchodilators
Antihistamines not containing ephedrine or other bronchodilators
Mucolytics not containing ephedrine
Nasal, ophthalmic and topical corticosteroids without systemic effects
Nasal decongestants
Antibiotics for acute infections
Influenza and pneumonia vaccines
Ophthalmic β-blocking agents (selective and non-selective), only if used at a constant dose for 2 months prior to Visit 1 without evidence of bronchospasm
Oral cardio-selective β-blocking agents, only if used at a constant dose for 2 months prior to Visit 1 without evidence of bronchospasm

Allowed Medication/Class of drug
All medications for other disorders as long as the dose remains constant wherever possible and their use would not be expected to affect lung function

Table 6 Restricted Medications

Restricted Medication/Class of drug	Usage/restrictions
Systemic corticosteroids (oral or injections)	Prohibited within 4 weeks (depot corticosteroids within 6 weeks) prior to Visit 1 and throughout the study. Exceptions: - Allowed to treat a COPD exacerbation, but no more than 14 days. - In patients who are steroid dependent, an equivalent of 5 mg prednisone per day or 10 mg every other day is allowed, provided stable dosing for at least 3 months prior to Visit 1 and throughout the study.
Theophylline	Allowed taken regularly ≤ 200 mg BD throughout the IP treatment period, provided stable dosing for at least 4 weeks prior to Visit 1. Should be withheld from 6h prior to site visits until visit completion.
Phosphodiesterase-4 Inhibitors	Allowed provided stable dosing for at least 2 months prior to Visit 1 and throughout the study.
Leukotriene antagonists	Allowed provided stable dosing for at least 1 month prior to Visit 1 and throughout the study.
Cromoglycate	Allowed provided stable dosing for at least 1 month prior to Visit 1 and throughout the study.
Oxygen	Allowed for intermittent use or ≤12 hours per day

Table 7 Screening period Medication and Rescue medication

Screening period Medication and Rescue medication	Usage
Study-supplied ipratropium bromide MDI 17 µg ex-actuator	2 inhalations QDS during the screening period. 6h of wash-out before Visit 2 and 3.
Study-supplied albuterol/salbutamol MDI 90 µg ex-actuator	As needed throughout the study, from Visit 1 to Visit 7. 6h of wash-out before each site visit.

Table 8 Prohibited COPD Medications

Prohibited COPD Medication/Class of drug	Minimum Washout Period Prior to Visit 2
LAMAs	Aclidinium: 3 days Umeclidinium: 3 days GP: 14 days Tiotropium: 14 days
LABAs (inhaled)	2 days (14 days for indacaterol and olodaterol)
Fixed combinations of LAMA/LABA	Umeclidinium/vilanterol: 7 days Aclidinium/formoterol 7 days GP/formoterol: 14 days Tiotropium/olodaterol: 14 days GP/indacaterol: 14 days
ICS	7 days
Any combination treatment of ICS/LABA	7 days
Maintenance treatment with any triple combination of ICS/LAMA/LABA	1 month
SAMA	6 hours
Fixed combinations of SABAs and SAMAs	6 hours
SABAs[a]	6 hours
Oral β-agonists	2 days
Theophylline (total daily dose >400 mg/day)[b]	7 days
Ephedrine containing medications	2 days

[a] Discontinue and use only sponsor-provided rescue albuterol/salbutamol MDI throughout the study.
[b] Theophylline (≤200 mg BD) is allowed provided stable dosing for at least 4 weeks prior to Visit 1.

Table 9 Other prohibited Medications

Other prohibited Medication/Class of drug	Minimum Washout Period
Oral non-selective β-blocking agents	2 weeks prior to Visit 1
Any other investigational drug	30 days or five half-lives (whichever is longer) prior to Visit 1
Any monoclonal or polyclonal antibody	6 months prior to Visit 1
Monoamine oxidase inhibitors, tricyclic antidepressants, and other drugs known to prolong the QTc interval	2 weeks prior to Visit 3
Strong CYP3A4 inhibitors	30 days prior to Visit 3

7.7.1 COPD Medication restrictions

7.7.1.1 Use of short-acting anticholinergics and short-acting β2-agonists

Patients will be provided ipratropium bromide MDI taken as 2 inhalations QDS for use as COPD maintenance therapy during the screening period. Use of any SAMA as rescue treatment for worsening COPD symptoms is not allowed from Visit 1 and throughout the study duration, with the exception of treatment during a COPD exacerbation.

Albuterol/salbutamol MDI will be dispensed at Visit 1 for use as rescue medication for worsening of COPD symptoms. No other SABA is allowed during the study outside of managing a COPD exacerbation. Rescue use of albuterol/salbutamol MDI will be recorded in the ePRO as number of inhalations per day (see Section 7, Table 7). Regularly scheduled use of albuterol/salbutamol MDI is not allowed. Prophylactic use in the absence of symptoms is discouraged. However, if deemed necessary by the patient and Investigator (e.g. prior to planned exercise), it can be used, but prophylactic inhalations should not be recorded in the daily ePRO. Such use should be documented in the medical notes and recorded in the eCRF.

Albuterol/salbutamol MDI rescue medication is not regarded as an IP, but will be provided by AstraZeneca locally according to local regulations, in order to ensure access for this therapy from enrolment and up to Week 24, unless the patient is withdrawn from the study.

7.7.1.2 COPD medication restrictions on the days of scheduled spirometry visits

Spirometry assessments will be performed at scheduled site visits (see Section 4, Table 1). There are no restrictions regarding patients' COPD medications prior to the spirometry at Visit 1 (other than those related to study eligibility), whereas important restrictions apply prior to the spirometry at the following visits:

Visit 2: patients will be asked to withhold ipratropium bromide MDI and albuterol/salbutamol MDI within approximately 6 hours of the first (pre-BD) spirometry assessment. Use of albuterol/salbutamol MDI should be avoided until the screening lung function assessments are

completed. Ipratropium bromide MDI may be administered following completion of the lung function assessments.

Visit 3: patients will be asked to withhold ipratropium bromide MDI and albuterol/salbutamol MDI within approximately 6 hours of the first (pre-BD) spirometry assessment. The treatment with ipratropium bromide MDI will be stopped, and the first doses of the two IP inhalers will be administered after completion of all pre-dose assessments. Use of albuterol/salbutamol MDI should be avoided until all lung function assessments are completed.

Visits 4-7: patients will be asked to withhold IP in the morning before the visits. The time from the previous dose until dosing of IP at the visit should be approximately 12 hours for the GFF/placebo inhaler, and approximately 24 hours for the UV/placebo inhaler. Use of albuterol/salbutamol MDI should be avoided for at least approximately 6 hours prior to the first scheduled spirometry. IP will be administered after completion of all pre-dose assessments. Albuterol/salbutamol MDI intake should be avoided until all lung function assessments are completed.

If IP was dosed incorrectly (missed or not taken as directed) on the day prior to a visit, the visit should be rescheduled to another day, as soon as possible and preferably within the visit window.

If IP was dosed at an incorrect time on the day prior to a visit (see Section 4.2), it is strongly recommended that the visit is rescheduled as above, but if this is not feasible for the patient, spirometry may be performed with a notation of the incorrect timing of IP.

