Clinical Study Protocol

Drug Substance	Budesonide/Formoterol
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A randomised, parallel-group, open-label, multicentre, 3-month phase IV, efficacy and tolerability study of budesonide/formoterol (Symbicort® Turbuhaler® 160/4.5µg/inhalation, 2 inhalations twice daily) added to ipratropium (Atrovent™ 20 µg/inhalation, 2 inhalations four times daily) + theophylline SR (0.1g/tablet, 1 tablet p.o. twice daily) compared with ipratropium (Atrovent™ 20 µg/inhalation, 2 inhalations four times daily) + theophylline SR (0.1g/tablet, 1 tablet p.o. twice daily)in severe chronic obstructive pulmonary disease (COPD) patients

Sponsor:

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The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

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

AstraZeneca

PROTOCOL SYNOPSIS

A randomised, parallel-group, open-label, multicentre, 3-month phase IV, efficacy and tolerabilitystudy of budesonide/formoterol (Symbicort® Turbuhaler® 160/4.5µg/inhalation, 2 inhalations twice daily) added to ipratropium (Atrovent™ 20 µg/inhalation, 2 inhalations four times daily) + theophylline SR (0.1g/tablet, 1 tablet p.o. twice daily) compared with ipratropium (Atrovent™ 20 µg/inhalation, 2 inhalations four times daily) + theophylline SR (0.1g/tablet, 1 tablet p.o. twice daily) in severe chronic obstructive pulmonary disease (COPD) patients

International Co-ordinating Investigator

[redacted]

Study centre(s) and number of subjects planned

In this study, it is planned to include approximately 570 randomised patients from China

Study period		Phase of development
Estimated date of first subject enrolled	Q3 2011	IV
Estimated date of last subject completed	Q4 2012	

Objectives

Primary objective

The primary objective of this study is to assess the efficacy of Symbicort Turbuhaler (160/4.5µg, two inhalations twice daily) on top of ipratropium (Atrovent™, Boehringer Ingelheim, 20µg/dose, two inhalations four times daily) + theophylline SR (Shufumei, Guangzhou Med Xinhua, 0.1g p.o. twice daily) compared to ipratropium (20µg/dose, two inhalations four times daily) + theophylline SR (0.1g p.o. twice daily).

Secondary objective

The secondary objective of the study is to evaluate safety by assessing the nature, incidence and severity of adverse events (AEs).

[redacted]

Study design

This will be a multicentre study with a randomised, parallel group, open-label design to assess the efficacy and tolerability of Symbicort Turbuhaler as an add-on treatment to ipratropium + theophylline SR in patients with severe COPD. Eligible patients will be enrolled to a 2-week run-in period during which their ordinary COPD treatment will be replaced with ipratropium + theophylline SR. The patients will be provided with a short-acting β_2-agonist, salbutamol pMDI (Ventolin®, GlaxoSmithKline), for symptom relief during the study. After the run-in period, patients who fulfil the eligibility criteria will enter the 12-week treatment period.

Target subject population

The subject population will be outpatients, men or women, ≥40 years of age, with a clinical diagnosis of COPD, symptoms for at least 2 years, and should have had a COPD exacerbation during the last year. The patients must be current or previous smokers with a smoking history of ≥10 pack years, have an FEV_1 ≤50% of predicted normal and an FEV_1/Forced Vital Capacity (FVC) <70% (both pre-bronchodilator). The patients should not have used systemic glucocorticosteroids (GCS) within 4 weeks and/or inhaled GCS within 2 weeks prior to Visit 2. Patients with a history of seasonal allergic rhinitis (before 40 years of age) and/or asthma are excluded from the study.

Investigational product, dosage and mode of administration

Symbicort (budesonide/formoterol) Turbuhaler 160/4.5 µg/inhalation, two inhalations twice daily

Comparator, dosage and mode of administration

None.

Additional drugs, dosage and mode of administration

Atrovent (ipratropium) pMDI, 20 µg/dose, 2 inhalations four times daily

Shufumei (theophylline SR), 0.1g /tablet, 1 tablet p.o. twice daily

Ventolin (salbutamol) pMDI, 0.1 mg/dose, as reliever medication

Duration of treatment

The study consists of a 2-week run-in period and thereafter a 12-week treatment period. The study visits will be enrolment visit (Visit 1), start of run-in (Visit 2), randomisation (Visit 3), and after 1, 3, 6, 9 and 12 weeks of treatment (Visit 4, 5, 6, 7 and 8).

Outcome variables

- Efficacy

Primary variable

The primary outcome variable will be the change in pre-dose Forced Expiratory Volume in 1 second (FEV_1) in the morning from baseline (Visit 3) to the mean of the treatment period visits (Visit 4, 6 and 8).

Secondary variables

1. Morning pre-dose FVC, IC and post-dose FEV_1, FVC at 5 minutes and FEV_1, FVC and IC at 60 minutes at clinic visit.

2. Morning PEF measured at home, pre- and post-intake of study drug at 5 minutes

3. Use of reliever medication

4. SGRQ-C Total score

5. Number of severe exacerbations requiring systemic steroids (oral ≥3 days or parenteral) or hospitalisation or emergency room treatment due to worsening of COPD symptoms

6. COPD symptoms (breathing, cough, sputum)

- Safety

Adverse Event (type, incidence, severity)

Statistical methods

Data for patients for whom any efficacy data have been collected after randomisation will be included in the efficacy analysis.

The change in FEV_1 from baseline to treatment period will be analysed using a multiplicative Analysis of Variance (ANOVA) model with treatment and centre fixed factors and the baseline values as a covariate. Treatment differences will be estimated from the model and 95% confidence limits will be calculated. The change in other spirometry variables will be analysed in the same way. For the Patient Reported Outcomes (PRO) and diary card variables the mean changes will be compared between treatments using an additive ANOVA model.

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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.

Abbreviation or special term	Explanation
AE	Adverse Event (see definition in Section 6.4.1)
ANOVA	Analysis Of Variance
Assessment	An observation made on a variable involving a patient judgement (assessment)
COPD	Chronic Obstructive Pulmonary Disease
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CRF	Case Report Form
E-code	Enrolment code = (E +4 digit study site number +3 digit serial number)
ePEF	electronic Peak Expiratory Flow meter
Ethics Committee	Synonymous to Institutional Review Board and Independent Ethics Committee
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GCS	Glucocorticosteroid
GMP	Good Manufacturing Practice
HRQL	Health Related Quality of Life
IC	Inspiratory Capacity
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
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.
ISF	Investigator's Study File
LABA	Long-acting β_2-agonist
LAMA	Long-acting anti-cholinergics
LSDT	Local Study Delivery Team
MC	Marketing Company

Abbreviation or special term	Explanation
MedDRA	Medical Dictionary for Regulatory Activities
MWD	Mini-Wright Digital Peak Flow Meter
OAE	Other Significant Adverse Event (i.e., adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the patient from study treatment; see definition in Section 6.4.1)
Outcome variable	A variable (usually a derived variable) specifically defined to be used in the analysis of a study objective
PEF	Peak Expiratory Flow
PN	Predicted Normal
Post-dose	After intake of study drug
Pre-dose	Before intake of study drug
Principal Investigator	A person responsible for the conduct of a clinical study at an investigational study site. Every investigational study site has a Principal Investigator.
PRO	Patient Reported Outcome
SABA	Short-acting β_2-agonist
SAE	Serious Adverse Event (see definition in Section 6.4.1)
SDT	Study Delivery Team
SDV	Source Data Verification
SGRQ-C	St. George's Respiratory Questionnaire for COPD patients
SOC	System Organ Class
Study drug	The term study drug covers investigational product and additional study drug. Study drug is subject to drug accountability procedures.
SR	Sustained Release
Variable	A characteristic or a property of a patient that may vary, e.g., from time to time or between patients

1. INTRODUCTION

1.1 Background

COPD is a leading cause of morbidity and mortality worldwide, resulting in an economic and social burden that is both substantial and increasing (World Health Report 2000). In patients with COPD, lung function deteriorates progressively over years and is largely irreversible and accompanied by symptoms such as dyspnoea, cough, and sputum production. Exacerbations occur with increasing frequency in the later stages of the disease and have a considerably negative impact on patients' daily activities and Health-Related Quality of Life (HRQL) (Seemungal et al 1998).

Current treatment guidelines recommend initialization of treatment with short- and long-acting bronchodilators in mild and moderate COPD, respectively (GOLD 2010). It had shown that short-acting anticholinergics ipratropium could improve lung function, symptoms and exercise tolerance of COPD patients (Akkoca et al 2006). Long acting β_2-agonists (LABAs), such as formoterol, have been shown to improve lung function, reduce symptoms, decrease the need for reliever medication, and improve exercise tolerance and HRQL in patients with COPD (Cazzola et al 2000, Mahler et al 1999, Rennard et al 2001, Dahl et al 2001, Aalbers et al 2002, Casaburi et al 2002).

Theophylline has been used as a bronchodilator in the treatment of COPD for many years, but lost popularity as better tolerated bronchodilators have been introduced. However, there are some new insights into the molecular action of theophylline which raises physicians' interest on this old drug in COPD treatment. Some recent evidences showed that Low-dose theophylline could enhance the anti-inflammatory effects of steroids, reduces nitrative stress and neutrophil infiltration in COPD airways to a larger extent than inhaled corticosteroid, improve Health-Related Quality of Life of COPD patients and prolong time to first COPD exacerbation (Hirano et al 2009, Cosio et al 2009, Zhou et al 2006)

Treatment with combination of inhaled corticosteroids and long-acting β_2-agonists (ICS/LABA) is recommended in patients with severe COPD, and has been shown to provide benefits through improvements of lung function, symptoms, HRQL and decreased frequency of exacerbation (Calverley et al 2003a , Calverley et al 2003b, Szafranski et al 2003).

Treatment with ICS or ICS/LABA combination has also shown to attenuate airway and systemic inflammation in patients with COPD (Sin et al 2004, Ozol et al 2005, Barnes et al 2006). There is also evidence that inhaled corticosteroid therapy or therapy with ICS/LABA combination products may be associated with reduced COPD-related morbidity and mortality (Soriano et al 2002, Sin et al 2003, Calverley et al 2006).

Ipratropium and theophylline are widely use in clinical practice as the first line treatments for COPD patients in China. Budesonide/formoterol (Symbicort) is indicated in severe COPD, especially in patients with a history of COPD exacerbations. It is of interest to investigate the

benefits of adding Symbicort Turbuhaler to treatment with ipratropium+ theophylline SR in patients with severe COPD, given that the drugs act through different mechanisms of bronchodilatation and anti-inflammation.

