Revised Clinical Study Protocol

Drug Substance	Budesonide/Formoterol
Study Code	D589UC00001
Edition Number	3
Date	

A Phase IIIB, 6-Month, Double-blind, Double-dummy, Randomized, Parallel-group, Multicenter Exacerbation Study of Symbicort® pMDI 160/4.5 µg x 2 Actuations Twice-daily Compared to Formoterol Turbuhaler 4.5 µg x 2 Inhalations Twice-daily in COPD Patients

The RISE study – Revealing the Impact of Symbicort in reducing Exacerbations in COPD

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

AstraZeneca Research and Development site representative

_____ _____

Date

The following Amendment(s) and Administrative Changes are included in this revised protocol:

Amendment No.	Date of Amendment	Local Amendment No.	Date of local Amendment

Administrative change No.	Date of Administrative Change	Local Administrative change No.	Date of local Administrative Change

PROTOCOL SYNOPSIS

The RISE study – Revealing the Impact of Symbicort in reducing Exacerbations in COPD

The RISE study – Revealing the Impact of Symbicort in reducing Exacerbations in COPD

International Co-ordinating Investigator

Study site(s) and number of subjects planned

Approximately 130 study sites worldwide in about 9 countries will randomize a total of 1136 subjects. The number of subjects, study sites and countries may increase depending on the result of the blinded sample size re-estimation based on the exacerbation rate.

Study period	Phase of development
Estimated date of first subject enrolled	Phase IIIB
Estimated date of last subject completed	

Study design

This is a 26-week, double-blind, double-dummy, randomized, parallel-group, multicenter phase IIIB study to evaluate efficacy in reducing exacerbations with Symbicort® pressurized metered-dose inhaler (pMDI) 160/4.5 µg x 2 actuations BID or formoterol Turbuhaler® 4.5 µg x 2 inhalations BID in subjects with moderate to very severe chronic obstructive pulmonary disease (COPD). The study will randomize approximately 1136 subjects. The number of subjects, study sites and countries may increase depending on the result of the blinded sample size re-estimation based on the exacerbation rate.

After the enrollment visit the entry criteria will be confirmed and the subject will enter a 4-week run-in period with Symbicort pMDI. Subjects who still meet the eligibility criteria will thereafter be randomized to a 26-week treatment period. A final follow-up telephone call will be conducted at week 28.

Objectives

Primary Objective:	**Outcome Measure:**
To compare the efficacy in reducing exacerbations with Symbicort pMDI 160/4.5 µg x 2 actuations BID versus formoterol Turbuhaler 4.5 µg x 2 inhalations BID in COPD subjects	The rate of moderate and severe COPD exacerbations defined as: Worsening of ≥2 major symptoms or worsening of 1 major symptom together with ≥1 minor symptom for ≥2 consecutive days. Moderate exacerbation: treatment of symptoms with systemic corticosteroids (≥3 days) and/or antibiotics. Severe exacerbation: symptoms that require hospitalization (including >24 hours in ED/urgent care setting). Major symptoms: • Dyspnea • Increase in sputum volume • Increase in sputum color/purulence Minor symptoms: • Sore throat • Colds (nasal discharge and/or nasal congestion) • Fever without other cause • Increased cough • Increased wheeze

Secondary Objective:	**Outcome Measure:**
To compare Symbicort pMDI and formoterol Turbuhaler treatments on the time to the first COPD exacerbation	• Time to first moderate or severe COPD exacerbation
To compare Symbicort pMDI and formoterol Turbuhaler treatments on health status/health-related quality of life	• St. George's Respiratory Questionnaire (SGRQ)
To compare Symbicort pMDI and formoterol Turbuhaler treatments on pulmonary function	• Pre-dose/pre-bronchodilator forced expiratory volume in one second (FEV_1) at the study site

To compare Symbicort pMDI and formoterol Turbuhaler treatments on rescue medication use	• Total rescue medication use (average puffs/day)
To compare Symbicort pMDI and formoterol Turbuhaler treatments on nocturnal awakenings	• Nights with awakening due to COPD

Safety Objective:	**Outcome Measure:**
To demonstrate the safety of Symbicort pMDI compared to that of formoterol Turbuhaler in subjects with COPD	• Adverse events (AE) • Serious adverse events (SAE) • Discontinuation of investigational product (IP) due to AE (DAE) • Vital signs

Target subject population

The subjects enrolled will be men or women, ≥40 years of age, with a clinical diagnosis of COPD, and with symptoms for more than 1 year, current or previous smoker with a history equivalent to 10 or more pack years, post-bronchodilator FEV_1/FVC <0.7 (70%) and FEV_1 ≤70% of predicted normal value, a score of ≥2 on the modified medical research council (MMRC) dyspnea scale at Visit 2, a documented history of at least 1 COPD exacerbation requiring a course of systemic corticosteroids and/or hospitalization within 2-52 weeks before Visit 1, and no history of asthma at or after 18 years of age.

Duration of treatment

Following the enrollment visit (Week –5) the subject will enter a 4-week run-in period, which is followed by a 26-week double-blind, double-dummy, randomized treatment period. A final follow-up telephone call will be conducted 2 weeks after the last study visit (Week 28). The total planned study duration is 33 weeks.

Investigational product, dosage and mode of administration

- Symbicort pMDI, budesonide/formoterol, 160/4.5 µg x 2 actuations BID, for oral inhalation
- Formoterol Turbuhaler, 4.5 µg x 2 actuations BID, for oral inhalation

Rescue medication

The rescue medication is administered as needed for relief of bronchospasm.

- Albuterol pMDI (US), 90 µg x 2 actuations, for oral inhalation

- Salbutamol pMDI (outside US), 100 µg x 2 actuations, for oral inhalation

Statistical methods

The primary efficacy variable is the exacerbation rate. The exacerbation rate in the Symbicort pMDI group will be compared to exacerbation rate in the formoterol Turbuhaler group using a negative binomial model including covariates of treatment group, country/region and the number of exacerbations in the year before the study. The logarithm of the follow-up time will be used as an offset variable in the model.

Time to first exacerbation will be analyzed to explore the extent to which treatment with Symbicort pMDI delays the time to first exacerbation compared with formoterol Turbuhaler. A Cox proportional hazard model will be fitted to data with the covariates of treatment, country/region and number of exacerbations in the year before the study.

The change from baseline in pre-dose FEV_1 will be compared between Symbicort pMDI and formoterol Turbuhaler using a mixed model repeated measures analysis on subjects with a baseline pre-dose/pre-bronchodilator FEV_1 and at least one post-randomization value. The dependent variable will be the change from baseline in FEV_1 at visits during the randomized treatment period. Treatment group will be fitted as the explanatory variable, and country/region and the baseline (Visit 3) pre-bronchodilator value will be used as covariates. Visit will be used as a categorical variable, and the variance-covariance matrix will be assumed to be unstructured. This model will also be used for the analysis of FVC, rescue medication use, nighttime awakenings and SGRQ.

The proportion of subjects with at least one exacerbation will be compared between treatment groups via a logistic regression. Treatment, region/country and the number of exacerbations in the year before the study will be included in the model. The proportion of SGRQ responders will also be analyzed using this method.

For efficacy variables, sensitivity analyses will be performed which include data captured after subjects have prematurely terminated their use of the study medication.

AEs will be summarized by means of counts summaries by study period (treatment period and follow-up period). AEs will be listed for each subject and summarized by System Organ Class (SOC) and Preferred Term (PT) assigned to the event by Medical Dictionary for Regulatory Activities (MedDRA).

Results for vital sign and physical examination variables will be summarized by visit and treatment group using standard summary statistics and plots as appropriate. Laboratory data will be collected and ECGs will be performed only prior to randomization.

Because the assumed exacerbation rate in the control (formoterol) group and assumed shape parameter from the negative binomial model can have a large impact on the sample size necessary to achieve a stated power (90% in our case), a blinded estimate of the formoterol exacerbation rate and shape parameter is planned. The review will be performed before the last patient is randomized and may result in an increase in sample size. The potential increase in sample size will be capped at a 50% increase above the planned number of 568 subjects per treatment group.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATS	American Thoracic Society
BID	Twice daily
CI	Confidence interval
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form (electronic/paper)
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CT	Computed tomography
CXR	Chest radiography
DAE	Discontinuation of Investigational Product (IP) due to Adverse Event
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDiary	Electronic diary
EoT	End of Treatment
ePRO	Electronic Patient Reported Outcome
ERS	European Respiratory Society
FDA	Food and Drug Administration (United States)
FEV_1	Forced Expiratory Volume in one second
Formoterol	Formoterol fumarate dihydrate
FVC	Forced Vital Capacity

Abbreviation or special term	Explanation
GCP	Good Clinical Practice
GLI	Global Lung Function Initiative
GMP	Good Manufacturing Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
Hb	Hemoglobin
HCP	Health Care Provider
HIV-1/2	Human immunodeficiency virus-1/2
IB	Investigator's brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICS	Inhaled corticosteroids
IM	Intramuscular
International Co-ordinating Investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the Investigators and/or activities internationally
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent to Treat
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LABA	Long-acting β_2-agonist
LAMA	Long-acting muscarinic antagonist
LTOT	Long Term Oxygen Therapy
MedDRA	Medical Dictionary for Regulatory Activities
MMRC	Modified Medical Research Council dyspnea scale
PI	Principal Investigator
pMDI	Pressurized Metered-Dose Inhaler
PN	Predicted Normal
PRO	Patient Reported Outcome
PT	Preferred term

Abbreviation or special term	Explanation
SABA	Short-acting β_2-agonist
SAE	Serious Adverse Event
SAMA	Short-acting inhaled anticholinergics
SAP	Statistical Analysis Plan
SDV	Source Data Verified
SGRQ	St. George's Respiratory Questionnaire
sNDA	Supplemental New Drug Application
SOC	System Organ Class
SPC	Summary of Product Characteristics
ULN	Upper Limit of Normal
WBC	White Blood Cell
WBDC	Web Based Data Capture

1. INTRODUCTION

1.1 Background and rationale for conducting this study

Chronic obstructive pulmonary disease (COPD) is a significant cause of morbidity and mortality worldwide. In contrast to other chronic diseases, COPD is increasing in prevalence and is projected to be the third-leading cause of death and disability worldwide by 2020 (Global Initiative for Chronic Obstructive Lung Disease (GOLD 2013)).

Acute exacerbations of COPD are responsible for a large portion of the economic burden of COPD. An acute exacerbation of COPD is defined as a sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD (Rodriquez-Roisin, 2000). In addition to a substantial economic burden, acute exacerbations of COPD are also responsible for much of the morbidity and mortality from COPD. Patients with frequent acute exacerbations of COPD show associated increased inflammation and accelerated decline in lung function as compared to patients with infrequent exacerbations (Donaldson et al 2002). According to the current GOLD guidelines (GOLD 2013), inhaled corticosteroids (ICS)/long-acting β_2-agonists (LABAs) as a class are listed as a first-choice treatment option for COPD patients considered high risk, based on reduced lung function and/or exacerbation history.

Symbicort® pressurized metered-dose inhaler (pMDI) is a fixed-dose combination product containing budesonide, an ICS, and formoterol fumarate dihydrate (formoterol), a LABA. In the US, Symbicort pMDI is indicated for the treatment of asthma in patients 12 years of age and older, and for the twice-daily maintenance treatment of airflow obstruction in COPD, including chronic bronchitis and emphysema. Symbicort pMDI is not approved in the US to reduce exacerbations in patients with COPD. However, two other ICS/LABA combination products are currently Food and Drug Administration approved for this indication. Symbicort pMDI is approved in 25 countries for the treatment of asthma and more than 10 countries for the treatment of COPD.

Three clinical trials have studied the effect of Symbicort pMDI on COPD exacerbations. The data from these 3 studies demonstrate that Symbicort reduces exacerbations in the COPD population (Sharafkhaneh et al 2012, Tashkin et al 2008, Rennard et al 2009). The definition of an exacerbation used in these studies was event based (defined as change in treatment with oral corticosteroids or hospitalization) and was implemented prior to formal FDA Guidance for Industry (FDA Guidance for Industry 2007) recommending the use of a symptom-based definition to define COPD exacerbations. The guidance included the following: 'Criteria to consider in defining exacerbation include worsening of shortness of breath, increased sputum volume, increased purulence of sputum, worsening in symptoms requiring changes in treatment, or worsening of symptoms requiring urgent treatment or hospitalization'.