If rescue medication was taken within 6 hours of the planned site visit spirometry, the patient should ideally remain at the site until such time that the 6 hours withholding time has been reached, given it does not exceed the spirometry window (see Section 5.1.1.2) or the stipulated time interval since IP intake on the previous day (see Section 4.2). Alternatively, patients can return on another day, as soon as possible and preferably within the visit window. If neither of options is feasible for the patient, spirometry may be performed with a notation indicating that the spirometry was conducted within 6 hours of rescue medication use.

7.7.1.3 Allowed Medications to treat a COPD exacerbation

For allowed medications to treat a COPD exacerbation, see Table 5.

Rescue use of SABA and/or SAMA administered via nebulization is allowed to manage an acute COPD exacerbation.

Medications to treat an exacerbation should not be used for more than 14 days. Recent data suggest that treatment with systemic steroids for shorter periods of time results in similar outcomes with less systemic steroid exposure. Therefore, it is recommended that patients are treated with a 5 day course. A single depot injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids.

Table 10 Allowed Medications to treat a COPD exacerbation

Allowed Medication to treat a COPD exacerbations	Usage
Systemic corticosteroids (oral or injections)	No more than 14 days. 4-week washout required before next scheduled site visit (6 weeks for depot injections).
Antibiotics	No more than 14 days
ICS (including nebulized)	Only during hospitalization/ER treatment. 7-day washout required before next scheduled site visit.
Additional SABAs and SAMAs, including nebulized treatment	Only concomitantly with systemic steroids and/or antibiotics
Xanthines (other than theophylline ≤400 mg/day ongoing since randomisation)	Only concomitantly with systemic steroids and/or antibiotics. 7-day washout required before next scheduled site visit.
Ephedrine containing medications	Only concomitantly with systemic steroids and/or antibiotics. 2-day washout required before next scheduled site visit.

7.7.2 Other concomitant treatment

Medication other than that described above, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the Case Report Form.

7.8 Post Study Access to Study Treatment

After completion of study treatment, patients will be prescribed appropriate COPD maintenance medication according to the Investigator's judgment and local medical practice. Consideration should be given to maintaining patients on at least double therapy, while ensuring appropriate follow-up and further evaluation of the prescribed treatment.

8. STATISTICAL ANALYSES

8.1 Statistical considerations

The primary objective of this study is to assess the effects of GFF relative to UV on lung function.

The primary null (H_0) and alternative (H_1) hypotheses, with μ representing the mean change from baseline in each treatment group, correspond to a null hypothesis of inferiority and an alternative hypothesis of non-inferiority, as follows:

H0: $\mu_{GFF} - \mu_{UV} \leq -\Delta$ (GFF is inferior to UV by Δ or more)

H1: $\mu_{GFF} - \mu_{UV} > -\Delta$ (GFF is inferior to UV by less than Δ)

These are one-sided tests assessed at a 2.5% significance level. P-values will thus be reported as one-sided for both the non-inferiority and superiority hypothesis testing. This will equivalently be presented by comparing the lower bound of a 2-sided 95% confidence interval to the pre-specified margin.

The primary analysis for each endpoint is assessed within a Per Protocol analysis set and if non-inferiority is demonstrated the consistency of this conclusion will be assessed within the full analysis set.

If non-inferiority is demonstrated then for selected key secondary endpoints superiority hypotheses will also be addressed within the full analysis set. Here the null (H_0) and alternative (H_1) hypotheses are as follows:

H0: $\mu_{GFF} - \mu_{UV} \leq 0$ (GFF is not superior to UV)
H1: $\mu_{GFF} - \mu_{UV} > 0$ (GFF is superior to UV)

The exception to this sequential testing of non-inferiority followed by superiority is the analysis of the proportion of patients with increase in FEV_1 of $\geq$100 ml from baseline at 5 minutes. For this endpoint testing will immediately be in terms of superiority hypotheses.

A comprehensive Statistical Analysis Plan (SAP) will be signed off prior to unblinding or to the review of any potentially treatment revealing data. Analyses will be performed by AstraZeneca or its representatives.

All personnel involved with the analysis of the study will remain blinded until the database is locked and all protocol violations are identified.

8.2 Sample size estimate

1000 patients (500 patients each in the GFF and UV treatment arms) are to be randomised in this study. Based upon Phase III studies of GFF, it is estimated that 12% of the patients randomised will be excluded from the Per Protocol Analysis Set, leaving around 440 patients in the primary analysis. This sample size will provide around 94% power to demonstrate that the difference between GFF vs UV in change from baseline in morning pre-dose trough FEV_1 over 24 weeks is greater than the non-inferiority margin of -50 mL. This calculation assumes a one-sided significance level of 0.025 and a true difference of -10 mL. Assumptions regarding variability for the primary endpoint are based on experience in previous GFF Phase III clinical studies. An effective standard deviation (SD) of 167 mL for the change from baseline in morning pre-dose trough FEV_1 over 24 weeks has been assumed. This value is based on a per-visit SD of 200 mL and a within-patient (between-visit) correlation of 60%. Under these assumptions, for non-inferiority to be achieved the point estimate of the difference in pre-dose trough FEV_1 over 24 weeks must be above -28mL.

For the secondary lung function endpoints of peak FEV_1 and IC over 24 weeks the power to show non-inferiority is expected to be at least that of the primary endpoint. For the secondary

endpoint of the TDI focal score over 24 weeks a non-inferiority margin of -1 unit is defined. However, note that the power to show non-inferiority would remain at least 90% with a margin of -0.75 units (three quarters of the MCID), assuming no difference between treatments and a standard deviation of 3 units.

8.3 Definitions of analysis sets

The primary analysis and all other non-inferiority analyses in this study will primarily be conducted using the per protocol analysis set. This will be used to compare GFF and UV when the treatments are used as planned at each visit, in the intended patients and without important protocol deviations. This will provide an estimate of the true biological efficacy of the treatments and counters the tendency for intention-to-treat analyses to favour a conclusion of equivalence. Non-inferiority comparisons will also be conducted in the full analysis set of all patients receiving IP, allowing for variation in clinical application whilst on treatment, as a comparison of their effectiveness when used in practice. If non-inferiority is also demonstrated in the full analysis set then this analysis set will be used to provide an assessment of superiority.

The All Patients Analysis Set

This analysis set comprises all patients screened for the study and may be used for the reporting of disposition and screening failures.

8.3.1 Efficacy analysis sets

Full Analysis Set

The Full Analysis Set will be defined as all patients randomised who received at least one inhalation of IP. Patients will be analysed according to the treatment they were assigned to at randomisation.

This analysis set will be used to demonstrate consistency in non-inferiority hypothesis tests and as the primary means of assessing superiority hypotheses.

Per Protocol Analysis Set

The Per Protocol (PP) Analysis Set will be used for the primary analysis and as the primary means of assessing other non-inferiority hypotheses.