1.2 Research hypothesis

Symbicort on top of ipratropium+ theophylline SR is superior to ipratropium + theophylline SR in pre-dose FEV_1 in COPD patients.

1.3 Rationale for conducting this study

Symbicort, ipratropium and theophylline SR are drugs that are commonly used for maintenance treatment of patients with severe COPD, separately or in combination. It is still not clear about the treatment benefits of adding Symbicort Turbuhaler to ipratropium + theophylline SR in this group of patients. This study was initiated to investigate the effects of combined treatment with these three classes of drugs in terms of improvement of lung function, symptoms and exacerbation in an Asian population with severe COPD.

1.4 Benefit/risk and ethical assessment

There is a substantial body of evidence on safety and tolerability of Symbicort, ipratropium and theophylline SR in patients with COPD, collected in clinical trials and medical practice, where the drugs are used alone or in combination. It is expected that there is no particular risk related to participation in the study over those that have previously been reported on use of these drugs. All patients will receive active treatment during the whole study period, and therefore, it is expected that all patients will obtain benefits from treatment with study drugs along with those that have been already described in the literature. The patient surveillance will be conducted throughout the study and all study procedures will follow Good Clinical Practice (GCP).

The main objective of the study is to thoroughly investigate the differences between both treatment regimens in terms of clinical benefit and risk. The study will help to answer an important clinical question regarding the treatment of patients with severe COPD in Asian population, and provide better insight to risk/benefit balance for combined use of these drugs, and will consequently benefit the future management of COPD.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of this study is to assess the efficacy of Symbicort Turbuhaler (160/4.5µg, two inhalations twice daily) on top of ipratropium (Atrovent™, Boehringer Ingelheim, 20µg/dose, two inhalations four times daily) + theophylline SR (Shufumei, Guangzhou Med Xinhua, 0.1g p.o. twice daily) compared to ipratropium (20µg/dose, two inhalations four times daily) + theophylline SR (0.1g p.o. twice daily).

Primary variable

The primary outcome variable will be the change in pre-dose Forced Expiratory Volume in 1 second (FEV_1) in the morning from baseline (Visit 3) to the mean values of the treatment period visits (Visit 4, 6 and 8).

Secondary variables

1. Morning pre-dose FVC, IC and post-dose FEV_1, FVC at 5 minutes and FEV_1, FVC and IC at 60 minutes at clinic visit.

2. Morning PEF measured at home, pre- and post-intake of study drug at 5 minutes

3. Use of reliever medication

4. SGRQ-C Total score

5. Number of severe exacerbations requiring systemic steroids (oral ≥3 days or parenteral) or hospitalisation or emergency room treatment due to worsening of COPD symptoms

6. COPD symptoms (breathing, cough, sputum)

2.2 Secondary objectives

The secondary objective of the study is to evaluate safety by assessing the nature, incidence and severity of AEs.

2.3 Exploratory objectives (Not applicable)

3. STUDY PLAN AND PROCEDURES

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca standard procedures.

3.1 Overall study design and flow chart

This will be a multi-centre, randomised, parallel-group, open-label study to assess the efficacy and tolerability of Symbicort Turbuhaler on top of ipratropium + theophylline SR in patients with severe COPD.

The primary outcome variable will be pre-dose FEV_1 in the morning assessed by spirometry at clinic visits.

- Secondary outcome variables will be:
  - Morning pre-dose FVC, IC and post-dose FEV_1, FVC at 5 minutes and FEV_1, FVC and IC at 60 minutes at clinic visit.

- Morning PEF measured at home, pre- and post-intake of study drug at 5 minutes.
- Use of reliever medication.
- SGRQ-C total score.
- Number of severe exacerbations requiring systemic steroids (oral ≥3 days or parenteral) or hospitalisation or emergency room treatment due to worsening of COPD symptoms.
- Adverse Event (type, incidence, severity).
- COPD symptoms (breathing, cough, sputum)

For further details, see Section 6.3, 6.4 and 6.5.

In this study, it is planned to include approximately 570 randomised patients, recruited from about 20 study sites in China.

The patient population will be outpatients, men or women, ≥40 years of age, with a clinical diagnosis of COPD with symptoms for more than 2 years, and should have had a history of at least one COPD exacerbation requiring a course of oral steroids and/or antibiotics within 1-12 months before Visit 2. The patients must be current or previous smoker with a history of smoking equivalent to 10 or more pack years (1 pack year = 20 cigarettes smoked per day for one year or equivalent), have an FEV_1 ≤50% of predicted normal value and an FEV_1/FVC <70% (both pre-bronchodilator). The patients should not have used systemic GCSs within 4 weeks and/or inhaled GCS within 2 weeks prior to Visit 2. Patients with a history of seasonal allergic rhinitis (before 40 years of age) and/or asthma are excluded from the study. See Section 4.1 and Section 4.2 for further details of the eligibility criteria.

Eligible patients will be enrolled to a 14 day run-in period, during which all patients will be given ipratropium 20 µg/dose two inhalations four times daily + theophylline SR 0.1g p.o. twice daily. The patients will be asked to record the diary card (including PEF, COPD symptoms, and use of reliever medication) as the baseline data.

After the 14 days run-in period, patients who fulfil the eligibility criteria at Visit 3 will be randomised to add Symbicort Turbuhaler 160/4.5 µg/inhalation, two inhalations twice daily on top of ipratropium + theophylline or continue their run-in treatment for 12 weeks. Salbutamol pMDI (Ventolin) will be used as reliever treatment throughout the study. The patients will visit the clinic at enrolment (Visit 1), run-in (Visit 2), randomisation (Visit 3), and after 1, 3, 6, 9 and 12 weeks of treatment (Visit 4, 5, 6, 7 and 8). For both groups, at each visit during the treatment, inhalation technique will be checked.

After completion of the treatment period the patients will return to their ordinary COPD therapy as judged by the Investigator.

See Figure 1 for study flow chart.

Figure 1 Study flow chart

Visit 1= Enrolment visit

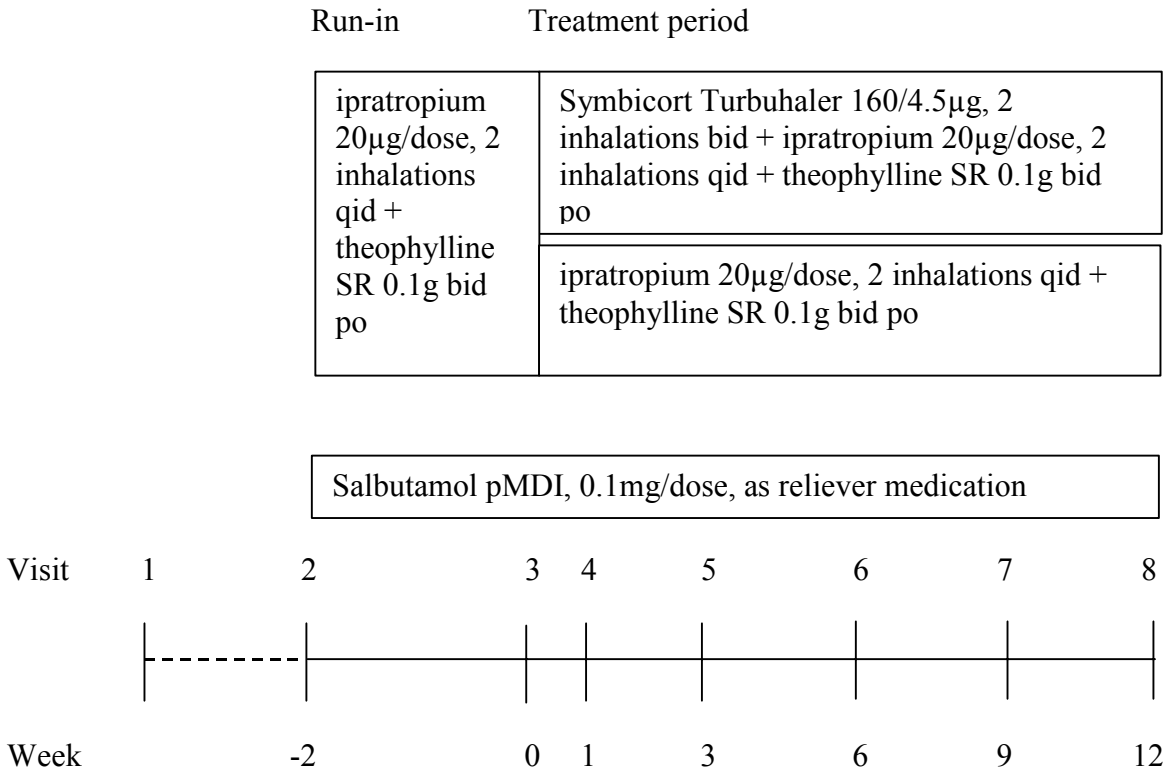
Visit 2= Start of Run-in period

Visit 3= Randomisation visit

Visit 4 and 6= Treatment visits

Visit 5 and 7= For MWD data downloading, recording of medication and AEs.

Visit 8= Study Completion visit



Clinic visits and study periods

See Table 1 for a summary of procedures at each visit.

At Visit 1 (enrolment visit) the study should be explained to the patient, the Informed Consent Form (ICF) will be signed, and demographic data will be collected. For those patients who use inhaled GCSs (including combination products) before the study, based on Investigator's judgement and after obtaining informed consent from the patients, the inhaled GCS will be

stopped at Visit 1, 2 weeks before entering the run-in period, to fulfil the eligibility criteria. All these patients will receive ipratropium + theophylline SR at the same occasion. Also, salbutamol pMDI could be dispensed at Visit 1 based on Investigator's judgement.

At Visit 2, all patients should be on ipratropium + theophylline SR as maintenance therapy and salbutamol pMDI as reliever medication, see Table 6. All patients should temporarily stop their ipratropium medication 8 hours and theophylline SR medications 24 hours before Visit 2 in order not to affect lung function measurement used for patient characteristics, and restart medication after clinical assessments.

Run-in period (Visits 2 to 3)
The run-in period will be two weeks.

At Visit 2 patients will perform reversibility test with salbutamol (see Section 6.3.1). Pulse and blood pressure will be tested, physical examination will be done and weight and height will be measured. Patients who meet all eligibility criteria will enter the run-in period, and will get training on how to fill out the diary card and use MWD.