This study, 'Revealing the Impact of Symbicort in reducing Exacerbations in COPD' (RISE study), is being conducted to provide data on the effect of Symbicort pMDI on reducing COPD exacerbations. This RISE study will use a symptom-based definition correlating changes in symptoms to treatment interventions for COPD exacerbations.

1.2 Rationale for study design, doses and control groups

The objective of this study is to compare efficacy of Symbicort pMDI 160/4.5 μg x 2 actuations BID to formoterol Turbuhaler 4.5 μg x 2 inhalations BID in reducing COPD exacerbations. The trial is required to support an expanded label claim for Symbicort pMDI to include reducing exacerbations in patients with COPD.

The primary outcome is the exacerbation rate. Secondary outcomes include time to first COPD exacerbation, patient reported outcomes (PRO) and pre-dose forced expiratory volume in one second (FEV_1).

In the US, Symbicort pMDI 160/4.5 μg x 2 actuations BID is indicated for the treatment of asthma in subjects 12 years of age and older, and for the maintenance treatment of airflow obstruction in subjects with COPD including chronic bronchitis and emphysema. Furthermore, Symbicort pMDI 160/4.5 μg x 2 actuations BID showed reductions in the number of overall COPD exacerbations (defined differently as compared to the present study) per patient-treatment year over formoterol Turbuhaler 4.5 μg x 2 inhalations BID treatment group in subjects with COPD, without compromising safety.

The comparison with the formoterol alone treatment arm will demonstrate the expected contribution of the budesonide component of Symbicort in reducing COPD exacerbations.

Target subject population has similar or slightly less severe disease with a post-bronchodilator $FEV_1 \leq 70\%$ as compared to previous COPD Symbicort studies into which subjects with a pre-bronchodilator $FEV_1 \leq 50\%$ were recruited.

The present study design closely resembles previous Symbicort pMDI studies demonstrating reduced exacerbations, but with the important differences that a symptom-based definition will be used to define COPD exacerbations and a study duration of 6 months. The 6-month study duration was chosen mainly to reduce the number of patients withdrawing from study participation. Previous data indicate that patients on less intensive treatment tend to withdraw more, reducing treatment effect over time (Keene OM et al 2007). Subjects will be required to have at least 1 exacerbation in the year prior to enrollment.

Subjects will be assessed for eligibility at Visit 1 and at Visit 2. Subjects fulfilling the eligibility criteria at Visit 2 will enter a 4-week run-in period and will be treated with Symbicort pMDI in order to standardize their clinical condition before randomization. Short-acting β_2-agonists (SABA) will be provided as rescue medication (see Section 7.7, Table 8) for use as needed from Visit 1 until the end of randomized treatment period.

Other LABAs, long-acting muscarinic antagonists (LAMA), LAMA/LABA combinations, other ICS/LABA combinations, other ICSs, phosphodiesterase inhibitors and/or xanthine-containing derivatives will not be allowed during run-in or randomized treatment (see Section 4, Table 1 and Section 7.7). However, patients treated with short-acting inhaled anticholinergics (SAMA) at a stable dose before enrollment will be permitted to continue that same treatment during the run-in and the randomized periods.

At Visit 3 subjects will be assessed for eligibility and must meet all inclusion/exclusion criteria in order to be randomized. Qualifying subjects will then be randomized to 1 of 2 possible treatment arms for the duration of the 6-month treatment period. Treatment plan assignments will be communicated utilizing an Interactive Voice Response System (IVRS) or Interactive Web Response System (IWRS). Including randomization, the study subjects will attend a total of 7 visits. At the conclusion of randomized treatment, subjects will attend a final visit and will be prescribed appropriate COPD medication according to the investigator's judgement and local medical practice. Subjects will be contacted by telephone 2 weeks after the final visit to collect any adverse events (AEs). Chest radiography (CXR) (frontal and lateral) will be required within 72 hours of all reported cases of pneumonia.

1.3 Benefit/risk and ethical assessment

The efficacy and safety profile of Symbicort pMDI in COPD is well established for the maintenance treatment of COPD. Although formoterol Turbuhaler is not approved in all countries, formoterol is approved for maintenance treatment of bronchoconstriction in subjects with COPD in many countries. Subjects randomized to the formoterol only arm will still benefit from a medication that is approved for the treatment of COPD as a monoproduct. Additionally, subjects using SAMA (at a stable dose) can continue this treatment during the study. Patients will be withdrawn from LAMA and other maintenance medication (see

Table 7) at run-in. All patients will be assessed for deterioration using explicit criteria prior to randomization. These criteria are defined in Section 3.3. The risk/benefit profile is considered to be acceptable for both treatment arms.

The study requires the documentation of a standard CXR within 6 months of enrollment. In patients with COPD, radiographs of the chest are frequently done to assess acute worsening symptoms. Additionally, chest radiographs are part of the standard diagnostic algorithm to assess suspected pneumonia.

The dose of radiation from standard chest radiographs is minimal and considered low risk. According to the United States Nuclear Regulatory Commission, the average American receives a radiation dose of about 620 millirem each year with half coming from background radiation and half coming from man-made sources including medical, commercial and industrial sources (United States Nuclear Regulatory Commission). The radiation dose from an x-ray of the chest is 10 millirem (in contrast to a full body CT scan

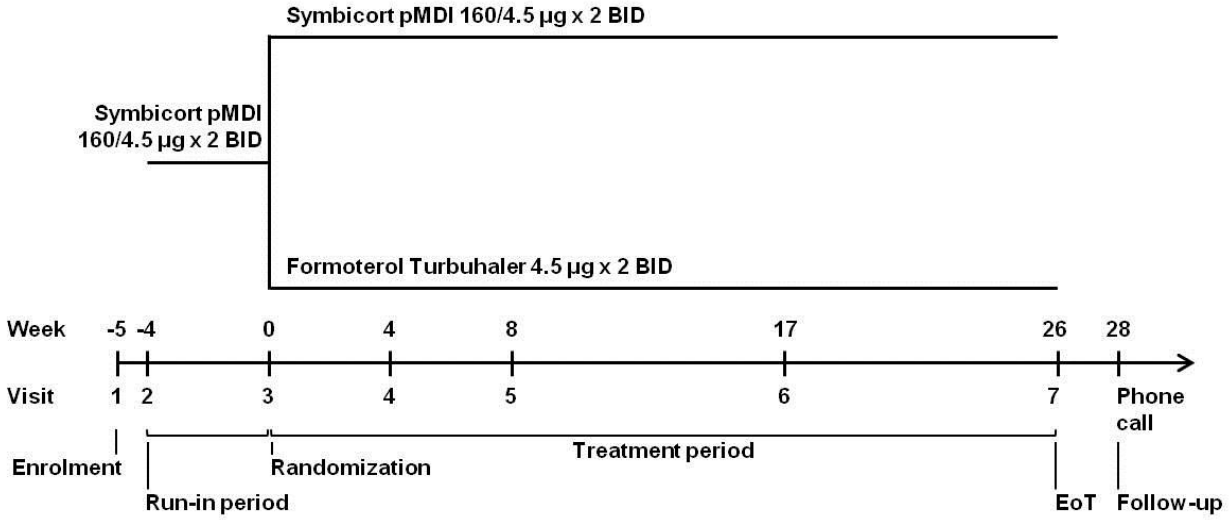
of 1,000 millirem). The requirement for CXR in this study introduces minimal radiation exposure and is a standard diagnostic test for pneumonia.

1.4 Study Design

This is a 26-week, double-blind, double-dummy, randomized, parallel-group, multicenter phase IIIB study to evaluate efficacy in reducing exacerbations with Symbicort pMDI 160/4.5 µg x 2 actuations BID or formoterol Turbuhaler 4.5 µg x 2 inhalations BID in subjects with moderate to very severe COPD. The study will randomize approximately 1136 subjects. The number of subjects may increase depending on the result of the blinded sample size re-estimation based on the exacerbation rate.

After the enrollment visit the entry criteria will be confirmed and the subject will enter a 4-week run-in period with Symbicort pMDI. At Visit 3, subjects who still meet the eligibility criteria will thereafter be randomized to a 26-week treatment period. A final follow-up telephone call will be conducted at week 28.

Figure 1 Study flow chart



2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	**Outcome Measure:**
To compare the efficacy in reducing exacerbations with Symbicort pMDI 160/4.5 µg x 2 actuations BID versus formoterol Turbuhaler 4.5 µg x 2 inhalations BID in COPD subjects	The rate of moderate and severe COPD exacerbations defined as: Worsening of ≥2 major symptoms or worsening of 1 major symptom together with ≥1 minor symptom for ≥2 consecutive days. Moderate exacerbation: treatment of symptoms with systemic corticosteroids (≥3 days) and/or antibiotics. Severe exacerbation: symptoms that require hospitalization (including >24 hours in ED/urgent care setting). Major symptoms: • Dyspnea • Increase in sputum volume • Increase in sputum color/purulence Minor symptoms: • Sore throat • Colds (nasal discharge and/or nasal congestion) • Fever without other cause • Increased cough • Increased wheeze

2.2 Secondary objectives

Secondary Objective:	**Outcome Measure:**
To compare Symbicort pMDI and formoterol Turbuhaler treatments on the time to the first COPD exacerbation	• Time to first moderate or severe COPD exacerbation
To compare Symbicort pMDI and formoterol Turbuhaler treatments on health status/health-related quality of life	• St. George's Respiratory Questionnaire (SGRQ)
To compare Symbicort pMDI and formoterol Turbuhaler treatments on pulmonary function	• Pre-dose/pre-bronchodilator FEV_1 at the study site

To compare Symbicort pMDI and formoterol Turbuhaler treatments on rescue medication use	• Total rescue medication use (average puffs/day)
To compare Symbicort pMDI and formoterol Turbuhaler treatments on nocturnal awakenings	• Nights with awakening due to COPD

2.3 Safety objectives

Safety Objective:	**Outcome Measure:**
To demonstrate the safety of Symbicort pMDI compared to that of formoterol Turbuhaler in subjects with COPD	• AE • Serious adverse events (SAE) • Discontinuation of investigational product (IP) due to AE (DAE) • Vital signs

3. SUBJECT SELECTION, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each subject 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 subjects should fulfill the following criteria:

1. Signed Informed Consent at Visit 1 obtained prior to conducting any study-related procedures including withdrawal of medications.

2. Outpatients; men or women ≥40 years of age.

3. A current clinical diagnosis of COPD with COPD symptoms for more than 1 year, according to the GOLD guidelines.

4. Current or previous smoker with a smoking history equivalent to 10 or more pack years (1 pack year = 20 cigarettes smoked per day for 1 year).

5. Post-bronchodilator FEV_1/forced vital capacity (FVC) <0.7 (70%) and FEV_1 ≤70% of predicted normal (PN) value.

6. Documented use of a short-acting inhaled bronchodilator (β_2-agonists or anticholinergics) as rescue medication within 6 months prior to study start.

7. A score of ≥2 on the modified medical research council (MMRC) dyspnea scale.

8. Documented history of ≥1 moderate or severe COPD exacerbation(s) that required treatment with systemic (oral, IM, IV) corticosteroids (a minimum 3 day course of an oral corticosteroid treatment or single depot corticosteroid injection), or hospitalization (defined as an inpatient stay or >24 hour stay in an observation area in the emergency department or other equivalent facility depending on the country and healthcare system) within 2-52 weeks before Visit 1 (i.e., not within the 14 days prior to Visit 1). A history of an exacerbation treated exclusively with antibiotics will not be considered adequate.

9. Ability to comply with all study procedures (including electronic diary (eDiary) completion) and to satisfactorily take study medication.

10. Able to read, write and use the electronic device.

Additional criteria to be checked prior to run-in:

11. Compliance with eDiary, defined as complete reports i.e. both morning and evening eDiary entries the same day for at least 4 days during the enrollment period.