The Per Protocol Analysis Set is the subset of the full analysis set containing patients with post-randomisation data obtained prior to important protocol deviations. Data obtained after important protocol deviations will be excluded from analyses using this set. The use of certain prohibited medications (such as inhaled corticosteroids) outside of the limitations described in Section 7.7 will be defined in the SAP as important protocol deviations and so data after the initiation of these will be excluded from per protocol analyses. Since receiving the wrong treatment will be a major protocol deviation, patients in the PP analysis set will be analysed as randomised (which for this population is identical to analysis by the actual treatment

received). Patients must also have a valid spirometry baseline to be included given that this is required to ensure that key inclusion criteria are met.

Patients who are found not to meet the inclusion criteria for clinical diagnosis of COPD or the COPD severity criteria or who did not have the required washout of prohibited medications prior to baseline will be excluded entirely for the PP analysis set. In addition, data from visits where patients do not comply with required restrictions will be removed from analyses which use the per protocol analysis set (see Section 8.4.3).

A detailed definition of the Per Protocol Analysis Set and data points to be excluded will be given in the Statistical Analysis Plan and defined prior to the review of any potentially treatment revealing data.

8.3.2 Safety analysis sets

Safety Analysis Set

All patients who received any IP will be included in the safety analysis set. Patients will be classified according to the treatment they actually received. If a patient received more than one randomised treatment, they will be analysed and included in summaries according to the treatment they received the most. Any major deviations from the randomised treatment assignment will be listed and considered when interpreting the safety data.

8.3.3 Other analysis sets

Rescue Medication User analysis set

Regional differences in rescue albuterol/salbutamol MDI usage are expected with some regions using virtually no rescue albuterol/salbutamol MDI at study entry. Therefore, the Rescue Medication User analysis set is defined as all patients in the full analysis set with average baseline rescue albuterol/salbutamol MDI use of $\geq$ 1 inhalation/day.

8.4 Outcome measures for analyses

8.4.1 Definition of baseline

All efficacy assessments are relative to pre-dose baseline obtained at randomisation at Visit 3.

For spirometry endpoints the mean of all available evaluable -60 and -30 minute pre-dose spirometry assessments conducted at Day 1 (Visit 3) will be used to establish baseline for all FEV_1, FVC, and IC parameters.

For the diary symptom score parameters and rescue medication usage, baseline will be the average of the non-missing values from the ePRO data collected in the last seven days before randomisation (i.e. excluding data recorded on the day of visit 3).

8.4.2 Visit windows

Data will be summarised according to the protocol-scheduled week for that visit. Data collected in spirometry and ePRO systems will be allocated to visit weeks based upon

assigned windows so as to allow rescheduled assessments to be included. Detailed definitions of visit windows and periods will be provided in the SAP.

For efficacy endpoints or derivation of AUC based on assessment times pre and post dosing, the assessments will be allocated to derived nominal collection time windows of minutes from IP dosing. These will be specified in the SAP.

8.4.3 Pulmonary Function Outcomes

All pulmonary function assessments that have at least one effort that meets ATS/ERS criteria for acceptability will be considered acceptable and contribute to the post-dose assessments for analyses using the full analysis set. If all the assessments at a specific timepoint were deemed to be of unacceptable quality the pulmonary function assessments obtained at the timepoint will not be included in any efficacy analysis and will be considered missing.

For the Per Protocol analyses additional requirements will have to be met in addition to the ATS/ERS criteria in order for pulmonary function data to be used in the analyses. Patients who do not comply with selected restrictions during a study visit (for example on smoking and bronchodilator or rescue medication use) will have their data from that visit removed from analyses which use the per protocol analysis set. Patients who do not take the morning and evening doses of blinded study inhalers on the day preceding a study visit will also have their data from that visit removed.

8.4.3.1 Morning pre-dose trough FEV_1

Change from baseline in the primary endpoint of morning pre-dose trough FEV_1 is defined as the average of the -60 and -30 minute pre-dose values at each visit minus baseline. Baseline is defined as the average of the non-missing -60 minute and -30 minute values obtained prior to dosing at Visit 3.

In patients missing either of these pre-dose assessments, the value will be calculated from the single measurement. In patients missing both pre-dose values, morning pre-dose trough FEV_1 at that visit will not be calculated.

The change from baseline in morning pre-dose trough FVC will be derived similarly.

8.4.3.2 Peak FEV_1 and Inspiratory Capacity post-dosing

Change from baseline in the secondary endpoint of Peak FEV_1 is defined as the maximum of the FEV_1 assessments within 2 hours post-dosing at each visit minus baseline. Similarly, change from baseline in the secondary endpoint of Peak IC is defined as the maximum of the IC assessments within 2 hours post-dosing at each visit minus baseline.

For the Per Protocol analyses, the peak change from baseline in FEV_1 and IC within 2 hours post-dosing will be included in analyses as long as there are at least 2 non-missing data points during the first 2 hours post-dose. Peak FEV_1 and IC will be included in analyses using the full analysis set as long as there is at least 1 non-missing post-dose value during the first 2 hours post-dose.

Further additional spirometry endpoints will also be derived. Change from baseline in peak FVC within 2 hours post-dose will be derived similarly to Peak FEV_1. The trapezoidal rule will be used to derive estimates of AUC_{0-2} for FEV_1 and FVC, normalised by time from first to last non-missing value, as long as there are at least 2 non-missing data points during the first 2 hours post-dose.

8.4.3.3 Increase in FEV_1 at 5 minutes post-dosing

To assess the early onset of action, a secondary endpoint of this study will be the proportion of patients with increase of FEV_1 of $\geq$100 ml from baseline at 5 minutes on day 1. Only data assigned to the 5 minute window will be used to determine response. Patients with missing data will be considered to be non-responders for the analysis.

Additional categorical endpoints will be derived similarly as the proportion of patients with increase of FEV_1 of $\geq$150 ml from baseline at 5 minutes and the proportion of patients with increase of FEV_1 of $\geq$12% from baseline at 5 minutes.

8.4.4 Patient Reported Outcomes

8.4.4.1 Transition Dyspnea Index (TDI) focal score

As a secondary endpoint assessing dyspnea, the TDI focal score will be derived at post-randomisation visits relative to the baseline severity of dyspnea assessed using the BDI at visit 3. The BDI and TDI consist of 3 individual components: functional impairment, magnitude of task, and magnitude of effort. These are summed to form a baseline total score for BDI (range 0-12) and a total TDI score (range -9 to +9). For the TDI, at each visit, if a response to any of the three questions is missing, then the focal score will also be considered missing. Otherwise, scoring and handling of missing items will be conducted in accordance with the user's guide for the TDI score.

The percentage of patients achieving the threshold of 1 unit or more in TDI focal score will be derived at each visit. For the TDI responder analyses, patients with missing data will be considered to be non-responders for the analysis.

8.4.4.2 Early Morning Symptoms COPD Instrument (EMSCI) and Night Time Symptoms COPD Instrument (NiSCI)

Patients will complete a daily ePRO questionnaire of their COPD symptoms with two parts covering symptoms "last night" and "this morning".

The change from baseline in the 6-item EMSCI Symptom Severity Score is a secondary endpoint. This is derived by averaging the responses from a patient on the six item-level symptom scores

The change from baseline in the 6-item NiSCI Symptom Severity Score will also be assessed. The change from baseline in the Overall COPD Symptom Severity score, Early Morning Activity score and Night-time Awakenings score will also be derived.