Treatment period (Visits 3 to 8)
At Visit 3 patients who meet all eligibility criteria will be randomised to either add-on treatment with Symbicort Turbuhaler or continue using ipratropium + theophylline SR. Patients will visit the clinic after 1, 3, 6, 9 and 12 weeks of treatment (Visit 4, 5, 6, 7 and 8). Spirometry and SGRQ-C will be performed at Visits 3, 4, 6 and 8. Patients will visit the clinic at Visit 5 and 7 for Digital Peak Flow Meter (PEF) data downloading.

Study drug

Investigational product
Investigational product is Symbicort® Turbuhaler® 160/4.5 µg/inhalation, which will be given in an open manner.

Additional drugs
Ipratropium (Atrovent™) 20 µg/dose and theophylline SR 0.1g/tablet will be given as maintenance medication in an open manner. During the whole study period salbutamol pMDI 0.1 mg/dose (Ventolin®) will be used as reliever medication.

Timing of clinic visits

Due to diurnal variations in lung function, it is of great importance that the clinic visits are scheduled so that spirometry measurement can take place ±1 hour in relation to the time of the Visit 3 measurement (baseline) and before 12:00am.

Table 1 Study plan

	Enrolment period	**Run-in period**	**Treatment period**					
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Visit description	**Enrolment**	**Start of run-in**	**Randomisation**	**Treatment**	**Treatment**	**Treatment**	**Treatment**	**Study completion**
Visit Window (No. Days ± No. Days)	**>-2 w before Visit 3[e]**	**-2w(+3d) before Visit 3**	**0 day**	**1w (+3d) after Visit 3[f]**	**3w (±3d) after Visit 3**	**6w (± 3d) after Visit 3**	**9w (±3d) after Visit 3**	**12w (±3d) after Visit 3**
Informed consent	X							
Allocation of enrolment code	X							
Allocation of randomisation code			X					
Demographics	X							
X-ray[a]		X						
Medical and surgical history		X						
Nicotine use/smoking habits		X						
Inclusion/exclusion criteria	X[g]	X[g]	X[g]					
Reversibility test		X						
Standard physical examination (including vital signs, weight and height)		X						
Spirometry		X[b]	X[c]	X[c]		X[c]		X[c]
Digital Peak Flow Meter data downloading.			X	X	X	X	X	X
SGRQ-C		X(training)	X[d]	X[d]		X[d]		X[d]
Pregnancy tests (for females with child-bearing potential, judged by investigator)		X						

	Enrolment period	**Run-in period**	**Treatment period**					
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Visit description	**Enrolment**	**Start of run-in**	**Randomisation**	**Treatment**	**Treatment**	**Treatment**	**Treatment**	**Study completion**
Visit Window (No. Days ± No. Days)	**>-2 w before Visit 3[e]**	**-2w(+3d) before Visit 3**	**0 day**	**1w (+3d) after Visit 3[f]**	**3w (±3d) after Visit 3**	**6w (± 3d) after Visit 3**	**9w (±3d) after Visit 3**	**12w (±3d) after Visit 3**
Check the use of inhalers		Demonstration of inhaler and inhalation training	Demonstration of inhaler and inhalation training	Check the use		Check the use		
Recording of COPD treatment	X	X	X	X	X	X	X	X
Recording of concomitant medication	X	X	X	X	X	X	X	X
Study medication (D=dispense, R=return)	(D)[h]	D	D/R			D/R		R
Diary card (I=issue, C=collect)		I	I/C	I/C		I/C		C
MWD (I=issue, C=collect)		I						C
Adverse events		X	X	X	X	X	X	X

[a] A historic x-ray is acceptable if they are within 6 months prior to visit 2 with medical documentation.

[b] Pre-bronchodilator and post-bronchodilator FEV_1 and FVC derived from reversibility test

[c] Pre-dose FEV_1, FVC, IC and post-dose FEV_1, FVC at 5 minutes and FEV_1, FVC and IC at 60 minutes will be done at visit 3, 4, 6 and 8.

[d] SGRQ-C performed before all other assessments

[e] According to exclusion criterion 2, patients using inhaled GCSs within 2 weeks prior to Visit 2, are not eligible for the study.

[f] Not earlier than day 8 after Visit 3.

[g] Inclusion/exclusion check list is on Visit 3 in CRF.

[h] Ipratropium, theophylline SR and reliever medication may be dispensed at Visit 1 or visit 2, depending on which treatment the patient uses prior to the study. Inhalation training will be performed before the patient receives the respective study drugs.

3.2 Rationale for study design, doses and control groups

The primary objective of the study is to evaluate lung function in patients treated with Symbicort Turbuhaler on top of ipratropium + theophylline SR. The primary outcome variable will be the change in pre-dose Forced Expiratory Volume in 1 second (FEV_1) in the morning from baseline (Visit 3) to the mean values of the treatment period visits (Visit 4, 6 and 8).

There will be a number of secondary variables, such as effects on lung function shortly after drug intake, symptoms, reliever medication use, and health-related quality of life. As observed in earlier studies, lung function and symptoms improve within the first days after initiation of treatment with long-acting bronchodilators (Vincken et al 2002, Aalbers et al 2002) or ICS/LABA combination products (Szafranski et al 2003) and continue to improve during the first weeks after initiation of treatment.

The main objective of the study is to investigate the clinical benefits from adding Symbicort Turbuhaler on top of ipratropium + theophylline SR. For this reason the study will be conducted in severe COPD patients, in whom all these drugs are indicated as a maintenance treatment. The patient population is in line with previous pivotal studies (Calverley et al 2003b, Szafranski et al 2003), which were a base for approval of COPD label for Symbicort within EU in year 2003. The inclusion criteria are to include patients with severe COPD, who have FEV_1 ≤50% of predicted normal value and FEV_1/FVC <70% (both pre-bronchodilator). It is important to note that spirometric classification of COPD severity is only orientational, as the FEV_1 limits have not been clinically validated as stated in the recent update of GOLD guidelines (GOLD 2010). All the drugs will be used in marketed doses for treatment of COPD; Symbicort Turbuhaler 160/4.5 µg/inhalation, two inhalations twice daily, ipratropium 20 µg/dose, two inhalations four times daily and theophylline SR 0.1g, p.o. twice daily. The eligible patients are those who are treated with ipratropium + theophylline SR only, without addition of other long-acting bronchodilators or inhaled corticosteroids at study start, as this could influence study outcome variables.

To enable meaningful conclusions that can apply to usual clinical practice, the same formulations of drugs as those available on the market, will be used in the study in doses that are indicated for treatment of COPD patients.

4. SUBJECT SELECTION CRITERIA

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

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.

4.1 Inclusion criteria

For inclusion in the study, patients must fulfil all of the following criteria:

Inclusion criteria at Visit 1/Visit 2

1. Signed and dated informed consent
2. Out-patient, men or women ≥40 years of age
3. Clinical diagnosis of COPD with symptoms for more than 2 years
4. A history of at least one COPD exacerbation requiring a course of oral steroids and/or antibiotics within 1-12 months before Visit 2
5. Current or previous smoker with a history of smoking equivalent to 10 or more pack years (1 pack year = 20 cigarettes smoked per day for one year or equivalent)
6. FEV_1 ≤50% of predicted normal value, pre-bronchodilator
7. FEV_1/FVC <70%, pre-bronchodilator
8. Able to comply with all study procedures (including diary completion) and to satisfactory take study medication, as judged by the investigator

To be randomised to the treatment period, the following criteria must be fulfilled at Visit 3:

9. Total symptom score of 2 or more per day for at least half of the run-in period (by totalling the breathing, cough and sputum scores from the diary card).
10. Complete morning recordings of MWD data at least 7 out of the last 10 days of the run-in period

4.2 Exclusion criteria

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

1. A history of asthma
2. Seasonal allergic rhinitis before 40 years of age

3. Patients who have experienced exacerbation of COPD requiring hospitalisation and /or emergency room treatment and/or a course of oral steroids and/or intravenous corticosteroids and/or antibiotics within 4 weeks prior to Visit 2 and/or during run-in period.

4. Use of systemic glucocorticosteroids (GCS) within 4 weeks and/or inhaled GCS within 2 weeks prior to Visit 2 and/or during run-in period.

5. Patients with significant or unstable ischemic heart disease, arrhythmia, cardiomyopathy, heart failure, uncontrolled hypertension as defined by the investigator or any other relevant cardiovascular disorder as judged by the investigator

6. Any current respiratory tract disorder other than COPD, which is considered by the investigator to be clinically significant

7. Any other significant diseases or disorders, e.g., gastrointestinal, liver, renal, neurological, musculoskeletal, endocrine, metabolic, malignant, psychiatric and major physical impairment which, in the opinion of the investigator, may put the patient at risk because of participation in the study, or influence the results of study, or the patients' ability to participate in the study.

8. Any clinically relevant abnormalities in, vital signs or physical examination taken at Visit 2, as judged by the investigator may put the patient at risk because of participation in the study (to be checked before allocation of randomisation code at Visit 3)

9. Patients taking non-cardioselective oral or ophthalmic beta-blocking agents

10. Women who are pregnant, breast-feeding or of child-bearing potential (female patients must have been menopausal for at least 12 months, surgically sterile or use oral or other reliable contraceptive as judged by the investigator. For female, who has the potential to pregnancy as judged by investigator, negative pregnancy tests at Visit 2 is required).

11. Known or suspected hypersensitivity to study therapy or excipients of the investigational products.

12. Patients with clinically significant narrow-angle glaucoma, significant prostatic hyperplasia or bladder-neck obstruction in whom treatment with ipratropium

maybe related to worsening of signs and symptoms related to these conditions, as judged by the investigator.

13. Scheduled hospitalization during the course of the study

14. Participation (having treatment) in another clinical study evaluating an investigational drug in the last 4 weeks prior to enrolment (Visit 1).

15. Alcohol addiction, drug abuse or any other condition associated with poor compliance

16. Patient participating in or scheduled for an intensive COPD rehabilitation program.

17. Planned donation of blood during the study

18. Previous enrolment or randomisation of treatment in the present study.

19. Use of non-allowed medication (see 5.6.1.2)

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

5. STUDY CONDUCT

5.1 Restrictions during the study

The patient will be asked to avoid strenuous exercise 2 hours and smoking, if applicable, within 1 hour before visiting the clinic.

5.2 Subject enrolment and randomisation

At Visit 1 all patients will sign the ICF. At Visit 2, eligible patients will enter the run-in period. During the run-in period, the patient will be treated with ipratropium 20 µg two inhalations four times daily + theophylline SR 0.1g p.o. twice daily.