Additional criteria to be checked prior to randomization:

12. Compliance with eDiary, defined as complete reports in morning and evening eDiary for at least 20 mornings (any 20) and 20 evenings (any 20) of the last 28 days of the run-in period.

13. Compliance with BID run-in medication, defined as at least 20 mornings (any 20) and 20 evenings (any 20) of the last 28 days of the run-in period.

3.2 Exclusion criteria

Any of the following is regarded as a criterion for exclusion from the study:

1. History of asthma at or after 18 years of age (except when the investigator in his or her medical judgment determines the prior diagnosis of asthma is unrelated to subject current condition – e.g. misdiagnosis, premature diagnosis or resolution of early onset disease).

2. Subjects with significant or unstable ischemic heart disease, arrhythmia, cardiomyopathy, heart failure (including significant cor pulmonale), uncontrolled hypertension as defined by the Investigator, or any other relevant cardiovascular disorder as judged by the Investigator.

3. Known homozygous alpha-1 antitrypsin deficiency.

4. Any significant disease or disorder (e.g., gastrointestinal, liver, renal, neurological, musculoskeletal, endocrine, metabolic, malignant, psychiatric, major physical impairment) which, in the opinion of the Investigator, may either put the subject at risk because of participation in the study, or influence the results of the study, or the subject's ability to participate in the study.

5. A history of malignancy (except basal cell carcinoma) within the past 5 years.

6. Active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, primary pulmonary hypertension, interstitial lung disease, or other active pulmonary diseases.

7. Subjects who have needed additions or alterations to their usual maintenance or change in formulation of rescue therapy for COPD due to worsening symptoms within the 14 days prior to Visit 1 and up to Visit 3.

8. CXR (frontal and lateral) with suspicion of pneumonia or other condition/abnormality that will require additional investigation/treatment, or put the subject at risk because of participation in the study.

9. Risk factors for pneumonia: immune suppression (HIV, lupus) or other risk for pneumonia (e.g. neurological disorders affecting control of the upper airway, such as Parkinson's disease, myasthenia gravis, etc.).

10. Pneumonia not resolved within 14 days of Visit 1.

11. Moderate or severe COPD exacerbation that has not resolved within 14 days prior to Visit 1 or a moderate or severe COPD exacerbation that occurs between Visit 1 and Visit 2.

12. Long-term oxygen therapy (LTOT) or nocturnal oxygen therapy required for greater than 12 hours a day.

13. Subjects who are currently in the intensive rehabilitation phase or scheduled to begin new participation (intensive rehabilitation phase) in a pulmonary rehabilitation program during the study or have started a new pulmonary rehabilitation program within 60 days of Visit 1. Subjects in the maintenance phase of pulmonary rehabilitation program are not excluded.

14. Treatment with oral, parenteral, or intra-articular corticosteroids within 2 weeks prior to Visit 1.

15. Omalizumab or any other monoclonal or polyclonal antibody therapy taken for any reason within 6 months prior to Visit 1.

16. Known or suspected hypersensitivity to the study therapy or excipients of the investigational products (IPs). In addition, patients with a history of severe milk protein allergy that, in the opinion of the investigator, contraindicates the patient's participation will also be excluded.

17. Known or suspected history of alcohol or drug abuse within the last 2 years.

18. Planned hospitalization or significant surgical procedure during the study.

19. Pregnancy, breast-feeding or planned pregnancy during the study; fertile women not using acceptable contraceptive measures, as judged by the Investigator. Female subjects who are not post-menopausal or surgically sterile must have a negative pregnancy test prior to randomization and must comply with contraception methods.

20. Subjects who have been randomized in a clinical study and received investigational drug in the last 30 days prior to Visit 1, or longer if the medication has a half-life long enough to potentially expose the subject to any significant systemic exposure, or who have been previously allocated a randomization code in this study.

21. Subjects with a history of a condition associated with poor compliance or with a history of poor compliance to therapy.

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

23. History of seropositivity for hepatitis B surface antigen, hepatitis C, or human immunodeficiency virus (HIV-1 or HIV-2).

24. Any clinically relevant abnormal findings in physical examination, clinical chemistry, hematology, urinalyses, vital signs or electrocardiogram (ECG), which in the opinion of the Investigator, may put the subject at risk because of his/her participation in the study.

25. Planned donation of blood during the entire study period.

26. Subjects with lung volume reduction surgery within the 12 months prior to Visit 1. Subjects with history of partial or total lung resection (only single lobe or segmentectomy is acceptable).

27. Clinical worsening during run-in in accordance with Section 3.3.

Procedures for withdrawal of incorrectly enrolled subjects see Section 3.4.1.

3.3 Explicit criteria to define clinical worsening during run-in

Subjects should not be randomized in the study if during the run-in period one of the following occurs:

1. Patient experiences deterioration in their COPD symptoms that would qualify as an exacerbation because it requires treatment with systemic corticosteroids, antibiotics, hospitalization (defined as an inpatient stay or >24 hour stay in an observation area in the emergency department or other equivalent facility depending on the country and healthcare system)

2. Patient increases use of rescue medication >4 puffs/day from baseline for 2 consecutive days. Baseline rescue medication use will be determined by the mean puffs/day reported for a minimum of 4 complete reports i.e. both morning and evening eDiary entries the same day from Visit 1 to Visit 2.

3. Investigator determines that due to worsening of symptoms, patients needs additional COPD medication (e.g. step-up treatment to ICS/LABA + LAMA)

3.4 Subject enrollment and randomization

Procedures for withdrawal of incorrectly enrolled or randomized subjects see Section 3.4.1.

Investigator(s) should keep a record, the subject screening log, of subjects who entered pre-study screening.

The Investigator(s) will:

1. Obtain signed informed consent from the potential subject before any study specific procedures are performed.

2. Assign potential subject a unique enrollment number, beginning with ‘E#’ via IVRS/IWRS.

3. Determine subject eligibility. See Section 3.1 and 3.2

4. Assign eligible subject unique randomization code via IVRS/IWRS.

If a subject withdraws from participation in the study, then his/her enrollment/randomization code cannot be reused.

A subject who experiences a COPD exacerbation within 14 days prior to Visit 1 or during the enrollment and run-in period may be re-screened (checked for eligibility criteria) once, no sooner than 14 days after their last dose of systemic steroids and/or antibiotics (see Section 4.1.3).

3.4.1 eDiary compliance requirements for Enrollment and Run-in

Study period	1. eDiary tasks
Enrollment period	• Rescue medication use during enrollment will be recorded to define baseline use prior to Run-in. Baseline rescue medication use will be determined by the mean puffs/day reported for a minimum of 4 complete reports i.e. both morning and evening eDiary entries the same day from Visit 1 to Visit 2 • If the subject is eligible, manually move subject from enrollment to Run-in in the eDiary
Run-in period	Prior to randomization: • Compliance with eDiary, defined as complete reports in morning and evening eDiary for at least 20 mornings (any 20) and 20 evenings (any 20) of the last 28 days of the run-in period • Compliance with BID run-in medication, defined as at least 20 mornings (any 20) and 20 evenings (any 20) of the last 28 days of the run-in period • If the subject is eligible, manually move subject from Run-in to Treatment in the eDiary

3.5 Procedures for handling incorrectly enrolled or randomized subjects

Subjects who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. Please see Section 4.1.3 for re-screening criteria. Subjects who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomized or initiated on treatment, and must be withdrawn from the study.

Where a subject does not meet all the eligibility criteria but is randomized 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 subject from treatment. The AstraZeneca study physician must ensure all decisions are appropriately documented.

3.6 Methods for assigning treatment groups

The Biometrics and Information Sciences group at AstraZeneca or a designee will be responsible for generating the randomization scheme. Subjects will be allocated to the two treatment groups in a 1:1 ratio. The randomization will be stratified by country/region and the randomization numbers will be grouped in blocks.

Specific information concerning the use of the IWRS/IVRS will be provided in a separate manual. Randomized subjects who discontinue from the IP administration will not be replaced.

3.7 Methods for ensuring blinding

All study medication will be labelled using a unique medication identification number (Kit ID) that is linked to a treatment arm. IVRS/IWRS will assign the study medication to be dispensed to each subject at each drug-dispensing visit. This is a double-dummy study and two different devices, pMDI and Turbuhaler, will be used. All study subjects will get two devices, one pMDI and one Turbuhaler, however only one of the devices will contain study drug, the other one will contain placebo.

3.8 Methods for unblinding

Individual treatment codes, indicating the treatment randomization for each randomized subject, will be available to the Investigator(s) or pharmacists from the IVRS/IWRS. Routines for this will be described in the IVRS/IWRS 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 subject requires knowledge of the treatment randomization. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to subject 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 subject have been made and documented.

3.9 Restrictions

- Subjects should avoid taking inhaled bronchodilators prior to spirometry (see Section 7.7, Table 4)
- Donation of blood is not allowed throughout the study
- Restrictions regarding concomitant medication are described in Section 7.7

3.10 Discontinuation of investigational product

Subjects may be discontinued from IP in the following situations:

- Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment
- AE

- Severe non-compliance with the study protocol
- Pregnancy
- Safety reasons as judged by the Investigator and/or AstraZeneca
- Intake of certain concomitant medications may necessitate withdrawal (see Section 7.7)

3.10.1 Procedures for discontinuation of a subject from investigational product

At any time, subjects are free to discontinue IP or withdraw from the study (i.e., IP and assessments – see Section 3.11), without prejudice to further treatment. A subject that decides to discontinue IP will always be asked about the reason(s) and the presence of any AEs.

Subjects who prematurely discontinue treatment should return to the study site and complete the procedures described for the end of treatment (EoT) as soon as possible or preferably within 2 days of discontinuation of the IP. The subject will bring the ePRO device to this visit. It is highly recommended that all study procedures, including ePRO completion, are continued until Visit 7, if possible.

At EoT visit, the subject will be given two options on how to be followed up:

- Ideally the subject should be encouraged to return for all scheduled study visits and procedures including continuing eDiary completion until he/she completes a total of 26 weeks in the study.
- If the subject cannot comply or does not wish to comply with the option above, he/she will be offered to be followed up via telephone calls at the same intervals as the planned visits in the Study Plan (Section 4, Table 1) while continuing eDiary completion, until the subject completes 26 weeks in the study. No further procedures will be performed.

The subject’s decision needs to be documented in the medical record.

The key elements that should be collected in the two above options are AEs/SAEs, changes in concomitant medications, smoking status and COPD exacerbation information.

The Investigator will be instructed to force data transfer from the ePRO device on the day of EoT visit and then re-dispense the device to the subject. ePRO alerts will still be in place to notify both the subject and the study site of a potential symptom worsening event (see Section 5.3.2.1). The subject will be asked to return the ePRO device to the study site after the subject completes participation in the study.

- If the subject refuses the two previous options, he/she will need to sign the specific withdrawal of consent portion of the informed consent form (ICF) and return all study materials to the study site.

AstraZeneca will continue to provide rescue medications from Visit 1 to end of treatment Visit 7 (see Section 7.7) unless the subject withdraws consent. It is the Investigator's responsibility to fully evaluate the subject upon discontinuation or withdrawal to ensure that the subject receives appropriate treatment according to his/her clinical status/condition.

If a subject is withdrawn from study, see Section 3.11.

3.11 Criteria for withdrawal

3.11.1 Screen failures

Screening/enrollment failures are subjects who do not fulfill the eligibility criteria for the study, and therefore must not be randomized. These subjects should have the reason for study withdrawal recorded as 'Incorrect Enrollment' (i.e., subjects do not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not randomized subjects). Subjects discontinuing the study prior to Visit 3 will be classified as screen failures.

3.11.2 Withdrawal of the informed consent

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

A subject who withdraws consent will always be asked about the reason(s) and the presence of any AE. The Investigator will follow up AEs outside of the clinical study. The subject will return ePRO devices.

If a subject withdraws from participation in the study, then his/her enrollment/randomization code cannot be reused. Withdrawn subjects will not be replaced.

Withdrawal of consent should be documented by the Investigator in the case report form (CRF) and in the medical records. If possible, the subject should complete EoT visit at the time of withdrawal of consent.

3.12 Discontinuation of the study

The study may be stopped if, in the judgment of AstraZeneca, trial subjects are placed at undue risk because of clinically significant findings that are not considered to be consistent with continuation of the study.