Each daily measure will be aggregated based upon the time periods between clinic visits. Data from the day of the clinic visit will not be used in these aggregates. These periods will be specified in detail in the SAP. If the measure is available on more than half of the days in a given period then an aggregate score will be computed as the average of all present daily values. Otherwise the score will be considered missing for that period. ePRO data recorded during the last 7 days of the screening period prior to Visit 3 will be used to calculate the baseline.

8.4.4.3 COPD Assessment Test (CAT) score

The COPD Assessment Test (CAT) is used to quantify the impact of COPD symptoms on health status. The CAT has a scoring range of 0-40, and it is calculated as the sum of the responses given for each of the 8 items (scored on a 6-point scale from 0 to 5), with higher scores indicating a higher impact of COPD symptoms on health status. If the response to 1 of the 8 items is missing, the missing item will be considered equal to the average of the 7 non-missing items for that patient. If more than 1 item is missing the score will be considered missing.

The change from baseline in CAT score will be derived at each visit relative to the baseline at visit 3. The percentage of patients achieving a MCID threshold for CAT of 2 units or more will be derived at each visit, with patients with missing data considered to be non-responders.

8.4.4.4 Daily rescue medication use

The number of inhalations of rescue albuterol/salbutamol MDI will be recorded in the patient ePRO in the morning and evening and these summed. The mean daily number of inhalations of rescue albuterol/salbutamol MDI will be calculated overall and in time periods between each clinic visit. These periods will be specified in detail in the SAP. ePRO data recorded during the last 7 days of the screening period prior to randomisation will be used to calculate the baseline. Change from baseline in mean daily rescue (albuterol/salbutamol MDI) use will then be derived. The denominator will be adjusted based on the number of days (or half days) with non-missing values.

A 'day with no rescue use' is defined from days where rescue albuterol/salbutamol MDI usage data is non-missing as any day where the patient reported no inhalations of rescue albuterol/salbutamol MDI in both the morning and evening. The percentage of days with no rescue use will be derived using a denominator of the number of full days in the period with no missing data.

8.4.4.5 EuroQol 5 Dimensions Questionnaire (EQ-5D-5L)

The EQ-5D-5L questionnaire assesses 5 dimensions which will be derived separately: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.

The patient will also be asked to rate current health status on a visual analogue scale from 0 - 100, with 0 being the worst imaginable health state. The change from baseline in visual analogue scale will be calculated.

8.4.4.6 Healthcare Resource Utilisation (HCRU)

Broad-based health care utilization event information will be collected by the Investigator/authorized delegate via patient interview at each visit and recorded in the appropriate eCRF module. Examples include aspects such as physician visits or telephone calls.

The number of moderate exacerbations (defined as those requiring antibiotics or ≥3 days of systemic steroids) or severe COPD exacerbations (defined as those leading to in patient hospitalisation, including >24 hours in emergency department/urgent care setting) will also be recorded.

8.4.4.7 Work Productivity and Activity Impairment – General Health (WPAI-GH)

The Work Productivity and Activity Impairment – General Health (WPAI-GH) will be collected. Measures summarised will include the patient's work time missed (absenteeism), impairment at work or reduced on-the-job effectiveness (presenteeism), overall work impairment (abseentism and presenteeism, ie, work productivity loss), and activity impairment outside the work environment. The WPAI-GH outcomes are expressed as impairment percentages whereby higher scores indicate greater impairment and less productivity (ie, worse outcomes).

8.4.5 Safety and tolerability

AEs experienced by the patients will be collected throughout the entire study and will be coded by the AstraZeneca designee using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

8.5 Methods for statistical analyses

8.5.1 Analysis of the primary variable (s)

The primary analysis will be conducted using the Per Protocol analysis set. The change from baseline in morning pre-dose trough FEV_1 will be analysed using a linear mixed effects model repeated measures (MMRM) approach. The model will include baseline FEV_1 and bronchodilator responsiveness to albuterol/salbutamol MDI as continuous covariates and stratification factors (prior treatment - rescue/maintenance monotherapy vs double maintenance therapy), region, visit, treatment, and treatment by visit, as categorical covariates (fixed effects). Patient will be considered a random effect. Baseline is defined as the average of the non-missing -60 min and -30 min values obtained prior to dosing at Visit 3. An unstructured matrix will be used to model the variance-covariance structure within patient. If this model fit fails to converge, more parsimonious covariance structures will be considered to model correlation between time-points from the same patient.

A contrast will be used to obtain an estimate of the treatment difference over the entire 24-week Treatment Period with two-sided 95% confidence interval (CI). Non-inferiority will be concluded if the lower bound of this confidence interval is greater than the pre-specified

margin of -50 mL. This is equivalent to a one-sided hypothesis test at the 2.5% significance level and so 1-sided p-values will be produced accordingly.

From the same model contrasts will also be used to produce estimates of the treatment difference at each individual time-point (for example at week 24).

A similar analysis will be conducted in the full analysis set using all data obtained while on treatment.

8.5.2 Analysis of the secondary variable(s)

8.5.2.1 Hierarchical testing strategy

A sequential testing hierarchy will be defined so as to strongly control 1-sided type I error at 2.5% across all non-inferiority hypothesis tests and account for the multiplicity of secondary endpoints. The primary and key secondary endpoints over 24 weeks will be tested against their respective non-inferiority margins in the following sequence using a 1-sided significance level of 2.5%:

Primary endpoint:

1. Change from baseline in morning pre-dose trough pre-dose FEV_1 over 24 weeks (non-inferiority only),

Key secondary endpoints:

2. Peak change from baseline in Inspiratory Capacity within 2 hours post-dosing over 24 weeks (non-inferiority with option to proceed to superiority),

3. Peak change from baseline in FEV_1 within 2 hours post-dosing over 24 weeks (non-inferiority with option to proceed to superiority),

4. Proportion of patients with increase of FEV_1 of $\geq$100 ml from baseline at 5 minutes on Day 1 (superiority only),

5. Change from baseline in TDI focal score over 24 weeks (non-inferiority only)

6. Change from baseline in EMSCI Symptom Severity Score over 24 weeks (non-inferiority with option to proceed to superiority),