If the patient is eligible and fulfils the inclusion criteria and meets none of the exclusion criteria at Visit 3, the patient will be allocated a randomisation code. Patients will be randomised to treatment with Symbicort Turbuhaler 160/4.5 µg/inhalation, two inhalations twice daily on top of ipratropium + theophylline SR or continue using ipratropium + theophylline SR.

Patients will receive randomisation codes strictly sequentially per site as patients are eligible for randomisation. If a patient discontinues from the study, the randomisation code will not be reused, and the patient will not be allowed to re-enter the study.

The randomisation code will be assigned from a randomisation list prepared by statistical team at AstraZeneca. The Investigator will be provided randomisation code for each patient. Patients will be randomised equally (ratio 1: 1) to the two treatment arms of this study.

Symbicort will be given via the dry powder inhaler Turbuhaler every morning and evening, see Table 3.

The inhalation of Symbicort Turbuhaler should be performed in the morning after bed rise and after recording of pre-dose PEF measurement, and in the evening before going to bed. The inhalation of ipratropium pMDI should be performed in the morning after bed rise and after recording of pre-dose PEF measurement, 30 minutes before Lunch and Supper, and then in the evening before going to bed. The theophylline SR should be taken in the morning after bed rise and after recording of pre-dose PEF measurement, and in the evening before going to bed. For the standardisation reason, in the Symbicort Turbuhaler add-on group, patients will inhale from ipratropium pMDI first and Symbicort Turbuhaler second, then taking theophylline SR orally.

The first dose of investigational product will be taken at the clinic on the day of Visit 3, and the last dose at the clinic on the day of Visit 8.

5.2.1 Procedures for randomisation

The Principal Investigator will:

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

2. Assign potential subject a unique enrolment number, beginning with ‘E#’.

3. Determine subject eligibility. See Sections 4.1 and 4.2

4. Assign eligible subject unique randomisation code (subject number), beginning with ‘#’. Enrolment code = (E +4 digit study site number +3 digit serial number)

5. Randomisation envelopes will be provided by AstraZeneca. Investigators should be opening the envelopes in running order.

5.3 Procedures for handling subjects incorrectly enrolled

Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule.

Where patients that do not meet the inclusion criteria are enrolled in error or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post initiation, the investigator should inform the AstraZeneca Global Study Delivery Team Physician immediately. The AstraZeneca Global Study Delivery Team Physician is to ensure all such contacts are appropriately documented.

5.4 Blinding and procedures for unblinding the study (Not applicable)

5.5 Treatments

5.5.1 Identity of investigational product(s)

Investigational products included in Table 2 will be provided by AstraZeneca to the patients throughout the study.

Table 2 Identity of investigational product

Investigational product	Excipients	Dosage form and strength	Manufacturer
Symbicort® Turbuhaler® (budesonide/formoterol fumarate dehydrate)	Lactose monohydrate	inhalation powder, 160 µg/4.5 µg/inhalation, 60 inhalations/Turbuhaler	AstraZeneca

5.5.2 Doses and treatment regimens

See Table 3.

Table 3 Investigational product during treatment period

	Symbicort Turbuhaler 160/4.5 µg/inhalation
Generic name	Budesonide/formoterol fumarate dehydrate
Route and mode of administration	Inhalation powder via Turbuhaler
Dose, and dose frequency	160 µg/4.5 µg/inhalation Two inhalations every morning and evening

	Symbicort Turbuhaler 160/4.5 µg/inhalation
Dosing details	Morning: Inhalation should be taken after Atrovent, then taking theophylline SR orally, after bed rise and after recording of pre-dose PEF measurement Evening: Inhalation should be taken after Atrovent, then taking theophylline SR orally, before going to bed At clinic visit 3, 4, 6 and 8: morning dose taken at the clinic
Instructions /Training	Inhalation training will be given at Visit 2 and 3 and checked at Visit 4 and 6
Duration of treatment period	12 weeks (treatment period)
First dose intake	At the clinic at Visit 3, after SGRQ-C and pre-dose spirometry measurement (together with Atrovent, then theophylline SR)
Last dose intake	At the clinic at Visit 8, after SGRQ-C and pre-dose spirometry measurement (together with Atrovent, then theophylline SR)

5.5.3 Additional study drug

Eligible patients will be enrolled to a 2 week run-in period, during which all patients will be treated with ipratropium 20 µg/dose, 2 inhalations four times daily + theophylline SR 0.1g twice daily.

All patients will be provided by AstraZeneca with maintenance and reliever medication throughout the run-in period and treatment period. ipratropium, theophylline SR and salbutamol pMDI will be dispensed at Visit 1 or Visit 2, depending on which COPD treatment patients use prior to the study, see Section 3.1. After Visit 8, the patients will return to their ordinary COPD treatment, at the discretion of the Investigator.

Maintenance medication: Ipratropium 20 µg/dose will be given via pMDI in an open manner, two inhalations four times daily, and theophylline SR 0.1g will be taken orally twice daily, in an open manner, throughout the study (from Visit 2 to Visit 8).

Reliever medication: Salbutamol pMDI 0.1 mg/dose will be provided as reliever medication for the whole conduct of the study. When receiving the study drugs the patient will be carefully instructed and trained on how to inhale from Turbuhaler and pMDI to ensure good inhalation technique during the study. Written information will be provided to each patient in their local language.

See Table 4 and Table 5 for details of additional study drugs.

Table 4 Identity of additional drugs

	Salbutamol pMDI, used as reliever medication during run-in and treatment period, and for reversibility testing at Visit 2	**Ipratropium, used for maintenance treatment during run-in and treatment period**	**Theophylline SR, used for maintenance treatment during run-in and treatment period**
Trade Name:	Ventolin	Atrovent	Shufumei
Active ingredients:	salbutamol	ipratropium	theophylline
Excipients:	-	-	-
Dosage form:	pMDI	pMDI	tablet
No. of doses:	200 doses/pMDI	200 doses/pMDI	24 tablets/box
Strength:	0.1 mg/dose	20 µg/dose	0.1g /dose
Manufacturer:	GlaxoSmithKline	Boehringer Ingelheim	Guangzhou Med Xinhua

Table 5 Additional study drug

	Ventolin Reliever medication	**Atrovent Maintenance medication**	**Theophylline SR Maintenance medication**	**Ventolin Reversibility test**
Generic name	salbutamol	ipratropium	Theophylline	salbutamol
Route and mode of administration	pMDI	pMDI	p.o.	pMDI
Dose and dose frequency	0.1 mg/dose To be used as needed	20 µg/dose 2 inhalations, q.i.d	0.1g/tablet 1 tablet, b.i.d	0.1 mg/dose 2 inhalations for reversibility test
Dosing details	To be used as needed	Morning: Inhalation should be taken after bed rise and after recording of and PEF measurement Noon and afternoon: Inhalation should be taken 30 minutes before lunch and supper Evening: Inhalation should be taken	Morning and evening: tablet will be taken after inhalation medication	To be used for reversibility test

	Ventolin Reliever medication	**Atrovent Maintenance medication**	**Theophylline SR Maintenance medication**	**Ventolin Reversibility test**
		before going to bed At clinic Visit 3, 4, 6 and 8: morning dose taken at the clinic		
Instructions /Training	Inhalation training will be given at Visit 1 or Visit 2	Inhalation training will be given at Visit 1 or Visit 2	-	Inhalation training will be given at Visit 2
Duration of treatment period	To be used as needed throughout the study (run-in and treatment)	As maintenance treatment throughout the study (run-in and treatment)	As maintenance treatment throughout the study (run-in and treatment)	Reversibility test at Visit 2
First dose intake	As needed after dispensed at Visit 2	Morning after dispensed at Visit 2	Morning after dispensed at Visit 2	Visit 2

5.5.4 Labelling

Re-packaging and re-labelling of study drugs will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language. Ipratropium dispensed at Visit 1 or 2 will be individually labelled with a detachable part that should be inserted into the CRF workbook when the drug is dispensed. So will the Theophylline SR. The E-code together with the visit number will be filled in by the study site.

After randomisation:

For ipratropium + theophylline SR treatment group, ipratropium and theophylline SR (maintenance medication) will be packed and dispensed as patient specified visit kit (Visit 3 and 6). Each visit kit will have a label with a detachable part which should be inserted into CRF workbook when the drug is dispensed. The E-code and randomisation code will be filled in by the study site.

For add-on treatment group, Symbicort Turbuhaler, ipratropium and theophylline SR will be packed and dispensed as patient specified visit kit (Visit 3 and 6). Each visit kit will have a

label with a detachable part which should be inserted into CRF workbook when the drug is dispensed. The E-code and randomisation code will be filled in by the study site.

Salbutamol (reliever medication) will be individually labelled and dispensed for the whole conduct of the study (Visit 1 or 2, Visit 3 and 6). The label has a detachable part which should be inserted into CRF workbook when the drug is dispensed. The E-code and randomisation code and visit number will be filled in by the study site.

The study drug should be dispensed and returned as outlined in Table 6.

Table 6 Number of dispensed and returned study drug per patient at each clinic visit

Visit No.	**Symbicort (160/4.5 µg x 60 inhalations) for treatment period**		**Atrovent (20µg x 200 doses/pMDI) for whole study period**		**Theophylline SR (0.1g/tablet x 24 tablets/package) for whole study period**		**Ventolin (0.1mg x 200 doses) for whole study period**	
	Dispensed	**Returned**	**Dispensed**	**Returned**	**Dispensed**	**Returned**	**Dispensed [a]**	**Returned**
Visit 1[b]			1 pMDI		2 packages		1 pMDI	
Visit 2			1 pMDI	1 pMDI[c]	2 packages	2 packages[c]	1 pMDI	1 pMDI[c]
Visit 3	3 Turbuhalers		2 pMDIs	1 pMDI	4 packages	2 packages	2 pMDI	1 pMDI
Visit 6	3 Turbuhalers	3 Turbuhalers	2 pMDIs	2 pMDIs	4 packages	4 packages	2 pMDI	2 pMDI
Visit 8		3 Turbuhalers		2 pMDIs		4 packages		2 pMDIs

[a] The patient may receive more reliever medication if needed.

[b] only for patients who need to dispense Atrovent, theophylline SR or Ventolin, at Visit 1, see Section 3.1.

c only for patients who get Atrovent, theophylline or Ventolin at Visit 1.

5.5.5 Storage

All study drugs must be kept in a secure place under appropriate storage conditions. A description of the appropriate storage conditions is specified in the document 'Procedure of storage conditions for investigational product'.