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

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

4. STUDY PLAN AND TIMING OF PROCEDURES

Table 1 Study Plan

Study Plan	**Enroll-ment**	**Run-in**	**Rando-mization**	**Treatment**			**EoT**	**Follow-up**	**UNS[k]**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8[a]**	
Week[m]	**-5**	**-4**	**0**	**4**	**8**	**17**	**26**	**28**	
Day[m] (±Visit Window)	**10(±3) before V2**	**-28 to -35[l]**	**0**	**30(±3)**	**60(±3)**	**120(±7)**	**180(±7)**	**14(±3) after V7**	
Informed consent	**X**								
Inclusion/exclusion criteria	**X**	**X**	**X**						
Randomization			**X**						
Vital signs		**X**	**X**	**X**	**X**	**X**	**X**		**X**
Demography	**X**								
Complete physical examination		**X[b]**					**X[c]**		**X**
Brief physical examination			**X**	**X**	**X**	**X**			
Pregnancy test[d]	**X**						**X**		
Medical history		**X**							
Surgical history		**X**							
History of COPD exacerbation	**X**								
Acute exacerbation of COPD evaluation		**X**	**X**	**X**	**X**	**X**	**X**		**X**
Smoking history (pack years)	**X**								
Smoking status		**X**	**X**	**X**	**X**	**X**	**X**		**X**
CXR[e]	**X**								

Study Plan	**Enroll-ment**	**Run-in**	**Rando-mization**	**Treatment**			**EoT**	**Follow-up**	**UNS[k]**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8[a]**	
Week[m]	**-5**	**-4**	**0**	**4**	**8**	**17**	**26**	**28**	
Day[m] (±Visit Window)	**10(±3) before V2**	**-28 to -35[l]**	**0**	**30(±3)**	**60(±3)**	**120(±7)**	**180(±7)**	**14(±3) after V7**	
Clinical chemistry, hematology, urinalysis, ECG[f]	**X**								
Pre-bronchodilator spirometry[g]		**X**	**X**	**X**	**X**	**X**	**X**		
Post-bronchodilator spirometry[h]		**X**							
Study medication training	**X**	**X**	**X**						
Discontinue medication and start unblinded Symbicort pMDI administration		**X**							
Discontinue unblinded Symbicort pMDI administration			**X**						
Study drug (D=Dispense, R=Return)			**D**	**D/R**	**D/R**	**D/R**	**R**		
Rescue medication (D=Dispense, R=Return)	**D**	**D/R[i]**	**D/R[i]**	**D/R[i]**	**D/R[i]**	**D/R[i]**	**R**		
SGRQ[j]		**X**	**X**	**X**	**X**	**X**	**X**		
MMRC dyspnea scale		**X**							
Dispense ePRO device and train the subject per the training guidelines	**X**								
Check ePRO eDiary compliance		**X**	**X**	**X**	**X**	**X**	**X**		
Adverse events		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Concomitant medication		**X**	**X**	**X**	**X**	**X**	**X**		**X**

[a] Telephone contact only
[b] Including height and weight
[c] Including weight

[d] In women with child-bearing potential only, urine pregnancy test (dipstick)
[e] CXR (frontal and lateral) will be performed at Visit 1 if not done within 6 month before enrollment. CXR will also be done within 72 hours of all cases of pneumonia.
[f] Results of ECG, clinical chemistry, urinalysis and hematology must be reviewed prior to randomization. All laboratory tests will be performed locally. No values will be entered in the eCRF.
[g] FEV_1, FVC
[h] FEV1, FVC, FEV_1/FVC
[i] Rescue medication returned as applicable, when utilized. The subjects will get new rescue medication as needed.
[j] SGRQ performed before all other assessments
[k] Unscheduled visits may be initiated as needed, and additional assessments performed at these visits, at the discretion of the Investigator
[l] The visit window between Visit 2 and Visit 3 need to be at least 28 days
[m] Days should be followed and weeks are approximate

4.1 Enrollment period

At enrollment, consenting subjects are assessed to ensure that they meet eligibility criteria. Subjects who do not meet these criteria must not be enrolled in the study.

4.1.1 Enrollment (Visit 1)

Each potential subject will provide written informed consent prior to any study specific procedures and undergo assessments applicable for the visit as listed in the Study Plan (see Section 4, Table 1).

The Visit 1 assessments are primarily concerned with confirmation of the COPD disease state, smoking history, and exacerbation history. A record of a physician-diagnosed COPD, and COPD exacerbation(s) in the prior year (Section 3.1) is required source documentation. A subject's verbal history suggestive of COPD symptoms and/or prior COPD exacerbation(s), but without supporting documentation, is not sufficient to satisfy these inclusion criteria.

CXR (frontal and lateral) will be performed at Visit 1 if not done within 6 month before enrollment. A local laboratory test for clinical chemistry and hematology will be drawn and a urine sample will be collected. An ECG will also be taken at Visit 1.

Examples of acceptable documentation of the COPD disease state and prior COPD exacerbation(s) include clinic visit (primary or specialist health care provider (HCP)), emergency department or hospital records listing COPD as a current problem, plus documentation of at least one COPD exacerbation during the 12 months prior to Visit 1. A qualifying historical COPD exacerbation is:

- Use of systemic corticosteroids (oral, IM, IV) for at least 3 days; a single depot injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids and/or
- An inpatient hospitalization including a emergency department stay for >24 hours, due to COPD

Subjects will continue on their current COPD treatment until Visit 2 (see Section 7.7, Table 4).

Subjects will be issued an eDiary at Visit 1 and instructed how to use it. From Visit 1 to Visit 2 subjects will be instructed to complete the eDiary questions (except study maintenance medication use) including the use of rescue medication.

4.1.2 Run-in (Visit 2)

Visit 2 should occur one week after Visit 1. The run-in period should be minimum of 4 weeks in duration (from Visit 2 to Visit 3). Throughout the run-in period all study subjects will take Symbicort pMDI 160/4.5 µg 2 actuations BID. Assessments applicable for the period are listed in the Study Plan (Section 4, Table 1).

Visit 2 is primarily concerned with the medical and surgical history, the requisite level of

severity based on MMRC and spirometry measurements pre- and post-bronchodilator, evaluating whether lung function meets the study eligibility criteria.

The subject's eligibility should be evaluated at each visit during the enrollment/run-in period with the relevant documentation entered in the source documents and electronic CRF (eCRF).

4.1.3 Re-screening

Subjects who experience a COPD exacerbation within 14 days prior to Visit 1 or during the enrollment or run-in period should be screen failed. They may be re-screened no sooner than 14 days after their last dose of systemic steroids and/or antibiotics and/or hospitalization.

Subjects may be re-screened if spirometry at Visit 2 is deemed technically unacceptable by central spirometry reviewers. Subjects may also be re-screened if eDiary compliance requirements from Visit 1 to Visit 3 (Randomization) are incomplete, making the patient ineligible due to factors other than patient non-compliance (e.g. device technical malfunction or due to human error).

Re-screening for the above mentioned reasons is allowed only once for each subject. The subject must keep the same enrollment code.

The subject cannot be re-screened if any other eligibility criteria are not fulfilled.

A new informed consent will need to be completed at re-screening and the date entered in the eCRF.

4.2 Treatment period

The inclusion/exclusion criteria at the randomization visit (Visit 3) will be confirmed. The subject's compliance with their run-in medications and ePRO completion must be confirmed prior to randomization.

Subjects confirmed to be eligible will be randomized at Visit 3 in a 1:1 ratio to receive Symbicort pMDI or formoterol Turbuhaler according to Section 7.2.

Following randomization, the subject will enter the 26-week double-blind, double-dummy treatment period.

Subjects will continue to record their nocturnal awakenings, COPD symptoms, study medication intake and rescue medication using the ePRO device throughout the 26-week treatment period (see Section 5.3.1 for details).

At week 26, subjects will come to the study site for the EoT visit.

4.3 Follow-up period

All subjects will be followed up 2 weeks after the EoT by a telephone call and asked about their overall health and whether they have had any problems, discomfort or hospitalizations since their last visit.

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 in the eCRFs as specified in the study protocol and in accordance with the instructions provided.

The Investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement (CSA). The Investigator will sign the completed eCRF. A copy of the completed eCRF will be archived at the study site.

5.1 Efficacy assessments

5.1.1 Assessment of COPD exacerbations

For the purpose of the protocol, a COPD exacerbation will be defined as a worsening of symptoms that lead to any of the following:

- Use of systemic corticosteroids for at least 3 days; a single depot injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids and/or
- Use of antibiotics
- An inpatient hospitalization (including >24 hours in emergency department/urgent care setting) due to COPD

Symptoms will be assessed each morning for the purpose of a symptom worsening alert via the eDiary (see Section 2.1). The purpose of this alert is to notify both the subject and the study site of a potential symptom worsening event that warrants contact between the subject and the study site for further evaluation.

If an exacerbation is not associated with a worsening of symptoms in Section 2.1, the Investigator will have to justify the decision for defining the event as an exacerbation and record it in the eCRF.

The start of an exacerbation is defined as the start date of systemic corticosteroids and/or antibiotics or hospital admission, whichever occurs earlier, and the end date is defined as the last day of systemic corticosteroids and/or antibiotics or hospital discharge, whichever occurs later.

A COPD exacerbation that occurs ≤7 days of hospital discharge**,** the last dose of systemic steroids (oral, IM, IV) or antibiotics (≤10 days of the last depot injectable dose of corticosteroids), prescribed for a prior exacerbation, will be counted as the same exacerbation event.

The subject may remain in the study after an exacerbation and continue to receive IP if the Investigator judges that it is medically appropriate for the subject to do so.

Study site evaluations for a COPD worsening may occur as an unscheduled visit or as part of an ordinary site visit if the worsening happens to coincide within a scheduled visit window. If symptoms have not been recorded by the patient in the eDiary, the investigator should document symptoms in the eCRF using the form 'Interview to Evaluate the Exacerbation Status of Subjects in the Absence of Daily Diary Data' (Appendix F). A copy of the medical record should be obtained for exacerbations evaluated and treated at non-study sites (e.g. by the primary HCP or at an emergency department/hospital) and details entered into the exacerbation eCRF in a timely fashion. Changes in concomitant medication due to an exacerbation must be recorded in the appropriate module of the eCRF.

5.1.2 Spirometry (pre- and post-bronchodilator assessments at clinic visits)

General requirements

Lung function (FEV_1 and FVC) at the study site 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 trained by the vendor. Spirometry calibration will be detailed in a separate spirometry procedures manual.

Important! Subjects should be instructed not to use their study medication within 12 hours of scheduled site visit spirometry as this will affect the pre bronchodilator FEV_1 value; study medication may be taken subsequently, at the study site. ***For the same reason subjects should avoid using their rescue medication (albuterol/salbutamol) within 6 hours of a scheduled site visit spirometry.*** This restriction is particularly critical for efficacy measures taken during the treatment period, but should also facilitate meeting the enrollment FEV_1 criteria. See Section 7.7, Table 4 for restriction period before spirometry for other medications.

Options for handling subjects who have inadvertently taken their COPD medication within the restricted window are described in Section 7.7.2.3.

Time of day for scheduled site visit spirometry

Spirometry testing must be initiated in the morning between 6:00 AM and 11:00 AM only. All post-randomization spirometry assessments should be performed within ±1.5 hours of the time that the randomization spirometry was performed. For example, if the randomization

spirometry was started at 8:00 AM, then all subsequent spirometry testing needs to be initiated between 6:30 AM and 9:30 AM.

Spirometry technique

Subjects should avoid engaging in strenuous exertion for at least 30 minutes prior to spirometry measurements. Subjects should avoid eating a large meal for at least 2 hours prior to spirometry measurements at the study site. Subjects should not have smoked within at least 1 hour of testing. Forced expiratory maneuvers should be performed with the subject seated in an upright position. If this is not comfortable for the subject, standing is permitted. The same position should be used by the subject for each forced expiratory maneuver from enrollment throughout the study. The head must not be tilted during maneuvers and the thorax should be able to move freely; hence tight clothing should be loosened. A nose-clip should be used for the maneuver. The subject should use mouthpieces of the same dimension and shape from enrollment throughout the study.