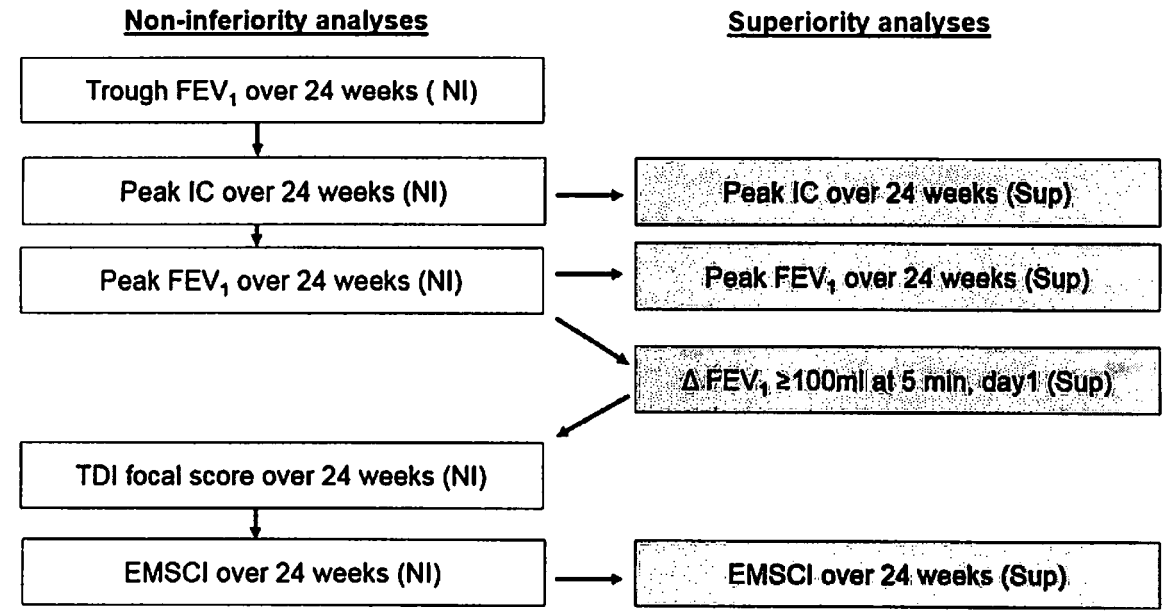
If non-inferiority is demonstrated for an endpoint, then testing may proceed to the next endpoint in the hierarchy, and a superiority test of the endpoint will also be conducted in the full analysis set for those endpoints indicated. Proceeding to the next endpoint is not contingent on demonstrating superiority.

An exception to this sequential non-inferiority/superiority testing procedure is the secondary endpoint Onset of action (proportion of patients with increase in FEV_1 of $\geq$100 ml from baseline at 5 minutes at day 1). For this endpoint, superiority testing will immediately be

carried out and superiority is required in order to move to the next step in the testing hierarchy.

This sequential testing hierarchy is illustrated in Figure 2:

Figure 2 Sequential testing hierarchy



NI = Non-inferiority, Sup = Superiority

Other secondary endpoints not included in the sequential testing procedure include the following:

- Change from baseline in CAT score over 24 weeks and proportion of patients achieving a MCID threshold for CAT of 2 units or more at week 24
- Change from baseline in NiSCI symptom severity score over 24 weeks
- Proportion of patients achieving a MCID threshold of 1 unit or more in TDI focal score at week 24
- Change from baseline in mean daily rescue (albuterol/salbutamol MDI) use over 24 weeks
- Change from baseline in morning pre-dose trough FVC over 24 weeks
- Peak change from baseline in FVC within 2 hours post-dose over 24 weeks
- Change from baseline FEV_1 AUC_{0-2} and FVC AUC_{0-2} over 24 weeks

8.5.2.2 Pulmonary Function over 24 weeks

The peak change from baseline in FEV_1 and IC within 2 hours post-dosing will each be analysed using a similar MMRM model to morning pre-dose trough FEV_1. The estimates of treatment difference over 24 weeks will also be referred to a non-inferiority margin of -50mL.

If non-inferiority is demonstrated in the Per Protocol analysis then the Full Analysis Set will be used to assess the consistency of the non-inferiority conclusion using all evaluable data and a similar repeated measures model. This model will be used for the formal assessment of superiority hypotheses and 1-sided p-value and 2-sided 95% confidence intervals will be produced.

Contrasts will be used to produce estimates at individual visits. Other continuous pulmonary function endpoints such as morning pre-dose trough and post-dose peak FVC and AUC_{0-2} for FEV_1 and FVC will be analysed similarly. Estimated treatment differences will be interpreted using 95% CIs, but will not be formally assessed for non-inferiority.

8.5.2.3 Pulmonary Function at Day 1

On Day 1 at the assessment 5 minutes post-dosing, the proportion of patients achieving an improvement from baseline in FEV_1 of $\geq$100 ml will be estimated for each treatment. Logistic regression will be used to compare the treatment groups with baseline and bronchodilator responsiveness to albuterol/salbutamol MDI as continuous covariates and treatment, region and stratification factors as categorical covariates. This analysis will use the full analysis set and proceed immediately to testing of the superiority hypothesis. One-sided p-values and odds ratios with 2-sided 95% CI will be produced.

Similar analyses will be conducted at 5 minutes on day 1 using alternative thresholds (increase in FEV_1 of $\geq$150 ml from baseline and increase in FEV_1 of $\geq$12% from baseline).

8.5.2.4 Transition Dyspnea Index Focal Score

The difference between treatment groups in TDI over 24 weeks will be evaluated using a similar MMRM approach as for the primary endpoint. The model will include BDI (in place of baseline) and bronchodilator responsiveness as continuous covariates. Stratification factors, region, visit, treatment, and treatment by visit will be included as categorical covariates. Patient will be considered a random effect.

One-sided p-values and point estimates with two-sided 95% CIs will be produced for the treatment difference over 24 weeks. Non-inferiority will be concluded if the lower bound of this confidence interval is greater than the pre-specified margin of -1.0 units (the minimum clinically important difference). Estimates of treatment difference will also be produced at each individual timepoint. A supportive analysis will also be produced using the Full Analysis Set.

The individual components of the TDI: functional impairment, magnitude of task, and magnitude of effort will also be summarised. Furthermore as supportive analyses, responder analyses will be performed at each visit, where responders are defined as a response of 1.0 point or more. Logistic regression will be used to compare the treatment groups with BDI as a continuous covariate and treatment group, region and stratification factors as categorical covariates. Odds ratios with 95% CIs will be produced.

8.5.2.5 Early Morning Symptoms COPD Instrument (EMSCI) and Night Time Symptoms COPD Instrument (NiSCI)

The difference between treatment groups in the change from baseline in EMSCI symptom severity score over 24 weeks will be evaluated using a similar MMRM approach as for the primary endpoint. Instead of visit, the relevant time interval will be used as a categorical covariate in the model. The model will include baseline and bronchodilator responsiveness as continuous covariates and stratification factors, region, time interval, treatment, and treatment by time interval, will be included as categorical covariates. Patient will be considered a random effect.

One-sided p-values and point estimates with two-sided 95% CIs will be produced for the treatment difference over 24 weeks. Non-inferiority will be concluded if the lower bound of this confidence interval is greater than the pre-specified margin of -0.1 units. Estimates of treatment difference will also be produced at each individual time-point.

If non-inferiority is demonstrated in the Per Protocol analysis then the Full Analysis Set will be used to assess the consistency of the non-inferiority conclusion using all evaluable data and a similar repeated measures model. This model will be used for the formal assessment of superiority hypotheses and 1-sided p-values and 2-sided 95% confidence intervals will be produced.

Estimates of treatment differences will be produced similarly for the NiSCI symptom severity score. These will be interpreted using 95% CIs, but will not be formally assessed for non-inferiority. Other sub-scales and responses will be summarised descriptively by treatment group.

8.5.2.6 COPD Assessment Test (CAT) score

The difference between treatment groups in the change from baseline in CAT score over 24 weeks will be evaluated using a similar MMRM approach as for the primary endpoint. Treatment differences will be interpreted using 95% CIs, but will not be formally assessed for non-inferiority.