5.6 Concomitant and post-study treatment(s)

The ICF must be signed before conducting any study-related procedures, e.g., discontinuation of pre-study COPD treatment.

The Investigator should be familiar and comply with all applicable information regarding concomitant medications in the Investigators Brochure/prescribing information for the study drugs.

The not allowed medication described in this section (see Table 7) will affect the study variables and is therefore restricted.

Other medication, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the Investigator(s). The administration of all medication must be recorded in the appropriate sections of the CRF.

Treatment after completion of the study (completed/discontinued) will be performed according to local medical practice.

5.6.1 Allowed and not allowed medication

5.6.1.1 Medication allowed from Visit 1/Visit 2 and throughout the study

- Ipratropium 20 µg/dose, two inhalations four times daily + theophylline SR 0.1g p.o. twice daily, as maintenance medication. Ipratropium and theophylline SR should be temporarily stopped 8 hours and 24 hours, respectively prior to Visit 2, and restarted after clinical assessments

- Salbutamol 0.1 mg/dose as reliever medication. Salbutamol should not be used within 6 hours prior to clinic visits.

5.6.1.2 Treatments to be withdrawn before/at Visit 2 and throughout the study

Table 7 Not allowed medication

Treatments to be withdrawn before/at Visit 2 and throughout the study	Time limits prior to Visit 2
1. Short-acting β2-agonists (other than salbutamol, see Section 5.6.1.1)	6 hours
2. Long-acting β2-agonists	48 hours
3. Inhaled short-acting anticholinergics (other than ipratropium, see Section 5.6.1.1)	8 hours
4. Inhaled long-acting anticholinergics	48 hours
5. Xanthine-containing derivates once daily	48 hours
6. Xanthine-containing derivates twice daily (other than theophylline SR used in this study, see Section 5.6.1.1)	24 hours
7. Any medication containing ephedrine	24 hours
8. Inhaled corticosteroids, including nasal steroids	2 weeks
9. Oral and parenteral steroids	4 weeks
10. Disodium cromoglycates	at Visit 2
11. Antihistamines	at Visit 2
12. Mucolytics (e.g., N-acetylcystein)	at Visit 2
13. Leukotriene antagonists and 5-LO inhibitors	48 hours
Medication (14 and 15) restricted for safety reasons - if patient needs this treatment he/she should be withdrawn from the study	
14. Non-cardioselective β-blockers, including eye-drops	From Visit 2
15. Systemic treatment with potent CYP 3A4 inhibitors (e.g., ketoconazole)	From Visit 2

5.6.1.3 Medication prior to clinic visit

The following is important in order not to affect the clinic assessments:

- All treatments specified in Table 7 will be stopped before/at Visit 2 (based on Investigator's judgement and after obtaining Informed Consent from the patients).

- The patient should temporarily stop his/her ipratropium and Theophylline SR medications 8 hours and 24 hours respectively before Visit 2 and restart after clinical assessments.

- The patient must not take study drugs at home in the morning of the clinic visit days, but will administer the dose during clinic visits.

- The patient will be asked to refrain from taking reliever medication at least 6 hours prior to the clinic visits.

- Study drug should be administered at the same time at clinic Visit 3 to 8 (±1 hour in relation to Visit 3, except Visit 5 and 7) and, in addition, at clinic Visit 4 to 8 (except Visit 5 and 7) the study drugs should be administered 12 hours ±1 hour after the evening dose of the study drug on the preceding day.

- If the patient has taken their maintenance medication prior to their clinic visit or reliever medication within 6 hours prior to the tests, the study visit must be rescheduled.

5.6.2 Medication allowed for treatment of exacerbation after Visit 3 and throughout the study

1. Oral steroids i.e., prednisolone/prednisone

2. Antibiotics allowed when signs of infection are present

3. Parenteral steroids (single injections but not depot formulations)

4. Medications included in No 1 to 12 (see Table 7) above are allowed during emergency room treatment/hospitalisation due to an exacerbation

Systemic steroids (oral and parenteral) and other treatment due to COPD exacerbation should be recorded in the CRF together with the start and the end date of each exacerbation. The start date is defined as the first day of hospitalisation/emergency room treatment or the first day of GCS treatment (oral or parenteral). The end date is defined as the last day of hospitalisation/emergency room treatment or the last day of GCS treatment (oral or parenteral). If the same exacerbation includes both hospitalisation/emergency room treatment and GCS treatment (oral or parenteral), the start and end dates are the first and last day that either of the criteria was fulfilled.

5.7 Treatment compliance

The administration of all study drugs (including investigational products) should be recorded in the appropriate sections of the Case Report Form.

Compliance with daily prescribed dose

The patient will record intake of study drug in the diary card on a daily basis (morning and evening [during run-in morning only]) throughout the whole study period. The study personnel must check the diary card at each clinic visit (except Visit 5 and 7).

Compliance with inhalation technique

When receiving the respective study drugs, the patient will be instructed by the study personnel in how to take the medication. The patient will practise inhalation technique with empty inhalation devices, as many times as the supervising Investigator/study nurse judges to be necessary, in order to inhale properly according to instructions. Patients will also be provided with written information in local language on how to correctly use Turbuhaler and pMDI. The importance of complying with the dose regimen will be emphasized.

5.7.1 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.

Dispensed and returned study drug will be recorded in the CRF workbook (see Table 6).

The destruction of used and unused study drug should preferably be done by the study site. If destruction at the study site is not possible, the monitor should return the study drug to the distribution site. All destruction of study drug must be done by an appropriately qualified organization.

5.8 Discontinuation of investigational product

Subjects may be discontinued from investigational product in the following situations:

- Voluntary discontinuation by the patient who is at any time free to discontinue treatment, without prejudice to further treatment
- Safety reasons as judged by the investigator and/or AZ
- Severe non-compliance to study protocol

- Incorrect enrolment or randomisation as judged by the investigator and AZ
- Patient lost to follow-up
- Pregnancy

5.8.1 Procedures for discontinuation of a subject from investigational product

A subject that decides to discontinue investigational product will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator(s). Adverse events will be followed up (See Sections 6.4.3 and 6.4.4); diary cards, questionnaires (e.g., for patient reported outcomes), all study drugs should be returned by the subject.

All patients who have signed ICF will be given an Enrolment code (E-code =E +study site number (4 digits) +serial number (3 digits)).

If an enrolled patient discontinues during the run-in period or fails to meet the eligibility criteria at Visit 3, the patient must not be randomised. The reason(s) for discontinuation should be recorded in the Case Report Form (CRF). The Investigator should record E-code and reason for withdrawal in the patient's hospital record. For patients withdrawn during the run-in period only assessment of AE will be performed.

For patients withdrawn due to incorrect enrolment or randomisation, no further assessments will be performed at the final visit, except for the assessments of AEs.

Randomised patients who discontinue during the treatment period should, if possible, be seen and assessed by the Investigator, and the assessments scheduled for the final visit (Visit 8) should be completed and recorded in the CRF.

If a patient discontinues the study due to deterioration of COPD, the reason for discontinuation should be recorded as AE.

The AstraZeneca monitor or representative should be informed whenever a patient is withdrawn or discontinues the participation in the study.

If a subject is withdrawn from study, see Section 5.9.

5.9 Withdrawal from study

Subjects are at any time free to withdraw from study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Such subjects will always be asked about the reason(s) and the presence of any adverse events. If possible,

they will be seen and assessed by an investigator. Adverse events will be followed up (see Section 6.4.3 and Section 6.4.4); diary cards, questionnaires, all study drugs should be returned by the subject.

Withdrawn subjects will not be replaced.

6. COLLECTION OF STUDY VARIABLES

The CRFs, MWD, diary cards, will be provided for the recording of all study related data. MWD data will be downloaded, winzipped, encrypted and sent to Tigermed by investigator.

6.1 Recording of data

The investigator will ensure that data are recorded on the CRF as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, legibility and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed CRF. A copy of the completed CRF will be archived at the study site.

6.2 Data collection and enrolment

The investigator is responsible for prompt reporting of accurate, complete, and legible data in the CRFs and in all required reports and will maintain a list of personnel authorized to enter data into the CRF. A CRF must only be completed, if the patient's enrolment is ensured.

Any change or correction to the CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. Use of correction fluid is not permitted. Corrections made after the investigator's review and signature of the completed CRF will be re-signed and dated by the investigator.

Each patient planned for study inclusion will be recorded in a patient screening log with initials, date of birth, date of signed consent and reason for possible screening failure. The investigator will keep a list containing all enrolled patients. This list remains with the investigator and is used for unambiguous identification of each patient. The list contains the subject number, full name, date of birth, date of enrolment and the hospital number or National Health Security number, if applicable.

The subject's consent and study inclusion must be recorded in the patient's medical record. These data should identify the trial and document the dates of the patient's participation.

CRFs/external electronic data will be entered/loaded in a validated electronic database. Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data. CRF data are entered into the clinical database using independent, double-data entry, with the exception of comment fields, which are verified by a second person.

An electronic audit trail system will be maintained within the system to track all data changes in the database once the data has been saved initially into the system or electronically loaded. Regular backups of the electronic data will be performed.

The following demographic information will be collected.

Pre-study Subject Review

In order to include eligible patients at Visit 2, the Investigator will be asked to perform a Pre-study Subject Review based upon:

- Age
- Diagnosis of COPD and duration of symptoms
- COPD exacerbation history
- Concomitant medication and medical history
- Smoking history

The following data are to be collected at Visit 1 and recorded in the CRF:

- Date of birth, sex and race
- COPD history: date of first appearance of symptoms and date of diagnosis
- Number of exacerbations in the previous 12 months and the date and treatment of the most recent exacerbation
- Current medication used by the patient at enrolment in the study and during the 30 days preceding enrolment

The remaining data are to be collected at Visit 2 and recorded in the CRF:

- Smoking habits (nicotine use)

- Medical and Surgical history: past and current medical and surgical history
- Weight and height (height will be measured in cm (without shoes) and weight in kg (light clothes and without shoes)
- Physical examination, see Section 6.4.6
- Vital signs (pulse and blood pressure), see Section 6.4.8
- Spirometry (FVC and FEV_1) before intake of any study drug, see Section 6.3.1
- Reversibility test, Section 6.3.1.

6.3 Efficacy

6.3.1 Lung function measurements

Lung function will be measured by spirometry, including FEV_1, FVC and IC.

Equipment

Spirometers used in this study should meet the American Thoracic Society (ATS) and European Respiratory Society (ERS) recommendations (ATS/ERS 2005) as certified by an independent laboratory or through a review of summary data from the manufacturer, and it must have IC recording properties. The same spirometer should be used for each subject throughout the study. The monitor is responsible for checking that the spirometer in use meets these recommendations.