The forced expiratory maneuver (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 subject to continue the expiration to be fast and forceful throughout the maneuver. 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).

Post-bronchodilator spirometry

Post-bronchodilator spirometry will be performed at Visit 2 for all subjects to evaluate inclusion, see Section 3.1.

Maximal bronchodilation will be induced using the rescue medication specified in Table 8 (albuterol pMDI 90 µg or salbutamol pMDI 100 µg) with or without a spacer device, 4 inhalations within 30 minutes ± 15 minutes before the post-bronchodilator spirometry performed at Visit 2. At the discretion of the Investigator a lower dose of albuterol or salbutamol (minimum 2 inhalations) can be used to avoid tremor or tachycardia.

Record keeping

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

Spirometry references

The Global Lung Function Initiative (GLI) equations will be used to determine the subjects predicted normal (PN) values and are 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

5.1.3 Patient reported outcomes

For information of all PROs used in the study, see Section 5.3.1.

5.1.3.1 Rescue Medication Use

The number of puffs of reliever medication taken during daytime and nighttime will be recorded by the subject in the eDiary from Visit 1 to the end of the study.

5.1.3.2 Nighttime awakenings

Nighttime awakening (yes/no) will be recorded in the morning upon wakening daily by the subject in the eDairy from Visit 1 to the end of the study. Subject should be instructed to record only awakenings due to respiratory symptoms (cough, worsening shortness of breath, wheezing).

5.1.3.3 St. George's Respiratory Questionnaire (SGRQ)

The SGRQ is a 50-item PRO instrument developed to measure the health status of subjects with airway obstruction diseases (Jones et al 1991). The questionnaire is divided into two parts: part 1 consists of 8 items related to the frequency of respiratory symptoms in the preceding 4 weeks; part 2 consists of 42 items related to the daily activity and psychosocial impacts of the individual's respiratory condition. The SGRQ yields a total score and three domain scores (symptoms, activity, and impacts). The total score indicates the impact of disease on overall health status. This total score is expressed as score from 0 to 100, in which 100 represents the worst possible health status and 0 indicates the best possible health status. Likewise, the domain scores range from 0 to 100, with higher scores indicative of greater impairment. Specific details on the scoring algorithms are provided by the developer in a user manual (Jones, 2009). The assessment of SGRQ will only be performed in countries and languages where validated translations are available. Patients who are not fluent in any of the local languages will not perform the SGRQ assessments, but they can still participate in the study. The original UK English version is included in Appendix C. The SGRQ will be completed by the subject at clinical visits. It takes approximately 10 minutes to complete the SGRQ.

5.2 Safety assessments

5.2.1 Laboratory safety assessments

Clinical chemistry (including assessment of electrolytes, glucose, renal function and liver function), hematology (WBC, hemoglobin, hematocrit, platelet count) assessments and urinalyses will be performed at Visit 1, see Table 2.

The clinical chemistry, hematology 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 analyses will be performed:

Table 2 Laboratory Safety Analyses

Hematology/Hemostasis (whole blood)	**Clinical Chemistry (serum or plasma)**
B-Hemoglobin (Hb)	S/P-Creatinine
B-Hematocrit	S/P-Bilirubin, total
B-Leukocyte count	S/P-Alkaline phosphatase (ALP)
B-Leukocyte differential count (absolute count)	S/P-Aspartate transaminase (AST)
B-Platelet count	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
U-Pregnancy (if applicable)	S/P-Glucose

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. Any laboratory abnormalities considered to be significant in the Investigators'/authorized delegate's judgment will preclude the subject from being randomized in the study. The laboratory results should be signed and dated and retained at study 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.

5.2.2 Physical examination

Physical examination will be done in accordance with the Study Plan provided in Section 4, Table 1. Baseline data will be collected at Visit 2. Any new finding(s) or aggravated existing finding(s), judged as clinically significant by the Investigator, will be reported as an AE as described in Section 6.1.

5.2.2.1 Complete physical examination

The complete physical examination will include an assessment of the following: general appearance, abdomen, cardiovascular and respiratory systems. Weight and height will be measured at Visit 2 and weight only at Visit 7.

5.2.2.2 Brief physical examination

The brief physical examination will include an assessment of the general appearance, abdomen, cardiovascular and respiratory system. For the brief physical examination only information on whether the assessment was performed or not is to be recorded.

5.2.3 Electrocardiogram

ECG will be performed at Visit 1. A 12-lead ECG taken in the supine position, after the subject has been resting for at least 5 minutes will be reviewed by the Investigator prior to randomization. The Investigator or authorized delegate will be responsible for the overall interpretation and determination of clinical significance of any potential ECG findings. ECG findings that are unexplained by the subject's history (including arrhythmia, conduction abnormalities, ischemia, infarction, etc.) or findings that would lead to further medical evaluation will preclude the subject from being randomized in the study.

5.2.4 Vital signs

Pre-dose vital signs (pulse, blood pressure, respiratory rate and body temperature) will be obtained in accordance with the Study Plan provided in Section 4, Table 1. The vital signs will be taken prior to pulmonary function testing and administration of COPD maintenance therapy. Vital signs should also be taken prior to the per protocol bronchodilator administration if applicable for that visit.

5.2.4.1 Respiratory rate

The respiratory rate will be obtained after the subject has been resting for at least 5 minutes, by counting the number of breaths (how many times the chest rises) for one minute.

5.2.4.2 Pulse and blood pressure

The pulse and blood pressure should be measured after the subject has been resting for at least 5 minutes. The measurement will be taken in a sitting position. The pulse rate will be obtained before the blood pressure. Pulse rate (beats/min) will be measured over 30 seconds. Systolic and diastolic blood pressure (mmHg) will be measured using a cuff appropriate for arm circumference.

5.2.4.3 Body temperature

Body temperature will be measured in Celsius in accordance with local standards.

5.2.4.4 Weight and height

Weight (kg) and height (centimeters) will be measured at Visit 2 and weight will be measured at Visit 7 in accordance with the Study Plan (see Section 4, Table 1).

5.2.5 Chest radiography

A CXR (frontal and lateral) is to be performed at Visit 1 if not done within 6 months of the enrollment. A chest CT done within 6 months is also acceptable.

5.2.6 Smoking status

Smoking history will be evaluated at Visit 1 and expressed in pack years (1 pack year = 20 cigarettes smoked per day for 1 year). Smoking status will be evaluated at each subsequent visit by collecting the subject's response to a single yes/no question from study personnel: 'What is your smoking status as of today, do you currently smoke?

5.2.7 Other safety assessments (Not applicable)

5.3 Other assessments

5.3.1 Patient reported outcomes

Subjects will complete PRO assessments at the study site on paper (SGRQ) and at home using a handheld ePRO device (eDiary). 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 via an ePRO device:

For PRO instruments administered during site visits

- Administer before other procedures
  - Always administer PRO instruments before other study procedures
- Provide the right environment
  - Provide a quiet and private location to complete the instrument
- No right or wrong answers
  - Remind subjects that there are no right or wrong answers and that we're asking them to complete these questionnaires because we are interested in hearing directly from them on how they feel.
- Help with procedural questions
  - Make sure the subject 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 subjects will ask site staff to clarify the meaning of a question or response. To avoid introducing any bias, politely tell the subject 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 subject 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. If an item is left blank ask the subject if they intended to leave the item blank. Provide an opportunity for the subject to answer if they wish.

For PRO instruments captured at home using an ePRO device

- Guidelines similar to paper
  - Many of the same principles apply for ePRO as paper. Remind subjects that there are no right or wrong answers, avoid bias by not clarifying items, remind subjects that they should complete the ePRO questions in a quiet and private location without help from others.
- Train the subject on ePRO device usage
  - Train the subject on how to use the ePRO device using the materials and training provided by the ePRO vendor.
  - Provide guidance on who the subject 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 to identify problems early. If compliance drops below 80% a check-in call from the site to ask the subject if they are having difficulties is highly recommended.

Additional and more specific details concerning PRO instrument administration are provided in subsequent sections where each instrument is described.

5.3.2 eDiary Assessments

5.3.2.1 Major/minor symptom worsening assessment

Symptoms will be assessed from Visit 1 onward each morning for the purposes of a symptom worsening alert. The purpose of this alert is to notify both the subject and the study center of a potential symptom worsening event that warrants contact between the subject and center for further evaluation.

Each morning the subject will complete 3 questions pertaining to the major symptoms of a worsening event (dyspnea, sputum volume, and sputum color; (Anthonisen et al 1987)). Subject reported worsening of 1 or more of these symptoms will trigger assessment of the minor symptoms of a worsening event (sore throat, cold, fever without other cause, cough, and wheeze). All questions will have a 24-hour recall period. Questions pertaining to the severity of symptoms vs. their usual state will have 3 response options (e.g. How breathless have you been in the last 24 hours? Less breathlessness than usual, Usual level of breathlessness, More breathless than usual) whereas questions related to the presence or absence of a symptom will have a dichotomous response (e.g. Have you had a sore throat in the last 24 hours? No, Yes, I had a sore throat). For all ePRO questions, see Appendix E.

These questions will be used for a symptom worsening alert system. An alert will be triggered if two or more major symptoms (dyspnea, sputum volume, and sputum color/purulence) worsen for at least two consecutive days or if one major symptom and one minor symptom (sore throat, cold, fever without other cause, cough, and wheeze) worsen for at least two consecutive days. When either of these criteria is met the subject will be alerted via the ePRO device to contact the study site for further evaluation. Likewise the study site will be alerted to contact the subject if he or she has not yet contacted the study site for further evaluation.

5.3.2.2 Rescue Medication Use

See Section 5.1.3.1.

5.3.2.3 Study Medication Use

Study Medication administration will be recorded in the eDiary in the morning and in the evening as “yes” or “no”.

5.3.2.4 Nighttime awakenings

See Section 5.1.3.2.

5.3.2.5 St. George’s Respiratory Questionnaire (SGRQ)

See Section 5.1.3.3.

5.3.2.6 The Modified Medical Research Council (MMRC) dyspnea scale

The MMRC dyspnea scale uses a simple grading system to assess a subject’s level of dyspnea that consists of five statements about perceived breathlessness. It is an interviewer-administered ordinal scale on which subjects provide their dyspnea according to five grades of increasing severity (scores ranges from 0 (none) to 4 (very severe)) This will be recorded at

Visit 2 and a score of ≥2 will be required for inclusion into the study (see Section 3.1). A copy of the MMRC dyspnea scale is included in Appendix D.

5.4 Pharmacokinetics (Not applicable)

5.5 Pharmacodynamics (Not applicable)

5.6 Pharmacogenetics (Not applicable)

5.7 Biomarker analysis (Not applicable)

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

The principal Investigator (PI) 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 AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

6.2 Definitions of serious adverse event

A SAE is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix B.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

AEs will be collected from Visit 2 throughout the treatment period and including the follow-up period until the last telephone follow-up, or the last contact.

SAEs will be recorded from the time of informed consent throughout the study.

6.3.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the subject's last AE assessment in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

6.3.3 Variables

The following variables will be collect for each AE;

- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to IP
- AE caused subject's withdrawal from study (yes or no)
- Outcome

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

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Other medication
- Causality assessment in relation 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.

Maximum intensity refers to the complete course of the AE. The subject will be asked to assess the maximum intensity of the reported AEs according to the following scale:

- mild (awareness of sign or symptom, but easily tolerated)
- moderate (discomfort sufficient to cause interference with normal activities)
- severe (incapacitating, with inability to perform normal activities)

6.3.4 Causality collection

The Investigator will assess causal relationship between IP and each AE, and answer yes/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, study procedures and additional study drug. 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 B.

6.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel: *'Have you had any health problems since the previous visit/you were last asked?'*, or revealed by observation will be collected and recorded in the eCRF. The question will be put to each subject in local language from Visit 2 to the last follow-up telephone contact. When collecting AEs, the recording of diagnoses is preferred (when possible) to 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

Vital signs data will be summarized in the clinical study report. Deterioration as compared to baseline in protocol-mandated vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the IP.

If deterioration in a vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated vital sign will be considered as

additional information. In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

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 symptoms of disease under study).