Responder analyses will be performed at each visit, where responders are defined as a response of 2 units or more. Logistic regression will be used to compare the treatment groups with baseline CAT score as a continuous covariates and treatment group, region and stratification factors as categorical covariates. Odds ratios with 95% CI will be produced for each treatment comparison.

8.5.2.7 Daily Rescue Medication Use

The difference between treatment groups in the change from baseline in mean daily rescue albuterol/salbutamol MDI use will be evaluated using a MMRM approach using the Rescue Medication User Analysis Set. Instead of visit, the relevant time interval will be used as a categorical covariate in the model. The model will include baseline and bronchodilator responsiveness as continuous covariates and stratification factors, region, time interval, treatment, and treatment by time interval, will be included as categorical covariates. Patient

will be considered a random effect. Treatment differences will be interpreted using 95% CIs, but will not be formally assessed for non-inferiority.

Additionally daytime and night-time mean albuterol/salbutamol MDI use and the percentage of days with 'no rescue use' will be evaluated and summarized.

8.5.3 Subgroup analysis

Subgroup analyses of the primary endpoint will be produced according to prior treatment at entry (rescue therapy only, single maintenance therapy, LABA/LAMA maintenance therapy, LABA/ICS maintenance therapy).

Selected symptomatic endpoints will be analysed within subgroups of patients with varying levels of baseline symptom scores as measured by CAT.

Further subgroup analyses may be defined in the SAP.

8.5.4 Interim analysis - Not applicable

No interim analyses are planned for this study.

8.5.5 Sensitivity analysis

Although the primary and secondary endpoints are primarily addressed using estimates of the effects over 24 weeks contrasts will also be used to produce estimates at each individual visit.

As described in Section 8.3, the primary analysis and all other non-inferiority analyses in this study will primarily be conducted using the per protocol analysis set and non-inferiority comparisons will also be conducted in the full analysis set to assess consistency when all patients and evaluable data are used.

The methods used primarily in these analyses rely on the assumption that data is missing at random (MAR) given the covariates included in the models. Sensitivity analyses will be conducted to assess the robustness of conclusions to this assumption, including under Missing Not at Random (MNAR) scenarios.

Multiple imputation methods will be used under varying assumptions about treatment effects in the unobserved data and assuming differing effects according to the patterns of missingness and reason for withdrawal. Full details will be given in the Statistical Analysis Plan.

8.5.6 Safety and tolerability

All safety variables will be summarized using the safety analysis set and data presented according to treatment received. No hypothesis tests will be performed.

AEs will be summarized by System Organ Class and Preferred Term assigned to the event using MedDRA. For each PT, the number and percentage of patients reporting at least one occurrence will be presented by treatment group i.e., for a patient multiple occurrences of an

AE will only be counted once. SAEs, Deaths, AEs leading to discontinuation (DAEs) and AEs deemed causally related to IP by the Investigator will be summarised by treatment group.

8.5.7 Exploratory analysis

The EQ-5D-5L responses from each dimension and the visual analogue scale (VAS) will be summarised descriptively by treatment group and period.

COPD-related and non-COPD-related health resource utilisation will be summarized by treatment group. The frequency and rate per year of COPD exacerbations will also be summarised.

WPAI-GH responses will be summarised using descriptive statistics by treatment group.

9. STUDY AND DATA MANAGEMENT

9.1 Training of study site personnel

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and the ePRO, eCRF, IWRS/IVRS systems utilised.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.2 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the Clinical Study Protocol, that data are being accurately and timely recorded in the CRFs and that IP accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (e.g., clinic charts)

The AstraZeneca representative will be available between visits if the Investigator(s) or other staff at the site needs information and advice about the study conduct.

9.2.1 Risk based quality management

Quality by design will be implemented, including a focus on identifying key risks to patient safety, data quality, and GCP/regulatory compliance. A risk based approach to monitoring will be applied. A mix of monitoring strategies will be implemented: on-site monitoring, remote monitoring (site level monitoring activities performed at a location other than the research site) and centralized monitoring systems. Monitoring strategies will be tailored to risks, permit timely oversight (through central/remote monitoring and use of technology), and will be focused on Critical Processes and Critical Data.

Central monitoring will be used to check that data is consistent and complete, identify unusual distribution of data, identify higher risk sites to target additional monitoring, and to ensure routine review of data is completed in real time.

9.2.2 Source data

The location of source data is defined in the Clinical Study Agreement. The Principal Investigator must provide direct access to source data/documents for study-related monitoring, audits, IRB/IEC review, and regulatory inspection.

9.2.3 Study agreements

The Principal Investigator at each/the site should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the Clinical Study Agreement shall prevail.

Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place, or patients are enrolled.

9.2.4 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Agreement (CSA).

9.3 Study timetable and end of study

The study is expected to start in Q2 2017 and to end by Q3 2018. The end of the study is defined as 'the last visit of the last patient undergoing the study'.

The expected recruitment period is 6-8 months and AstraZeneca will notify Investigators when recruitment is complete.

The study may be terminated at individual sites if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the

entire study prematurely if concerns for safety arise within this study or in any other study with GFF.

9.4 Data management by AstraZeneca

Data management will be performed by AstraZeneca Data Management Centre staff at Cognizant, according to the Data Management Plan.

The data collected through third party sources will be obtained and reconciled against study data.

AEs and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the WHO Drug Dictionary. All coding will be performed by the Medical Coding Team at the AstraZeneca Data Management Centre.

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

When all data have been coded, validated, signed and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

Serious Adverse Event (SAE) Reconciliation

SAE reconciliation reports are produced and reconciled with the Patient Safety database and eCRF.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Patient data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

10.3 Ethics and regulatory review

An Ethics Committee should approve the final Clinical Study Protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the patients. The Investigator will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site personnel.

The opinion of the Ethics Committee should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrolment of any patient into the study.

The Ethics Committee should approve all advertising used to recruit patients for the study.

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the Clinical Study Protocol should be re-approved by the Ethics Committee annually.

Before enrolment of any patient into the study, the final Clinical Study Protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements.

For the US and Canada, may also be applicable to other countries:

Each Principal Investigator is responsible for providing the Ethics Committees/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IP. AstraZeneca will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

10.4 Informed consent

The Principal Investigator(s) at each site will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided

- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee.

10.5 Changes to the Clinical Study Protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca.

If there are any substantial changes to the Clinical Study Protocol, then these changes will be documented in a new version of the study protocol.

The new version of the Clinical Study Protocol is to be approved by the relevant Ethics Committee and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for new versions of Clinical Study Protocols.

AstraZeneca will distribute any new versions of the Clinical Study Protocol to each Principal Investigator(s). For distribution to Ethics Committee see Section 10.3.

If a change to a Clinical Study Protocol requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's Ethics Committee are to approve the revised Informed Consent Form before the revised form is used.

10.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the site, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the Clinical Study Protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the site.

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Appendix A Additional Safety Information

Further Guidance on the Definition of a Serious Adverse Event (SAE)

Life threatening

'Life-threatening' means that the patient was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the patient's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (e.g., hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (e.g., bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the patient or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (e.g., neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation

Development of drug dependency or drug abuse

A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?

- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?

- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility

Appendix B COPD Assessment Test (CAT)

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) (1) (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

English for Worldwide

Appendix C EuroQol 5 Dimensions Questionnaire (EQ-5D-5L)

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ☐
I have slight problems in walking about ☐
I have moderate problems in walking about ☐
I have severe problems in walking about ☐
I am unable to walk about ☐

SELF-CARE

I have no problems washing or dressing myself ☐
I have slight problems washing or dressing myself ☐
I have moderate problems washing or dressing myself ☐
I have severe problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ☐
I have slight problems doing my usual activities ☐
I have moderate problems doing my usual activities ☐
I have severe problems doing my usual activities ☐
I am unable to do my usual activities ☐

PAIN / DISCOMFORT

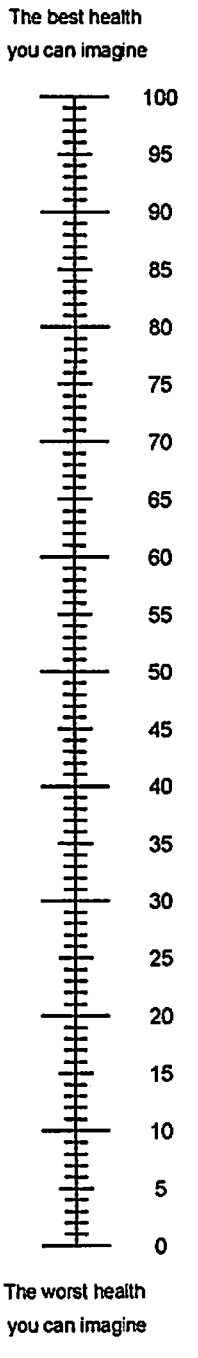
I have no pain or discomfort ☐
I have slight pain or discomfort ☐
I have moderate pain or discomfort ☐
I have severe pain or discomfort ☐
I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION

I am not anxious or depressed ☐
I am slightly anxious or depressed ☐
I am moderately anxious or depressed ☐
I am severely anxious or depressed ☐
I am extremely anxious or depressed ☐

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix D Work Productivity and Activity Impairment Questionnaire - General Health (WPAI-GH)

Work Productivity and Activity Impairment Questionnaire: General Health V2.0 (WPAI:GH)

The following questions ask about the effect of your health problems on your ability to work and perform regular activities. By health problems we mean any physical or emotional problem or symptom. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? ____ NO ____ YES
   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of your health problems? *Include hours you missed on sick days, times you went in late, left early, etc., because of your health problems. Do not include time you missed to participate in this study.*

   _____HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0", skip to question 6.)*

5. During the past seven days, how much did your health problems affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If health problems affected your work only a little, choose a low number. Choose a high number if health problems affected your work a great deal.

Consider only how much health problems affected productivity while you were working.

Health problems had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Health problems completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your health problems affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If health problems affected your activities only a little, choose a low number. Choose a high number if health problems affected your activities a great deal.

Consider only how much health problems affected your ability to do your regular daily activities, other than work at a job.

Health problems had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Health problems completely prevented me from doing my daily activities

CIRCLE A NUMBER

Appendix E Nighttime Symptoms of COPD Instrument and Early Morning Symptoms of COPD Instrument (NiSCI and EMSCI)

Nighttime Symptoms of COPD Instrument (NISCI) and Early Morning Symptoms of COPD Instrument (EMSCI)

- We would like you to complete this diary every day, in the morning, anytime between 7 AM and 11 AM.
- The diary asks you questions about the symptoms of your chronic obstructive pulmonary disease, also called COPD.
- COPD is a lung disease that makes breathing difficult.

The diary is made up of two parts:

1. The first part of the diary asks you a few questions about your COPD symptoms LAST NIGHT.
   - When you think about LAST NIGHT, we would like you to think about the time from when you went to bed last night until you woke up and got out of bed this morning to start your day.
2. The second part of the diary asks you a few questions about your COPD symptoms after you woke up this morning.
   - When you think about THIS MORNING, please think about the time since you got out of bed to start your day.

This is the first part of the diary that asks you about your COPD symptoms LAST NIGHT.

When you think about LAST NIGHT, we would like you to think about the time from when you went to bed last night until you woke up and got out of bed this morning to start your day.

Please complete the NIGHTTIME SYMPTOM diary now.

---

1. **Last night, did you wake up because of your COPD symptoms?**
   ☐ No
   ☐ Yes

1a. **How many times did you wake up because of your COPD symptoms?**
   _____times

---

2. **Did you experience any of the following last night?**

2a. Cough	☐ No	☐ Yes
2b. Wheezing	☐ No	☐ Yes
2c. Shortness of breath	☐ No	☐ Yes
2d. Tightness in your chest	☐ No	☐ Yes
2e. Chest congestion	☐ No	☐ Yes
2f. Difficulty bringing up phlegm	☐ No	☐ Yes

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You indicated that you experienced a cough last night...

2a.i. How severe was your cough?
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

You indicated that you experienced wheezing last night...

2b.i. How severe was your wheezing?
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

You indicated that you experienced shortness of breath last night...

2c.i. How severe was your shortness of breath?
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

You indicated that you experienced tightness in your chest last night...

2d.i. How severe was the tightness in your chest?
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

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You indicated that you experienced chest congestion last night...

2e.i. How severe was your chest congestion?

- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

You indicated that you experienced difficulty bringing up phlegm last night...

2f.i. How severe was the difficulty with bringing up phlegm?

- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

3. Overall, how severe were your COPD symptoms last night?

- ☐ I did not experience any symptoms
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

4. How many puffs of your rescue medication did you take last night?

_____ puffs

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This is the second part of the diary.

This part asks you about your COPD symptoms THIS MORNING.

When you think about THIS MORNING, please think about the time since you got out of bed to start your day.

---

1. **Did you experience any of the following this morning?**

1a. Cough	☐ No	☐ Yes
1b. Wheezing	☐ No	☐ Yes
1c. Shortness of breath	☐ No	☐ Yes
1d. Tightness in your chest	☐ No	☐ Yes
1e. Chest congestion	☐ No	☐ Yes
1f. Difficulty bringing up phlegm	☐ No	☐ Yes

You indicated that you experienced a cough this morning…

1a.i. **How severe was your cough?**
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

You indicated that you experienced wheezing this morning…

1b.i. **How severe was your wheezing?**
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

You indicated that you experienced shortness of breath this morning…

1c.i. **How severe was your shortness of breath?**
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

You indicated that you experienced tightness in your chest this morning…

1d.i. **How severe was the tightness in your chest?**
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

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You indicated that you experienced chest congestion this morning...

1e.i. **How severe was your chest congestion?**
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

You indicated that you experienced difficulty bringing up phlegm this morning...

1f.i. **How severe was the difficulty with bringing up phlegm?**
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

2. **Overall, how severe were your COPD symptoms this morning?**
- ☐ I did not experience any symptoms
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

3. **How much have you limited your activities this morning because of your COPD symptoms?**
- ☐ Not at all
- ☐ A little
- ☐ Moderately
- ☐ A good deal
- ☐ A very great deal

4. **How many puffs of your rescue medication did you take this morning?**
_____puffs

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Appendix F Baseline/Transitional Dyspnea Index (BDI/TDI)

Baseline/Transition Dyspnea Index (BDI/TDI)

BASELINE DYSPNEA INDEX

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 categorised.
____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 categorised.
____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 categorised.
____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

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 vigour 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 he 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.