Spirometry data should be given at body temperature, barometric pressure and saturated with water vapour, using a calibrated spirometer. Calibration should be in accordance with each trademark specification. If nothing else is specified, calibration should be performed every day when a patient visits the clinic. Instead of using a 3 L syringe, a 1 L can be used three times. The accuracy of the calibration must be within ±3% of the reading or ±0.05 L, whichever is greater. All calibration reports should be signed, dated and filed in the Investigator Study File (ISF) along with a signed and dated copy (if the calibration reports are not on archive-proof paper). If a calibration report cannot be printed, the results should be documented in writing in the ISF.

The spirometer should be serviced once a year or according to the manufacturer's instruction at an authorized facility. All service measures and repairs must be documented.

Measurements/Conditions

Spirometry should be performed according to the ATS and ERS recommendations (ATS/ERS 2005).

If the patient has taken his/her morning dose of study drug prior to their clinic visit or reliever medication within 6 hours prior to the tests, the study visit must be rescheduled.

At Visit 2, the spirometry measurement will be performed after the physical examination, pulse rate and blood pressure measurement.

It is of great importance that all spirometry measurements, including post-dose measurements at Visit 4, 6, 8 take place ±1 hour relative to the time of the Visit 3 measurement (baseline) and before 12am.

For standardization of spirometry testing, each patient must be instructed to take his/her evening dose of study drug 12 ±1 hours prior to the morning pre-dose spirometry at each visit. This may mean that the dose of study drug taken the evening prior to a study visit will be administered at a slightly different time than usual.

At days for clinic Visit 3 to 8 (except Visit 5 and 7), the inhalation of study drug should be performed at the clinic after the pre-dose measurements.

After pre-dose measurement, for add-on treatment group, both inhalers should be prepared, and the patient will inhale from both inhalers in the directed order. The second inhalation should be taken immediately, no later than 30 seconds after the first one. The post-dose spirometry should be performed after 5 minutes and 1 hour respectively, measured from the latest inhalation of study drug.

Before spirometry testing, the patients should avoid strenuous exercise within 2 hours and smoking, if applicable, within 1 hour and throughout the assessment. Neither should measurements be performed shortly after meals and the patient should rest for at least 15 minutes prior to the test.

The same spirometer should be used for each patient at each study site and the same study personnel should be present for all visits and encourage the patient during the spirometry tests.

The print-outs from the lung function measurements must be signed, dated, and marked with study code, E-code/randomisation code, date and time of measurement, visit number, and patient initials and must be filed in the ISF. It is accepted to file only one spirometry print-out from each separate manoeuvre if the spirometer in use automatically selects and prints the best

of the curves. If the print-outs are not archive-proof (i.e., will fade over time), signed and dated photocopies of the print-outs should be filed together with the originals in the ISF.

FEV_1, FVC, IC

The spirometry will be performed in a sitting upright position. The patient will wear a nose-clip, and the thorax should be able to move freely, hence tight clothing should be loosened.

The spirometry measurements should start with slow manoeuvres (IC) and will be followed with forced expiratory manoeuvres (FEV_1, FVC). Between slow and forced manoeuvres, the patient will be allowed to take a rest by breathing freely for about 1-2 minutes.

Inspiratory Capacity (IC)

IC will be measured at Visit 3 to 8 (except Visit 5 and 7). The measurements will be performed pre-dose and 1 hour after inhalation of study drug. The IC is the sum of the Tidal Volume and the Inspiratory Reserve Volume.

Before the actual measurement starts, the patient should have taken 3-5 normal breaths. The patient will then be prompted that after the next normal exhalation, breath in until their lungs are full and then try to give an extra effort to fill up even more. They will be asked to do this fairly quickly so as not to interrupt breathing for very long. The manoeuvre will end with a normal, unforced exhalation. At each time-point, the highest out of two measurements will be recorded.

Forced Expiratory Volume in 1 second (FEV_1) and Forced Vital Capacity (FVC)

FEV_1 and FVC will be conducted at all clinic visits, except Visit 5 and 7. At Visit 2 FEV_1 and FVC will be performed for patient characteristics, together with reversibility test. At Visit 3 to 8 (except Visit 5 and 7), FEV_1 and FVC measurements will be performed pre-dose and 5 minutes and 1 hour after inhalation of study drug.

Lung function tests will consist of three expiratory manoeuvres, during which the patient should exhale from full inspiration as hard and fast as possible. The FVC manoeuvres should be technically satisfactory and reproducible, i.e., the difference between the highest and second highest FEV_1 should not vary by more than 5% or 0.1 L whichever is greater. FEV_1 values will be taken from the FVC manoeuvres and the highest values of FEV_1 and FVC should be recorded in the CRF. The highest FEV_1 and FVC can come from different curves.

If reproducibility is not fulfilled, up to eight manoeuvres should be performed to meet the above criteria. If they are still not fulfilled after the maximum of performed manoeuvres, a

note should be made on the spirometry print-out and the highest of the values should be reported in the CRF.

Reversibility measurement

At Visit 2, FEV_1 will be measured before and 15±5 minutes after two inhalations of Ventolin 0.1 mg/dose, and will be recorded as demographic data. The reversibility is calculated as follows in Equation 1.

$$Reversibility = \frac{FEV_{1(after)} - FEV_{1(before)}}{FEV_{1(before)}} X\,100 \quad (1)$$

Predicted normal FEV_1

The Predicted Normal (PN) FEV_1 value will be calculated according to the European Steel and Coal Community (Quanjer et al 1993):

FEV1 PN			
Women	FEV1 PN	=	(3.953 x H[a]) - (0.025 x A[b]) - 2.604
Men	FEV1 PN	=	(4.301 x H) - (0.029 x A) - 2.492

[a] H: standing height in metres.

[b] A: age (year). For ages >70 years, an age of 70 should be used in the equation.

Pre-bronchodilator FEV_1 expressed as % of PN value will be calculated according to the formula below:

$$FEV_1\,\%\text{ of PN} = \frac{FEV_1}{FEV_1 PN} X\,100$$

6.4 Safety

The safety variable is adverse events (nature, incidence and severity) within the treatment groups.

6.4.1 Definitions of adverse events

An adverse event 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.

6.4.2 Definitions of serious adverse event

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

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the 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 to the Clinical Study Protocol.

6.4.3 Recording of adverse events

Adverse Events will be collected from Visit 1 until the end of study (Visit 8). SAEs will be recorded from the time of informed consent. Any further visit(s) after Visit 8 can be required, if necessary, by investigators' judgement.

Follow-up of unresolved adverse events

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

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 Investigational Product (yes or no)
- Action taken with regard to investigational product
- 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 serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- 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

Causality collection

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

For SAEs causal relationship will also be assessed for other medication and 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 to the Clinical Study Protocol.

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 CRF. The question will be put to each subject in local language at Visit 2-8. 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.

Maximum Intensity

Maximum intensity refers to the complete course of the AE. The patients 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)

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 6.4.2. 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 an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

Concomitant medication

All changes in the patient's ordinary medication, e.g., dose change or addition of new medication, must be reported in the medication log. Reasons for changes in medication, which reflect an AE, must be recorded on the AE module.

Diary

The patients will be provided with a diary card to record study variables. The investigator is responsible to review the diary card together with the patient and transfer any indications of AEs to the AE form.

Symptoms of the disease under study

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

- The sign or symptom is serious according to definitions, see Section 6.4.2 and/or
- The patient discontinues the study due to the sign or symptom and/or
- The sign or symptom is new to the patient or not consistent with the patient's pre-existing COPD history (defined as within 1 year of Visit 2) as judged by the Investigator

Abnormal findings

All cases of diagnosed pneumonia should be confirmed by chest X-ray and CRP.

Overdose

Should an overdose (accidental or deliberate) occur, it must be reported in accordance with the procedures described in Section 13.2, Procedures in case of overdose, regardless of whether the overdose was associated with any symptom or not. All symptoms associated with the overdose should be reported as AEs.

Pregnancy

Should a pregnancy occur, the patient must be discontinued from the study and the pregnancy must be reported in accordance with the procedures described in Section 13.3, Procedures in case of pregnancy. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

Coding of AEs

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). For data in the study database, coding will be performed by Tigermed using the Tigermed ClinStReport application. The standard dictionaries MedDRA and AstraZeneca Drug Dictionary will be used.

MedDRA includes five levels: lowest level terms, preferred terms, high level terms, high level group terms, and system organ class (SOC) terms. Lowest level terms are used on the input side (data entry) to reflect as closely as possible the term used by the Investigator or patient to describe the event. Preferred terms are mainly used on the output side (data presentation) to group terms that are synonymous or closely related. High level terms and high level group terms are also used on the output side. SOC terms group AEs pertaining to the same body system.

6.4.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives within one day i.e., immediately but **no later than the end of the next business day** 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 one calendar day** of initial receipt for fatal and life threatening events **and within five calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events 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 the end of the next business day** of when he or she becomes aware of it.

Investigators and other site personnel should inform (emergency report) appropriate AstraZeneca representatives of any SAE that occurs at his or her site in the course of the study within 1 day (in this section, within 1 day is defined as 'immediately but no later than the end of the next business day') of when he or she becomes aware of it (initial SAE report). This should apply whether or not the SAE is considered causally related to the study treatment or to the study procedure(s). The Principal Investigator should provide detailed information to

AstraZeneca in writing within 4 calendar days of the initial report. The Principal Investigator should notify the serious adverse events in writing to the head of the study site immediately.

Follow-up information on SAEs should also be reported to AstraZeneca by the investigator(s) within the same time frames. If a non-serious AE becomes serious, this and other relevant follow-up information should also be provided to AstraZeneca within 1 day as described above.

The following information is required in the initial SAE report to AstraZeneca from the investigator(s); study code, site number, Enrolment code, adverse event, seriousness, start date. The following detailed information should be sent to AstraZeneca as soon as it becomes available;

Severity, outcome (including stop date, if available), causality (investigational product and if applicable any other concomitant drug), date when a non-serious AE became serious, withdrawal of study treatment, treatment of adverse event, concurrent therapy (except for treatment of AE), concurrent medication (including pre-study medication if the causality of the AE cannot be assessed), date of birth, sex, other current illnesses, relevant medical history and if applicable, date and course of death.