6.3.7 Hy's Law

Cases where any labs that are collected from a subject shows an AST or ALT ≥3 x ULN or total bilirubin ≥2 x ULN may need to be reported as SAEs if criteria for Hy's law are fulfilled. AstraZeneca study physician should be contacted if a case of Hy's law is suspected.

6.3.8 Adverse events of Pneumonia requiring a confirmed diagnosis

Events of suspected pneumonia are to be confirmed by the presence of a new infiltrate on CXR within approximately 48 hours, but no later than 72 hours of a clinical diagnosis of pneumonia, as well as at least 2 of the following signs and symptoms: increased cough, increased sputum purulence or production, consistent auscultatory findings, dyspnea or tachypnea, fever, leukocytosis, or hypoxemia.

Radiographs will be evaluated locally and the results (infiltrate compatible with pneumonia yes/no) entered in the eCRF.

If the investigator becomes aware that a diagnosis of pneumonia was made without a CXR performed, he or she should obtain a CXR (frontal and lateral) up to 10-14 days after the date of pneumonia diagnosis and document the results (infiltrate compatible with pneumonia yes/no) in the eCRF.

6.3.9 Symptoms of the disease under study

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 subject discontinues the study due to the sign or symptom and/or
- the sign or symptom is new to the subject or not consistent with the subject's pre-existing COPD condition including COPD exacerbation history (defined as within 1 year of Visit 1) as judged by the investigator

A COPD exacerbation should not be recorded as AEs unless it fulfills any of the above criteria. All COPD exacerbations should be recorded in the exacerbation eCRF.

6.3.10 eDiary

The subject will use an eDiary to record study variables. The Investigator is responsible to review the eDiary together with the subject and transfer any indications of AEs to the AE form.

6.3.11 Concomitant medications

All changes in the subject's ordinary medication, e.g. dose change or addition of new medication, even those noted in the diaries, must be reported on the medication form. Reasons for changes in medication, which reflect an AE, must be recorded on the AE form.

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 procedure(s). All SAEs will be recorded in the eCRF.

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 (IB) for the AstraZeneca drug and the EU Summary of Product Characteristics (SPC) for the active comparator product (including any AstraZeneca comparator).

6.5 Overdose

Background

The risks associated with overdosage of Symbicort are considered to be small, as the safety margins for inhaled budesonide and formoterol are substantial. Administration of a Symbicort Turbuhaler dose of 1600/45 µg over one hour on top of maintenance treatment with daily doses of 640 µg budesonide and 18 µg formoterol in asthmatic subjects raised no safety concerns, nor did a formoterol dose of 90 µg over three hours in adult subjects with acute bronchoconstriction or a budesonide dose of 7200 µg in healthy volunteers.

Symptoms

Glucocorticosteroids have a low toxicity, and are virtually without harmful effects after a single or a few doses, even if the doses are very high. Acute overdosage with budesonide – even in excessive doses – is not of clinical importance. As with all ICSs, systemic glucocorticoid effects may appear if used chronically in excessive doses.

There is limited clinical experience regarding overdosage with inhaled formoterol. An overdose would likely lead to effects typical for β2-agonists such as tremor, headache and palpitations. Other symptoms and signs reported with formoterol from isolated cases are tachycardia, hyperglycemia, hypokalemia, prolonged QTc-interval, arrhythmia, nausea and vomiting.

Experience with other β2-agonists has shown that overdoses may also cause restlessness, irritability, excitation, somnolence, convulsions and hyper- or hypotension. Metabolic effects may include acidosis and in serious cases, possibly rhabdomyolysis and renal failure.

Treatment suggestions

Normally, an overdose with Symbicort should not require any special treatment. However if signs of adrenergic effects occur these should be counteracted by supportive and symptomatic treatment, according to local routines.

Procedures for reporting

For the purpose of this study, an accidental or deliberate intake of blinded treatment of more than 20 inhalations (3200/90 µg Symbicort or 90 µg formoterol) during one day is defined as an overdose and must be reported as such as described below:

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

If an overdose on an AstraZeneca study drug 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 subject becomes pregnant during the course of the study IP should be discontinued immediately.

Pregnant women, as well as those who are planning pregnancy or are breast-feeding, are excluded from the study. In addition, fertile women not using acceptable contraceptive measures, as judged by the Investigator, should not be included in the study.

Clinical experience with Symbicort pMDI in pregnant women is limited and subjects that become pregnant must be discontinued from the study. However, reports from clinical studies and post-marketing surveillance with Symbicort Turbuhaler do not indicate an increased risk when used during pregnancy.

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 subject 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 1 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 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.

The PREGREP module in the eCRF is used to report the pregnancy and the PREGOUT paper form is used to report the outcome of the pregnancy.

6.7 Management of IP related toxicities (Not applicable)

6.8 Study governance and oversight (Not applicable)

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

Table 3 Investigational products

Investigational product	Dosage form and strength	Manufacturer
Symbicort pMDI 160 µg/4.5 µg	pMDI, aerosol for oral inhalation, budesonide/formoterol 160 µg/4.5 µg, 120 doses	AstraZeneca
Placebo for Symbicort pMDI	pMDI, aerosol for oral inhalation, placebo, 120 doses	AstraZeneca
Formoterol Turbuhaler 4.5 µg	Formoterol powder for oral inhalation 4.5 µg, 60 doses	AstraZeneca
Placebo for formoterol Turbuhaler	Placebo powder for oral inhalation, 60 doses	AstraZeneca

Symbicort pMDI and matching placebo pMDI units will be packed together with desiccant bags in sealed pouches and placed in cartons. Placebo training pMDI units will be delivered in cartons together with bags of extra actuators.

Formoterol Turbuhalers, matching placebo Turbuhalers and empty training Turbuhalers will be packed in cartons. Formoterol and matching placebo Turbuhalers contain lactose as part of the filling material.

The training devices will be used in the clinic only and will not be dispensed to the subjects to take home. The training pMDI and Turbuhaler will be labelled with English label only.

7.2 Dose and treatment regimens

Enrollment

At Visit 1 subjects will receive rescue medication (see Section 7.7.1) to be administered as needed during enrollment, run-in and the randomized treatment period.

Instructions will be given to the subject on how to use the pMDI inhaler (inhalation technique and priming instructions). In order to inhale properly according to instructions the subject will practice inhalation technique with a training pMDI, as many times as judged necessary by the supervising study personnel. Instructions on how to use the pMDI will be provided to the subjects in local language.

Run-in period

After assessment for eligibility at Visit 2 subjects will be instructed to stop using COPD medication in accordance with Section 7.7 and enter a 4-week run-in phase to be treated with

unblinded Symbicort pMDI 160/4.5 µg x 2 actuations BID. The first dose of Symbicort should be taken at the study site at Visit 2 after spirometry assessments.

Double-blind treatment period

Upon qualification for randomization at Visit 3, subjects will be randomized to either the Symbicort or the formoterol treatment arm, assigned a randomization code and the appropriate blinded study medication through IVRS/IWRS, and enter a 6-month treatment period. The first dose of double-blind treatment should be taken at the study site at Visit 3 after spirometry.

Before taking the first dose of double-blind medication the subject will be instructed by the study personnel on how to prime and use the Turbuhaler. Subject will practice inhalation technique with an empty training Turbuhaler. Instructions on how to use the Turbuhaler will be provided to the subjects in local language.

Treatment arms:

- Symbicort treatment arm: Symbicort pMDI 160/4.5µg + Placebo Turbuhaler
- Formoterol treatment arm: formoterol Turbuhaler 4.5µg + Placebo pMDI

Dosing:

- Symbicort or placebo pMDI: 2 actuations BID (morning and evening)
- Formoterol or placebo Turbuhaler: 2 inhalations BID (morning and evening)

At all study visits, subjects will receive enough double-blind medication and rescue medication to cover for treatment need until the next study visit.

Priming of pMDI inhaler

The run-in Symbicort pMDI and double-blind study medication pMDIs will require priming when initially dispensed, if dropped or if not used for greater than 7 days.

Prepare the pMDI inhaler according to the following instructions:

- Shake well for 5 seconds to mix the contents of the canister
- Remove the mouthpiece cover by squeezing gently on both sides, then pulling out
- Hold the inhaler upright and press the top of the canister firmly to release a shot of medicine into the air
- Release your finger from the top of the canister to allow it to reset
- Wait for at least 10 seconds, and then repeat this procedure one more time

The pMDI inhaler is now ready for use.

Priming of Turbuhaler inhaler

The double-blind study medication Turbuhaler will require priming before its initial use. The priming should not be repeated even if the inhaler is not used regularly.

Prepare the Turbuhaler inhaler according to the following instructions:

- Remove cover
- Hold the inhaler in an upright position. Use the other hand to hold the inhaler in the middle. Do not hold the Turbuhaler at the top of the mouthpiece
- Twist the grip as far as it will go in one direction and then fully back again in the other direction until it stops. It does not matter which way you turn it first. You will hear a "click" during one of the twisting movements
- Repeat this procedure one more time

The Turbuhaler is now ready for use and the first dose can now be loaded.

7.3 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfill GMP Annex 13 requirements for labelling. Label text will be translated into local language, except for the training inhalers that will have English label only.

7.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The IP label on the study drug specifies the appropriate storage. On each kit there will be an instruction illustrating its proper orientation, which must be adhered to.

7.5 Compliance

Each subject is required to comply with the prescribed treatment regimen throughout the study. Subjects will be instructed on how to use the inhalers correctly. In order to ensure correct inhalation technique, training devices will be available at each study site for instructional purposes as well as for subjects to practice the correct inhalation technique. Instruction and practice should occur prior to dispensing study medication. These devices will be used in the clinic only and will not be dispensed to subjects for use at home.

Site staff will review and emphasize the importance of study medication compliance with the subject at each scheduled study visit and make a note in Medical records.

The administration of all study drugs (including IPs) should be recorded in the appropriate sections of the eCRF.

Twice daily, the subjects will be asked if they have taken the study medication when filling in the eDiary. If the subject is not compliant, he or she will receive additional training on how to use the inhalers.

7.6 Accountability

The study drug provided for this study will be used only as directed in the study protocol.

The study personnel will account for all study drugs dispensed to and returned from the subject.

Subjects will be asked to bring all used and unused pMDIs and Turbuhalers to the site at each on-site visit. The Investigator or delegate will review the inhalers and make an assessment regarding subject treatment compliance. Any subject found to be noncompliant would be counseled on the importance of taking their study medication as prescribed.

Any study medication deliberately or accidentally destroyed must be recorded. Any discrepancy between dispensed and returned study medication should be explained.

Study site personnel, if applicable, or the AstraZeneca monitor will account for all study drugs received at the site, unused study drugs and for appropriate destruction. Certificates of delivery, destruction and return should be signed.

Study Drug is destroyed once there are satisfactory records of product accountability by the Monitor and the Study Leader has given authorization. The destruction will be performed according to local procedure.

7.7 Concomitant and other treatments

For allowed medications during the study, see Table 5 and

Table 6. For not allowed medications during the study, see Table 7.