Instructions for Administration of the Baseline and Transition Dyspnea Index

The objective of the Baseline and Transition Dyspnea Indexes is to measure the severity of breathlessness (sensation of breathlessness, shortness of breath) in symptomatic patients. The Baseline Dyspnea Index (BDI) measures the severity of dyspnea at the beginning of the trial and the Transition Dyspnea Index (TDI) evaluates changes from this baseline (transition period). The test is applicable to patients with dyspnea on exertion or at rest due to respiratory disease. Administration of the Index should be undertaken before any lung physiologic measurements on the test day and the interviewer must be blinded to other parameters evaluated for this patient.

The Dyspnea Indices were devised such that grading breathlessness could be performed as part of obtaining a history from the patient. The indices include the categories Functional Impairment, as well as Magnitude of Task and Magnitude of Effort which provoke breathlessness. The interviewer asks specific questions based on the criteria of the various grades of impairment or change in the mentioned categories. This approach was selected instead of a questionnaire answered by the patient himself in order to allow an interviewer with medical training or background to grade breathlessness in a simple and brief encounter.

The BDI as well as the TDI are composed of the three categories mentioned. The BDI includes five grades of severity from zero (very severe impairment) to four (no impairment) and the categories are summed to create the focal score (zero to twelve). The TDI ranges from minus three (major deterioration) to plus three (major improvement) including a zero score to indicate "no change". Also for the TDI the three categories are added to obtain a focal score ranging from minus nine, including zero, to plus nine. Provision is made for circumstances when dyspnea cannot be rated: in the BDI, score "X" if no information on the severity can be obtained, "W" if there is generally insufficient information, or "Y" if the patient's capacity is compromised by factors other than respiratory. In the TDI, score "Z" if reduction of activities, effort or functional impairment is caused by reasons other than respiratory.

An interviewer, who should be experienced in history taking for respiratory disease, administers the test. The interviewer should be a physician, nurse, respiratory therapist, cardiopulmonary technician or have a similar qualification with advanced knowledge or training concerning dyspnea in respiratory disease. Evaluation and scoring is performed during the interview and needs the same level of experience. It is preferred that the same person conducts all evaluations for each patient.

The initial question addressed to the subject should be "Do you experience shortness of breath?" If the subject answers "No", then the interviewer should ask whether any physical activities cause the subject to experience breathlessness. If the answer to the questions is "Yes", then additional questions follow to achieve the specific grading. Questions concerning the patient's shortness of breath should be open-ended, and concentrate on how the shortness of breath affects his/her daily life, e.g. the maintenance or upkeep of residence, gardening, or shopping. The interviewer should focus on the specific criteria for the severity of breathlessness as specified in the indices and the patient should be rated based on the responses to these questions. The interviewer circles one answer in the index that best describes how the patient's daily activities are affected by his/her respiratory disease.

The interview process at each visit (baseline and follow up) should not take longer than five minutes.

At the baseline visit (BDI):

Functional impairment:
The first component focuses on finding out which types of everyday life functions at home or in his/her job the patient is still able to perform. Are there any activities that he has had to give up or change due to his shortness of breath compared to the level of activity before the onset of his respiratory disease ? (e.g. can he/she mow the lawn or do house work, can he/she climb the stairs to the office or apartment as previously, can he/she walk uphill or cycle as previously, can he/she do the shopping, can he/she dress him/herself, can he/she care for the pet?). It is important that the

interviewer takes notes of the types of activities and the attached form may serve as an example (not part of the CRF) of a record of the identified events that can be referred to at follow up visits for the TDI. Circle the grade of impairment in the BDI.

Magnitude of task:
The second component focuses on the level and extent to which the individual tasks can be performed until breathlessness is noticed. Again, it is important to record the level in the form to be able to compare at follow up visits. Ask which activities make the patient feel breathless (e.g. to what extent can he/she do the daily household chores, can he/she mow the lawn, can he/she cycle on ground level, gentle slopes uphill, moderate slopes uphill, which distance can he/she walk?). Provide the examples of the various grades and then circle a grade for magnitude of task in the index.

Magnitude of effort:
The third component focuses on the level of effort (exertion, vigor) that can be invested to perform the individual tasks. Again allude to individual tasks and define the effort that makes a patient feel breathless (e.g. shortness of breath only with extraordinary effort when mowing the lawn, or can just be done at normal pace, or can do it very slowly, or need many pauses, can do the house work as rapidly as usual, or takes much longer than previously, or need many pauses). Again, it is important to take notes of examples and patient's description to be able to assess changes at follow up visits. Provide the examples of the various grades for magnitude of effort from the index and circle one.

At follow-up visits (TDI):

The TDI measures changes from the baseline state in the three categories. The interviewer refers to his records of the individual patient's reported activities that result in breathlessness, their magnitude of the task required to evoke breathlessness, and the effort of performance possible. The record sheet and grades from the BDI serve as references and for reminding the interviewer as well as the patient of his/her selections before selecting a grade from the TDI. At each follow up visit the interviewer refers back to the BDI and his original records and not to the previous TDI.

Change in Functional Impairment:
Review with the patient his/her functional status and the types of activities performed as recorded at baseline. Ask the patient if there are any changes or modifications in his/her activities since the baseline visit (e.g. has he/she given up or taken on activities). Select a score from the index based on these changes, or circle zero if unchanged.

Magnitude of Task:
Review the level, i.e. magnitude of the specified activities that cause breathlessness. Ask the patient which level now causes breathlessness and if there is a change from baseline (e.g. can he climb less or more flights of stairs, can he/she walk longer or less, can he/she walk steeper or less steep slopes than recorded at the baseline visit?). Select a grade from the index considering that a change of plus/minus one should indicate the minimum that can be recognised by the patient, a plus/minus three means a major change and plus/minus two means any change in between.

Magnitude of Effort:
Review with the patient the effort (exertion, vigor) he/she was able to perform at baseline with the recorded activities until he experienced breathlessness. Ask the patient how much effort now causes breathlessness and whether there is a change from baseline (e.g. does it take more or less time for a certain activity, does he/she need to take less or more pauses and can he perform with more or less effort (exertion, vigor)?). Circle a grade for change in the index or select zero if no change.

Key Reference: Mahler D.A., Weinberg, D.H., Wells, C.K., & Feinstein, A.R. (1984). The measurement of dyspnea: Contents, interobserver agreement and physiologic correlates of two new clinical indexes. Chest, 85, p.751-758.

Dyspnea Recordings at Baseline (BDI)		Date:	Patient Initials:
	Functional Impairment (Type/kind of activities)	**Magnitude of Task (Level, magnitude, extent)**	**Magnitude of Effort (Time needed, pauses, exertion)**
Job			
House Work, Shopping			
Leisure Activities, Gardening			
Social Activities			
Washing/Dressing			
At Rest			
Any Other			
BDI Total Score	Functional Impairment:	Magnitude of Task:	Magnitude of Effort:

Instruction: Describe activities still possible or given up and characterize under the three categories.

3

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