6.4.5 Laboratory safety assessment (Not applicable)

6.4.6 Physical examination

Physical examination will be performed on all patients according to normal clinic routines. At Visit 2 a full/standard examination will be performed in order to establish demography, including general appearance, head and neck, lymph nodes, cardiovascular, lungs, and abdomen.

6.4.7 ECG (Not applicable)

6.4.8 Vital signs

Vital signs (blood pressure and pulse rate) measurements will be performed at Visit 2.

Pulse (beats/min) will be measured over 30 seconds in a sitting position, after a 5-minute rest. Thereafter, systolic and diastolic blood pressure (mmHg) will be measured using the same cuff size, appropriate for arm circumference, throughout the study.

6.4.9 Other safety assessments (Not applicable)

6.5 Patient-Reported Outcomes (PRO)

6.5.1 St. George's Respiratory Questionnaire for COPD patients (SGRQ-C)

The PRO questionnaire used in this study is the SGRQ-C. The SGRQ-C will be administered at the clinic Visit 3, 4, 6 and 8 (and at Visit 2 for training purposes).

The SGRQ-C is a modified and shorter version of the St. George's Respiratory Questionnaire (SGRQ), which has been developed to measure the impact of respiratory disease on health status (Jones et al 1991). The SGRQ-C contains 3 domains: Symptoms (distress due to respiratory symptoms, 7 questions), Activity (disturbance of physical activity, 13 questions), and Impacts (overall impact on daily life and well-being, 20 questions). The original SGRQ has undergone rigorous validation and has shown to have strong evaluative and discriminative measurement properties (Jones et al 1992). For COPD patients, SGRQ-C has been shown to have even more favourable measurement properties than the original SGRQ (Meguro et al 2005). Linguistically validated translations of SGRQ-C into local languages will be used. The English version is included in Appendix C.

Administration of SGRQ-C

It is important to administer the SGRQ-C questionnaire and other questions included in the diary card according to the guidelines for standardized administration. A brief introduction on how to complete the SGRQ-C questionnaire will also be given at Visit 2 prior to the assessment. The patients will answer the questions in SGRQ-C at clinic Visit 3, 4, 6 and 8 before any other study related procedures take place except at Visit 2 (training session). At Visit 2 the SGRQ-C will be done after the lung function test has been performed. It takes approximately 10 minutes to answer the questionnaire.

At clinic visits, the SGRQ-C should be completed in a quiet place without influence from study personnel or accompanied family or friend. The patient needs to be able to read and understand the local language to be able to answer the questions. The patient should be informed about the importance of their participation and be given adequate time to complete all items, i.e., no time limits for completing the questions should be given. The study personnel are not to help the patients to choose an answer and must be neutral in their response to any questions from the patient. The study personnel must neither interpret nor rephrase questions the patient may have. After completion of the questionnaire, the study personnel will review the questionnaire for completeness only.

6.5.2 Diary Card

The patient will be instructed to maintain a diary card throughout the study, to record data morning and evening. At Visit 2, all patients will be carefully instructed and trained in how to fill in the diary. Written information will be supplied to each patient.

The following information will be recorded in the diary cards (see Table 8):

- COPD symptoms
- Reliever medication
- Intake of study medication.

Table 8 Diary cards assessments

Run-in period	**Treatment period**
Morning	
Reliever medication (use during night)	Reliever medication (use during night)
PEF pre-dose	PEF pre-dose, 5 minutes post dose
Intake of study drug (morning)	Intake of study drug (morning)
Evening	
COPD symptoms (Breathing, Cough, Sputum)	COPD symptoms (Breathing, Cough, Sputum)
Reliever medication (use during day)	Reliever medication (use during day)
Intake of study drug (evening*)	Intake of study drug (evening*)

*For ipratropium, it also includes inhalations before lunch and supper

6.5.2.1 COPD symptoms

The COPD symptom questions include one question each on breathing, cough, sputum due to COPD symptoms. Linguistically validated translations of the questions about COPD symptoms will be used. The English version of these questions is included in Appendix C.

The COPD symptom questions will be used as a daily diary and will be included in the diary card. Throughout the run-in period and the 12 treatment weeks, COPD symptom questions will be asked in the evening. The patients need to be able to read and understand the local language to be able to answer the questions.

6.5.2.2 Reliever use

Questions about the use of reliever medication will be answered in the diary card morning and evening during the run-in and treatment periods.

The total number of inhalations taken during the day (from rising from bed until going to bed) will be recorded in the evening, and the total number of inhalations taken during the night (from going to bed until rising from bed) will be recorded in the morning.

6.5.2.3 Intake of medication

Intake of study drug will be recorded in the diary card morning and evening as "yes" or "no". This does not mean that the patients have an option not to take the medication but will be used as a measure of compliance.

6.5.3 Morning Peak Expiratory Flow (PEF) assessments

A Digital Peak Flow Meter (Mini-Wright Digital, MWD) will be given to the patient at Visit 2, and the same MWD should preferably be used during the entire study.

Morning PEF measurements, expressed in L/min, will be performed at home during run-in and treatment periods. The measurements should be made while standing.

The patient will be instructed to perform at least three manoeuvres each time before intake of study drug, 5 minutes after intake of drug. The pre-dose morning PEF measurement must be done upon rising after the patient has cleared out mucus, before intake of study drug.

When performing the PEF measurements, the MWD will also generate the FEV_1 values. Both PEF and FEV_1 values will be stored in MWD until they are downloaded at the next clinic visit (i.e. at Visit 3 to 8) The FEV_1 data will be considered exploratory and may be reported separately from the Clinical Study Report (CSR).

For standardisation reasons, patients will be instructed to complete morning assessments without interruptions, therefore it will be recommended that patient will go to the toilet and urinate and/or defecate before the morning assessments. The measurements should be conducted within approximately 30 minutes after the patient gets out of bed, but before bathing, showering, or washing him- or her-self, and before getting dressed and having breakfast.

The patient should refrain from taking reliever medication before finalisation of morning measurement.

The patients will visit the clinic at Visit 5 and 7 for MWD data downloading (due to the limited storage capacity of MWD device), recording of medication and AEs.

Training on how to use the MWD

At Visit 2, all patients will be carefully instructed and trained in how to use MWD correctly. The patient must understand and be willing to use the MWD and know how to seek help if problems occur. The patient will be provided with written instructions. The Principal Investigator will be responsible to ensure that this training is performed at Visit 2 and that the patient is encouraged to use the correct technique throughout the study.

In the morning of clinic Visit 3, 4, 6 and 8, only the pre-dose assessments will be performed, as no study drug should be taken at home these mornings.

6.6 Pharmacokinetics (Not applicable)

6.7 Pharmacodynamics (Not applicable)

6.8 Pharmacogenetics (Not applicable)

6.9 Health economics (Not applicable)

7. BIOLOGICAL SAMPLING PROCEDURES (NOT APPLICABLE)

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

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

8.2 Subject data protection

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

8.3 Ethics and regulatory review

An Ethics Committee should approve the final study protocol, including the final version of the Informed Consent Form 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 Ethics committee and to the study site staff.

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

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

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

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

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

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

AstraZeneca will provide Regulatory Authorities, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

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

8.4 Informed consent

The Principal Investigator(s) at each centre 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 the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the 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 informed consent form that is approved by an Ethics Committee.

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the Regional co-ordinating 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 Clinical Study Protocol).

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

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to Ethics Committee see Section 8.3.

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

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

8.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the centre, 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, Good Clinical

Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

9. STUDY MANAGEMENT BY ASTRAZENECA

9.1 Pre-study activities

Before the first subject is entered into the study, it is necessary for a representative of AstraZeneca to visit the investigational study site to:

- Determine the adequacy of the facilities
- Determine availability of appropriate subjects for the study
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement between AstraZeneca and the investigator.

9.2 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 Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and MWD utilised.

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

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

9.3 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, that biological samples are handled in accordance with the Laboratory Manual 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)

- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

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

9.3.1 Source data

Refer to the Clinical Study Agreement for location of source data for more detail.

9.4 Study agreements

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

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

9.4.1 Archiving of study documents

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

9.5 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 Q3, 2011 and to end by Q4, 2012.

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with Symbicort Turbuhaler.

10. DATA MANAGEMENT

Data management will be performed by Tigermed.

When the completed Case Report Forms/diary card, questionnaires received by Data Management Site, the data are double entered into the study database and verified.

The data collected by MWD will be uploaded in the main database. Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed in Tigermed ClinStReport application.

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.

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

11. EVALUATION AND CALCULATION OF VARIABLES

11.1 Calculation or derivation of efficacy variable(s)

The primary efficacy outcome variable will be the change in pre-dose FEV_1 from randomisation (Visit 3) to the mean of the treatment period visits (Visit 4, 6 and 8). The change in pre-dose FEV_1 will be expressed as the ratio between the mean of the treatment period visit (Visit 4, 6 and 8) and randomisation visit (treatment mean/Visit 3).

The change in 5 and 60 minutes post-dose FEV_1 is expressed as the ratio between the mean of the treatment period visit (Visit 3, 4, 6 and 8) and pre-dose FEV_1 at the randomisation visit (post-dose treatment mean/pre-dose Visit 3).

FVC will be measured pre-dose and 5 and 60 minutes post-dose at the clinic. IC will be measured pre-dose and at 60 minutes post-dose at the clinic. The change in FVC and IC at each time point is expressed as the ration between the mean of the treatment period visits (Visit 4, 6 and 8) and randomisation visit (treatment mean/Visit 3).

11.2 Calculation or derivation of safety variable(s)

11.2.1 Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and DAEs. Based on the expert's judgement, significant adverse events of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the Clinical Study Report. Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

11.3 Calculation or derivation of patient reported outcome variables

11.3.1 St. George's Respiratory Questionnaire for COPD patients (SGRQ-C)

Each domain is scored individually and the domains are calculated from the summed questions using weights. The total score is calculated using all questions including their weights. Scores range from 0 (perfect health) to 100 (worst possible state). The minimal clinically important difference has been defined as a change in score of ≥4 units in either the total score or the impact domain score (Jones et al 2002).

The outcome variable for SGRQ-C will be the change in the total score from baseline (Visit 3) to Visit 8, using the last available value.

The domain scores will be handled in the same way.

11.3.2 Diary card and MWD

The outcome variables for PEF before, 5 minutes after morning dose will be the change from the average of the last 10 days before randomisation in pre-dose morning PEF to the average value of the last week on treatment. In addition, another outcome variable for PEF before, 5 minutes after morning dose will be the change from the average of the last 10 days before randomisation in pre-dose morning PEF to the average value of the first week and the whole treatment period.