Table 4 Changes in medication on enrollment, beginning of run-in, and at randomization

Prior Therapy	**Action at Visit 1 (Enrollment)**	**Action at Visit 2 (Symbicort pMDI 160/4.5 µg x 2 actuations BID. Withhold the morning dose at the day of Visit 3.)**	**Visit 3 (Randomization to Symbicort 160/4.5 µg x 2 actuations BID or formoterol Turbuhaler 4.5 µg x 2 inhalations BID. Withhold the morning study medication at the day of the study visits until after the spirometry.)**
Inhaled ICS/LABA combinations	Continue but withhold for 48 hours prior to Visit 2	Discontinue	N/A
ICS	Continue	Discontinue	N/A
Inhaled SAMA	Continue	Continue but withhold for 6 hours prior to Visit 2	Continue but withhold for 6 hours prior to Visit 3 and all subsequent visits
Inhaled LAMA[a]	Continue, but withhold for 48 hours prior to Visit 2	Discontinue	N/A
Inhaled LAMA/LABA combinations[a]	Continue, but withhold for 48 hours prior to Visit 2	Discontinue	N/A

Prior Therapy	**Action at Visit 1 (Enrollment)**	**Action at Visit 2 (Symbicort pMDI 160/4.5 µg x 2 actuations BID. Withhold the morning dose at the day of Visit 3.)**	**Visit 3 (Randomization to Symbicort 160/4.5 µg x 2 actuations BID or formoterol Turbuhaler 4.5 µg x 2 inhalations BID. Withhold the morning study medication at the day of the study visits until after the spirometry.)**
Inhaled LABA[a] Inhaled or nebulized SABA, or SAMA/SABA combinations[b] Oral β_2 agonists Short-acting[b] Slow-release[c] Xanthine derivatives (e.g. theophylline) Once-daily[a] Twice-daily[c] Phosphodiesterase inhibitors[a] Leukotriene antagonists or synthase inhibitors[a] Ephedrine containing medications[a]	Continue but withhold prior to Visit 2 (see footnotes)	Discontinue	N/A
Albuterol pMDI (US), 90 µg x 2 actuations as needed[d] Salbutamol pMDI (outside US), 100 µg x 2 actuations as needed[d]	Dispensed to all subjects for use as rescue medication. Instruct patients to withhold for 6 hours before every clinic visits.		

[a] Withhold 48 hours
[b] Withhold 6 hours
[c] Withhold 24 hours
[d] From Visit 1 onward, subjects must use study provided albuterol/salbutamol. It should not be used within 6 hours of clinic visits.

Table 5 Allowed medications

Medications allowed from Visit 1 and throughout the study
– Study supplied albuterol pMDI/salbutamol pMDI as rescue medication (cannot be used as maintenance or in a scheduled dose). In rare cases where a subject has an adverse or allergic reaction to albuterol/salbutamol, levalbuterol can be used. Levalbuterol will not be supplied by the sponsor.
– Ipratropium bromide (pMDI formulation only) if the subject is on a stable dose, not exceeding 2 puffs every 6 hours (not supplied by the sponsor)
– Antitussives PRN not containing ephedrine or other bronchodilators
– Antibiotics for acute infections
– Mucolytics not containing ephedrine
– Nasal, ophthalmic and topical corticosteroids without systemic effects
– Oral or ophthalmic cardioselective β-blocking agents only if the subject has been using these at a constant dose for the 6 months prior to Visit 1, without evidence of bronchospasm
– Antihistamines not containing ephedrine or bronchodilators
– Nasal decongestants
– Oxygen for intermittent use or when necessary ≤12 hours per day
– Influenza and pneumonia vaccines
– 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 Allowed medications to treat COPD exacerbations

Medications allowed, with restrictions, in event of a COPD exacerbation after Visit 3
– Systemic corticosteroids (tablets, injections or IV infusions). A single depot injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids
– ICS (including nebulized) other than study medication (only during hospitalization/ER treatment)*****
– Additional SABAs*****
– Acute use of xanthines, ipratropium*****

- Nebulized treatment with β_2-agonists and ipratropium*****
- Antibiotics
- Leukotriene antagonists, 5-lipoxygenase inhibitor, ephedrine, inhaled disodium cromoglycate or inhaled nedocromil sodium*

*****These medications can only be given concomitantly with systemic steroids and/or antibiotics during an exacerbation, use on their own or "step-up" is not allowed.

Table 7 Medications not allowed from Visit 2 to Visit 7 (in case of COPD exacerbation see Table 6

Medications not allowed from Visit 2 to Visit 7 (Run-in and Randomized treatment period)
- Inhaled LABAs (except randomized study medication) including LABA/LAMA combinations
- Inhaled LAMAs
- Inhaled SABA (except study-provided albuterol or salbutamol as required for relief of bronchospasm)
- Oral β2-agonists
- Ephedrine containing medication
- Leukotriene antagonists (e.g., Accolate® and Singulair®) and 5-lipoxygenase inhibitors (e.g., Zyflo®)
- Xanthine-containing derivatives
- Disodium cromoglycates
- Non-cardioselective β-blocking agents (including eye drops)
- ICS except randomized study medication
- Systemic treatment with potent cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ketoconazole)
- Omalizumab or any other monoclonal or polyclonal antibody therapy taken for any reason
- Treatment with oral, parenteral, or intra-articular corticosteroids
- Allergen immunotherapy
- High potency topical steroids that could give systemic effects

- Antibiotics taken for the prevention of a COPD exacerbation (e.g. macrolides, quinolones)
- Roflumilast (Daxas®, Daliresp®)
- Any other investigational drug within 30 days or five half lives (whichever is longer) of Visit 2

7.7.1 Rescue Medication

Albuterol pMDI and salbutamol pMDI units will be provided in their commercial cartons, but additionally labelled with a study specific labels.

Table 8 Rescue Medication

Rescue Medication:	Usage:
Albuterol (Ventolin) 90 µg pMDI for oral inhalation, 200 doses	Rescue medication in US To be dispensed to subjects at Visits 1 and each visit throughout the study
Salbutamol (Ventolin) 100 µg pMDI for oral inhalation, 200 doses	Rescue medication in non-US countries To be dispensed to subjects at Visits 1 and each visit throughout the study

7.7.2 COPD Medication restrictions

7.7.2.1 Use of short-acting β_2-agonists

Regularly scheduled SABA use is not allowed from Visit 1 and throughout the study duration.

Prophylactic use of SABA in the absence of symptoms is discouraged. However, if deemed necessary by the subject and Investigator (e.g. prior to planned exercise), it can be used, but prophylactic inhalations should not be recorded in the daily eDiary, such use should be documented in the medical notes and recorded in the eCRF.

SABA pMDI use is permitted as needed for worsening COPD symptoms (i.e. rescue medication use) and will be recorded in the eDiary as number of puffs (see Section 7, Table 8).

Rescue use of SABA administered via nebulization, outside of managing an acute COPD exacerbation event, is discouraged unless the Investigator deems access to nebulized SABA is essential for that subject. Occasions (# of times used) where SABA was administered via nebulization will be recorded separately from pMDI inhalations at each clinic visit.

7.7.2.2 Use of short-acting anticholinergics

Use of SAMA (e.g. ipratropium) as a rescue treatment for worsening COPD symptoms outside of managing a COPD exacerbation event is not allowed from Visit 1 and throughout the study duration.

Switching patients from SAMA/SABA combination (including nebulized form) or nebulized SAMA to SAMA pMDI is not allowed from Visit 1 and throughout the duration of the study.

7.7.2.3 COPD medication restrictions on the days of scheduled spirometry visits

Spirometry assessments will be performed at the study site at scheduled visits (see Section 4, Table 1). There are restrictions regarding the subject's COPD medications prior to the spirometry assessments.

Visit 2: Subjects will be asked to withhold their usual ICS/LABA, LABA or LAMA medications 48 hours prior to spirometry for the eligibility assessment (see Section 3.1). In addition, the SABA and/or SAMA should not be used within 6 hours of this spirometry assessment. The subject's will start run-in Symbicort medication following completion of the enrollment lung function procedures.

Treatment Visits 3-7: Subjects will be asked to withhold study medication on the mornings of the scheduled spirometry visits and preferably for at least 12 hours prior to the spirometry assessment. Subjects should withhold the use of SABA and/or SAMA 6 hours prior to these visits. Following spirometry assessments the medications can be resumed at the study site.

If the subject has taken the rescue medication within 6 hours of the planned site visit spirometry they should ideally remain at the site until such time that the 6 hours withholding time has been reached, if it does not exceed the 1.5 hour spirometry window; or return on another day, within the visit window. If neither of options is feasible for the subject, spirometry may be performed with a notation indicating that the spirometry was conducted within 6 hours of rescue medication use.

7.7.3 Other concomitant treatment

Medication other than described above, which is considered necessary for the subject's safety and well being, may be given at the discretion of the Investigator. This must be recorded in the appropriate sections of the eCRF.

Changes to the subject's COPD maintenance therapy are discouraged during the treatment period. If changes to maintenance medication are deemed clinically necessary by the Investigator such changes should be discussed with the AstraZeneca Study Team Physician that will consider if study withdrawal is necessary. All changes in the subject's maintenance therapy should be documented in the source notes along with the rationale for the change and recorded in the eCRF.

7.8 Post study access to study treatment

After completion of study treatment, subjects will be prescribed appropriate COPD maintenance medication according to the Investigator's judgment and local medical practice.

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

- All personnel involved with the analysis of the study will remain blinded until database lock and protocol violators identified.
- Analyses will be performed by AstraZeneca or its representatives.
- The Statistical Analysis Plan (SAP) will be prepared prior to first subject randomized and any subsequent amendments will be documented, with final amendments completed prior to unblinding of the data.

8.2 Sample size estimate

The sample size estimate for this study is based on a two-sided 5% alpha level test and power of 90%. The rate of exacerbations in the formoterol group is assumed to be 0.6 per patient. This is based on data from previous studies in Symbicort as well as published data from studies of other similar products. With a targeted reduction of 28% in the rate of exacerbations and an estimated negative binomial shape parameter of 0.6, the sample size is 568 subjects per treatment group. Allowing for a 10% loss of exposure due to early patient withdrawal.

Because the assumed exacerbation rate and assumed shape parameter from the negative binomial model has a large impact on the estimated sample size necessary to achieve a stated power (90% in this case), a blinded estimate of the exacerbation rate and shape parameter is planned. The review will be performed before the last subject is randomized. The exacerbation rate and shape parameter will be estimated using the maximum likelihood approach as proposed by Friede and Schmidli (Friede and Schmidli, 2010). If results of the blinded review indicate that the projected power falls to below 85%, the sample size will be increased to ensure a 90% projected power. Since this review will be performed in a blinded fashion, no adjustment for the type I error is needed. Additional blinded review(s) may be conducted if deemed necessary by the sponsor. The review(s) will be based on pooled, blinded data and will not use any treatment information. The blinding will be strictly maintained and not be affected by the review(s) in any way.

The potential increase in sample size will be capped at a 50% increase above the planned number of 568 subjects per treatment group.

8.3 Definitions of analysis sets

All efficacy analyzes will be performed using an intent to treat (ITT) approach based on the full analysis set. For consistency, demographic and baseline characteristics will be presented using the full analysis set. Safety objectives will be analyzed based on the Safety population.

8.3.1 All subject analysis set

This analysis set comprises all subjects screened for the study and will be used for reporting of disposition and screen failures.

8.3.2 Full analysis set

All subjects randomized to IP will be included in the full analysis set, irrespective of their protocol adherence and continued participation in the study according to the ITT principle. Analysis of primary and secondary variables will be based on data recorded up to the discontinuation of IP. Sensitivity analyses will be provided including the data post discontinuation of IP. Data for subjects who withdraw consent to participate in the study will be included up to the date of their study termination.

8.3.3 Safety analysis set

All subjects who received at least 1 dose of randomized treatment will be included in the safety analysis set. Subjects will be classified according to the treatment they actually received. All safety summaries will be based on this analysis set.

8.4 Outcome measures for analyses

8.4.1 Calculation or derivation of efficacy variables

The primary analysis will include data from the randomization visit (Visit 3) until the subject terminates the use of IP. Sensitivity analyses will include data from the randomization visit (Visit 3) until Visit 7, regardless of whether or not the subject terminated use of the IP.

If an exacerbation is not associated with a worsening of symptoms as defined in Section 2.1, these exacerbations will not be included in the primary analysis, but will be included in an additional sensitivity analysis.

8.4.1.1 Exacerbation rate

The annual exacerbation rate is the primary efficacy variable. In order to calculate the number of exacerbations experienced by a subject during the treatment period, the following rule will be applied.

The start of an exacerbation is defined as the start date of systemic corticosteroids (oral, IM, IV), antibiotics or hospital admission (see Section 5.1.1), whichever occurs earlier, and the end date is defined as the last day of systemic corticosteroids (IM depot injection end date is defined as 3 days after last dose), antibiotics or hospital admission, whichever occurs later. In the primary analysis, the number of exacerbations observed for a subject during the double-blind treatment period will be used as response variable.

In order to be counted for as a new exacerbation, an event (see Section 5.1.1) must be preceded by at least 7 days (≥10 days of the last depot injectable dose of corticosteroids) in which none of the criteria are fulfilled. Maximum follow-up time for a subject is approximately 26 weeks, defined as the time from randomization to the date of Visit 7. For a subject lost to follow-up, this will be defined as the time from randomization to the time point after which an exacerbation could not be assessed.

In the statistical analysis, the number of exacerbations experienced by a subject during the double-blind treatment period will be used as response variable, and the logarithm of the

subject's corresponding follow-up time will be used as an offset in the analysis to adjust for subjects having different exposure times during which the events occur. For the production of summary statistics, the annual exacerbation rate per subject is calculated, and standardized using data from the double-blind treatment period according to the formula described below.

Annual Exacerbation Rate = Number of Exacerbations * 365.25 / (Follow-up date – Visit 3 date + 1).

8.4.1.2 Proportion of subjects with at least one exacerbation

The proportion of subjects with at least one exacerbation during the randomized treatment period will be a supportive variable. This variable is defined in each treatment group as:

Number of subjects with at least one exacerbation / number of subjects in treatment group

8.4.1.3 Time to first exacerbation

Time from randomization to the first exacerbation will also be analyzed, and is calculated as follows:

Start Date of first exacerbation − Date of Randomization + 1

The time to first exacerbation for subjects who do not experience an exacerbation during the treatment period will be censored at the date of their last visit during the 26-week double-blind treatment period, or at the time point after which an exacerbation could not be assessed (for lost-to-follow-up subjects).

8.4.1.4 Pre-dose lung function variables

The change from baseline to each of the post-randomization visits (post Visit 3) up to and including the end of the double-blind treatment visit (Visit 7) will be used as secondary efficacy variables. The pre-bronchodilator measurement recorded at Visit 3 will be used as baseline. If the Visit 3 pre-bronchodilator measurement is missing, the pre-bronchodilator value from Visit 2 will be used as baseline instead.

8.4.2 Calculation or derivation of patient-reported variables

8.4.2.1 Rescue medication use and nighttime awakenings

Daily metrics (rescue medication use and nighttime awakenings) derived from the daily eDiary will be summarized as the mean for baseline period, the treatment period and the change from baseline.

Baseline is defined as the mean of the values recorded during the last 10 days before randomization, including the morning of the day of randomization. In order for a baseline to be valid, the patient must report at least 6 valid values for these 10 days, otherwise the patients baseline will be set to missing. The treatment period is defined as the mean of the values recorded during the randomized treatment period. The change from baseline to the treatment period will be used as secondary efficacy variables.

8.4.2.2 SGRQ

The change from baseline to each of the post-randomization visits (post Visit 3) up to and including the end of the double-blind treatment visit (Visit 7) will be used as secondary efficacy variables. The value recorded at Visit 3 will be used as baseline. An SGRQ responder is defined as a subject whose SGRQ total score decreases by at least 4 points from baseline.

8.5 Methods for statistical analyses

Analysis of primary and secondary variables will be based on data recorded up to the discontinuation of IP. Sensitivity analyses will be provided including the data post discontinuation of IP. Data for subjects who withdraw consent to participate in the study will be included up to the date of their study termination.

8.5.1 Analysis of the primary variable

The primary efficacy variable is the annual exacerbation rate and the primary analysis is to compare the exacerbation rate of Symbicort pMDI and formoterol Turbuhaler.

The null hypothesis is that the exacerbation rate on Symbicort pMDI is equal to the exacerbation rate on formoterol Turbuhaler. The alternative hypothesis is that the exacerbation rate on Symbicort pMDI is not equal to the exacerbation rate on formoterol Turbuhaler, i.e.:

H0: Rate ratio (Symbicort pMDI vs formoterol Turbuhaler) = 1

Ha: Rate ratio (Symbicort pMDI vs formoterol Turbuhaler) ≠ 1

The exacerbation rate in the Symbicort group will be compared to exacerbation rate in the formoterol group using a negative binomial model. The response variable in the model will be the number of exacerbations over the double-blind treatment period.

The model will include covariates of treatment group, country/region and the number of exacerbations in the year before the study. The logarithm of the follow-up time will be used as an offset variable in the model.

The estimated treatment effect (i.e., the rate ratio of Symbicort pMDI versus formoterol Turbuhaler), corresponding 95% confidence interval (CI), and two-sided p-value for the rate ratio will be presented. In addition, the exacerbation rate and the corresponding 95% CI within each treatment group will be presented.

8.5.2 Analysis of the secondary variable(s)

Secondary efficacy endpoints in this study are:

- Proportion of subjects with at least one exacerbation
- Time to first exacerbation
- Change from baseline in pre-dose FEV_1 and FVC

- Change from baseline in rescue medication use
- Change from baseline in nighttime awakenings due to respiratory symptoms
- Change from baseline in SGRQ
- Proportion of SGRQ responders at week 26

The proportion of subjects with at least one exacerbation will be compared between treatment groups via a logistic regression. Treatment, region/country and the number of exacerbations in the year before the study will be included in the model.

Time to first exacerbation will be analyzed to explore the extent to which treatment with Symbicort pMDI delays the time to first exacerbation compared with formoterol Turbuhaler. A Cox proportional hazard model will be fitted to data with the covariates of treatment, country/region and number of exacerbations in the year before the study.

The change from baseline in pre-dose FEV_1 will be compared between Symbicort pMDI and formoterol Turbuhaler using a mixed model repeated measures analysis on subjects with a baseline pre-dose/pre-bronchodilator FEV_1 and at least one post-randomization value. The dependent variable will be the change from baseline in FEV_1 at visits during the randomized treatment period. Treatment group will be fitted as the explanatory variable, and country/region and the baseline (Visit 3) pre-bronchodilator FEV_1 will be used as covariates. Visit will be used as a categorical variable, and the variance-covariance matrix will be assumed to be unstructured. If the procedure does not converge then a compound symmetric variance-covariance matrix will be used instead. The model is:

Change in FEV_1 = Treatment group + baseline FEV_1 + country/region + anti-cholinergic use + visit + treatment * visit

FVC will be analyzed using the same model with its pre-bronchodilator value at Visit 3 serving as the covariate.

The change from baseline in rescue medication use and nighttime awakenings will be analyzed by an analysis of covariance (ANCOVA) with the baseline value as a covariate.

The change from baseline in SGRQ will be analyzed using a mixed model repeated measures analysis on subjects with a baseline SGRQ and at least one post-randomization value. The dependent variable will be the change from baseline in SGRQ at visits during the randomized treatment period. Treatment group will be fitted as the explanatory variable, and country/region and the baseline (Visit 3) SGRQ will be used as covariates. Visit will be used as a categorical variable, and the variance-covariance matrix will be assumed to be unstructured. If the procedure does not converge then a compound symmetric variance-covariance matrix will be used instead. The model is:

Change in SGRQ = Treatment group + baseline SGRQ + country/region + anti-cholinerigc use + visit + treatment * visit

The proportion of SGRQ responders will be compared between treatment groups via a logistic regression. Treatment, region/country, the use of maintenance anti-cholinergics and the number of exacerbations in the year before the study will be included in the model.

8.5.3 Blinded sample size re-estimation

As described in Section 8.2, there will be a blinded analysis for the purpose of checking assumptions used in the estimation of sample size. As such, no adjustment for Type I error is required.

8.5.4 Sensitivity analysis

The following sensitivity analyses will be performed for the primary variable.

Inclusion of exacerbations not meeting the defined symptom criteria (see Section 2.1).

The COPD exacerbation rate will be analysed including those exacerbations not meeting the symptom criteria following the principles described above for the primary efficacy analysis.

Inclusion of data post discontinuation of randomized treatment.

Efficacy data will continue to be collected for those subjects who stop the use of the randomized treatment but who remain in the study (i.e., those who did not withdraw consent or were not lost to follow-up), to allow for a range of sensitivity analyses to be performed. These analyses will be performed following the principles described above for the primary efficacy analysis. In particular,

- The effect of treatment will be assessed incorporating all data post discontinuation of randomized treatment, except for data recorded after subjects were switched to maintenance therapy with an ICS/LABA, LABA, LAMA or LAMA/LABA combination product.

- The effect of treatment will be assessed incorporating all data post discontinuation of randomized treatment, regardless of any subsequent switch to maintenance therapy with an ICS/LABA, LABA, LAMA or LAMA/LABA combination product.

Potential impact of non-ignorable missing data (missing not at random).

The primary analysis assumes that data are missing at random. Different missing data assumptions will be explored including the extreme assumption that subjects who stop taking the therapy will no longer benefit from it in the future (e.g. jump to reference) and less extreme assumptions, such as varying assumptions dependent on the reason for missing data.

Variation of treatment effects across country/region.

The variation of treatment effects across country/region will be assessed by reviewing the results graphically by country/region.

8.5.5 Analysis methods for safety variables

AEs will be summarized by means of counts summaries by study period (treatment period and follow-up period). AEs will be listed for each subject and summarized by System Organ Class (SOC) and Preferred Term (PT) assigned to the event by Medical Dictionary for Regulatory Activities (MedDRA).

Results for vital sign variables will be summarized by visit and treatment group using standard summary statistics and plots as appropriate.

Results of physical examination variables will be summarized by visits and treatment group. Laboratory data will be collected and ECGs will be performed only prior to randomization.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site personnel

Before the first subject is entered into the study, an AstraZeneca representative will review and discuss the requirements of the CSP and related documents with the investigational staff and also train them in any study specific procedures and system(s) utilized.

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

The PI 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 protocol, that data are being accurately and timely recorded in the CRFs, and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (e.g., clinic charts)

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

9.2.1 Source data

Refer to the CSA for location of source data.

9.2.2 Study agreements

The PI at each study site should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this CSP and the CSA, the terms of CSP shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the CSA shall prevail.

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

9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.3 Study timetable and end of study

The end of the study is defined as 'the last visit of the last subject undergoing the study'.

The study is expected to start in Q2 2014 and to end by Q1 2016. The recruitment period is expected to start in Q2 2014 and end by Q2 2015.

The study may be terminated at individual sites if the study procedures are not being performed according to Good Clinical Practice (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 Symbicort pMDI or formoterol Turbuhaler.

9.4 Data management by Cognizant DMC

Data will be entered in the WBDC system at the study site. Trained study personnel will be responsible for entering data on the observations, tests, assessments specified in the protocol into the WBDC system and according to the eCRF instructions. Data entered into the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail.

Site personnel will enter the data in the eCRFs. The data will then be source data verified (SDV), reviewed/queried and updated as needed. The PI will then sign the eCRF electronically. The data will be frozen and locked to prevent further editing. Clean file occurs when all data have been declared clean, locked and signed by the Investigator. A copy of the eCRF will be archived at the study site when the study has been locked.

Data management will be performed by Cognizant DMC, according to the Data Management Plan. AEs and medical/surgical history will be classified according to the terminology of the latest version the MedDRA. Medications will be classified according to the AstraZeneca Drug Dictionary. Classification coding will be performed by Cognizant DMC.

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

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/or the investigational site.

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 International Conference on Harmonisation (ICH)/GCP, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Subject data protection

The ICF 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 (EC) should approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the subjects. The Investigator will ensure the distribution of these documents to the applicable EC, and to the study site staff.

The opinion of the EC should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrollment of any subject into the study.

The EC should approve all advertising used to recruit subjects for the study.

AstraZeneca should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the EC annually.

Before enrollment of any subject into the study, the final study protocol, including the final version of the ICF, 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, EC and PI with safety updates/reports according to local requirements.

Each PI is responsible for providing the EC/Institutional Review Board (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 PI so that he/she can meet these reporting requirements.

10.4 Informed consent

The PI(s) at each study site will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each subject is notified that they are free to discontinue from the study at any time
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure re-screened subjects provides a new signed and dated informed consent before conducting any study procedures
- Ensure the original, signed ICF(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed ICF is given to the subject
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the ICF that is approved by an EC.

10.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the international co-coordinating Investigator and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised CSP).

The amendment is to be approved by the relevant EC and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each PI(s). For distribution to EC see Section 10.3.

If a protocol amendment requires a change to a site's ICF, AstraZeneca and the site's EC are to approve the revised ICF before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each EC.

10.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an EC 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 protocol, GCP, guidelines of the 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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