The outcome variables for number of inhalations of reliever medication used during the night, and during the day will be the change from the average of the last 10 days before randomisation to the average value of the full treatment period.

The outcome variables for the COPD symptoms (breathing, cough, sputum), will be the change from the average of the last 10 days before randomisation to the average value of the treatment period.

Other outcome variables for number of inhalations of reliever medication used during the night, and during the day will be respectively the change from the average of the last 10 days before randomisation to the average value of the last week on treatment and to the average value of the first week.

The outcome variable for intake of study drug will be a percentage of days recorded in the diary. Only descriptive measures will be given for this measure of compliance.

The outcome variables for exacerbations will be the number of exacerbations and the time to the first exacerbation

11.4 Calculation or derivation of pharmacokinetic variables (Not applicable)

11.5 Calculation or derivation of pharmacodynamic variable(s) (Not applicable)

11.6 Calculation or derivation of pharmacogenetic variables (Not applicable)

11.7 Calculation or derivation of health economic variables (Not applicable)

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

A comprehensive Statistical Analysis Plan will be prepared before the first patient will be enrolled in this study. All hypothesis testing will be done using two-sided alternatives. P-values less than 5% will be considered statistically significant.

12.1 Description of analysis sets

12.1.1 Efficacy analysis set

Data for patients for whom any efficacy data have been collected after randomisation will be included in the efficacy analysis.

12.1.2 Safety analysis set

Data for patients who took at least one dose of the add-on treatment with Symbicort or Atrovent or Theophylline SR and for whom any data have been collected after randomisation will be included in the safety analysis. Throughout the safety results sections, erroneously treated subjects (e.g., those randomised to treatment A but actually given treatment B) will be accounted for in the actual treatment group.

12.2 Method of statistical analysis

The change in pre-dose FEV_1 from Visit 3 to the average value of available data for treatment period (Visit 4, 6 and 8), expressed as a ratio, will be analysed using a multiplicative ANOVA model with treatment and centre as fixed factors and the Visit 3 value as a covariate. Treatment differences will be estimated from the model and 95% confidence limits will be calculated. The change in pre-dose FVC and IC post-dose FVC (5 and 60 minutes) and IC (60 minutes) will be analysed in the same way. For post-dose FEV_1 at 5 and 60 minutes, the treatment period includes Visit 3, 4, 6 and 8. Other calculation is the same as pre-dose FEV_1.

The change in average values in pre-dose, 5 and minutes post-dose of morning PEF, from run-in to the last week of the treatment period will be analysed in the same way using an additive ANOVA model with treatment and centre as fixed factors and the run-in mean of pre-dose morning PEF as a covariate. Treatment differences will be estimated from the model, and 95% confidence limits will be calculated. The change from run-in to the first week and whole treatment period will be analysed in a similar way.

The change in average values in total number of inhalations of reliever medication, number of inhalations of reliever medication used during the night and day, from run-in to the treatment period will be analysed in a similar way as the PEF in the morning. COPD symptoms (breathing, cough and sputum) from run-in to the treatment period will also be analysed in a similar way as the PEF in the morning.

The total number of COPD exacerbations will be compared between the treatment groups using a Poisson regression model, adjusted for centre and the duration time in study as an offset variable, defined as the day of the randomisation date to the final assessment of exacerbation status. The confidence limits and the p-value will be adjusted for overdispersion.

In addition, the number of exacerbation days will be summarised by treatment group. The time to the first COPD exacerbation will be described using Kaplan-Meier curves, and the treatment groups will be compared using a log-rank test.

The change in SGRQ-C total score from Visit 3 to Visit 8 (or last available visit) except Visit 5 and 7 will be analysed using an additive ANOVA model with treatment and centre as fixed factors and the Visit 3 value as a covariate.

The time to discontinuation from study will be compared between treatments using a log-rank test.

AEs will be analysed at AstraZeneca Regional Office, by means of descriptive statistics and qualitative analysis (see also Section 6.4.5, and/or Section 11.2, Calculation or derivation of safety variable(s)).

12.2.1 Interim analyses (Not applicable)

12.3 Determination of sample size

Sample size calculation was performed based on the data obtained from SUN (D5899C00001), SHINE (D5899C00002) and CLIMB studies (D5892C00015). The primary variable will be the change in pre-dose FEV_1 in the morning from randomisation to the full treatment period as assessed by spirometry at clinic visits. The standard deviation (SD) of the primary variable was assumed 0.175 on the natural logarithm scale. With a two-sided test at level 0.05 and 259 subjects per treatment group, the power will be 90% to detect a difference between two treatment groups assuming that the true mean difference on the natural logarithm scale is 0.05. In order to compensate for a potential withdrawal rate of about 10%, 285 subjects per treatment group will be randomized in the study.

12.4 Data monitoring committee (Not applicable)

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such,** see Section 6.4.4

In the case of a medical emergency the investigator may contact the Study Delivery Team Leader. If the Study Delivery Team Leader is not available, contact the Study Delivery Team **Physician/other physician at the AstraZeneca Regional Office.**

Name	Role in the study	Address & telephone number
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

13.2 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 patients raised no safety concerns, nor did a formoterol dose of 90 µg over three hours in adult patients 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. Thus, acute overdosage with budesonide – even in excessive doses – is not a clinical problem. As with all inhaled GCSs, 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 that are typical of β_2-agonists such as tremor, headache and palpitations. Symptoms and signs reported with formoterol from isolated cases are tachycardia, hyperglycaemia, hypokalaemia, prolonged QTc-interval, arrhythmia, nausea and vomiting.

Experience with other β_2-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 investigational drug of more than 20 inhalations (>3200/90 µg Symbicort) 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 CRF and on the Overdose CRF module.
- An overdose without associated symptoms is only reported on the Overdose CRF module.
- If an overdose on an AstraZeneca study drug occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives within one day, i.e., immediately but no later than the end of the next business day 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 SAE, 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 or life threatening events and **within 4 calendar days** of initial

receipt for all other SAEs. For other overdoses (i.e., without symptoms or with non-serious adverse events), reporting should be done within 5 calendar days.

13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

13.3.1 Maternal exposure

If a subject becomes pregnant during the course of the study investigational product 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 in pregnant women is limited and patients that become pregnant must be discontinued from the study. However, reports from clinical studies and post-marketing surveillance do not indicate an increased risk when using Symbicort Turbuhaler during pregnancy.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product 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 investigators or other site personnel inform appropriate AstraZeneca representatives **within one day** i.e., immediately but no later than the **end of the next business day** 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 days for SAEs, see Section 6.4.4 and within 30 days for all other pregnancies. The outcome of the pregnancy should be reported as soon as it is known.

The same timelines apply when outcome information is available.

13.3.2 Paternal exposure (Not applicable)

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Clinical Study Protocol Appendix A

Drug Substance	Budesonide/Formoterol
Study Code	D589BL00022
Edition Number	1.0
Date	12 May 2011
Protocol Dated	12 May 2011

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A randomised, parallel-group, open-label, multicentre, 3-month phase IV, efficacy and tolerability study of budesonide/formoterol (Symbicort® Turbuhaler® 160/4.5µg/inhalation, 2 inhalations twice daily) added to ipratropium (Atrovent™ 20 µg/inhalation, 2 inhalations four times daily) + theophylline SR (0.1g/tablet, 1 tablet p.o. twice daily) compared with ipratropium (Atrovent™ 20 µg/inhalation, 2 inhalations four times daily) + theophylline SR (0.1g/tablet, 1 tablet p.o. twice daily)in severe chronic obstructive pulmonary disease (COPD) patients

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

[redacted]

[redacted]

ASTRAZENECA SIGNATURE(S)

A randomised, parallel-group, open-label, multicentre, 3-month phase IV, efficacy and tolerability study of budesonide/formoterol (Symbicort® Turbuhaler® 160/4.5µg/inhalation, 2 inhalations twice daily) added to ipratropium (Atrovent™ 20 µg/inhalation, 2 inhalations four times daily) + theophylline SR (0.1g/tablet, 1 tablet p.o. twice daily) compared with ipratropium (Atrovent™ 20 µg/inhalation, 2 inhalations four times daily) + theophylline SR (0.1g/tablet, 1 tablet p.o. twice daily)in severe chronic obstructive pulmonary disease (COPD) patients

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

[redacted]

ASTRAZENECA SIGNATURE(S)

A randomised, parallel-group, open-label, multicentre, 3-month phase IV, efficacy and tolerability study of budesonide/formoterol (Symbicort® Turbuhaler® 160/4.5µg/inhalation, 2 inhalations twice daily) added to ipratropium (Atrovent™ 20 µg/inhalation, 2 inhalations four times daily) + theophylline SR (0.1g/tablet, 1 tablet p.o. twice daily) compared with ipratropium (Atrovent™ 20 µg/inhalation, 2 inhalations four times daily) + theophylline SR (0.1g/tablet, 1 tablet p.o. twice daily) in severe chronic obstructive pulmonary disease (COPD) patients

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

[redacted]

SIGNATURE OF INTERNATIONAL CO-ORDINATING INVESTIGATOR

A randomised, parallel-group, open-label, multicentre, 3-month phase IV, efficacy and tolerability study of budesonide/formoterol (Symbicort® Turbuhaler® 160/4.5µg/inhalation, 2 inhalations twice daily) added to ipratropium (Atrovent™ 20 µg/inhalation, 2 inhalations four times daily) + theophylline SR (0.1g/tablet, 1 tablet p.o. twice daily) compared with ipratropium (Atrovent™ 20 µg/inhalation, 2 inhalations four times daily) + theophylline SR (0.1g/tablet, 1 tablet p.o. twice daily) in severe chronic obstructive pulmonary disease (COPD) patients

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This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

[redacted]

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Clinical Study Protocol Appendix B

Drug Substance	Budesonide/Formoterol
Study Code	D589BL00022
Edition Number	1.0
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Appendix B
Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

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

Hospitalisation

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

Important medical event or medical intervention

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

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

Examples of such events are:

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

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

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

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

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

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

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

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

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

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

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

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Clinical Study Protocol Appendix C

Drug Substance	Budesonide/Formoterol
Study Code	D589BL00022
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Appendix C
Patient Reported Outcomes Questionnaires

LIST OF PATIENT REPORTED OUTCOMES QUESTIONNAIRES

- St. George's Respiratory Questionnaire for COPD patients (SGRQ-C)
- Breathlessness, Cough and Sputum Scale

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE for COPD patients

(SGRQ-C)

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life.
We are using it to find out which aspects of your illness cause you most problems, rather than what the doctors and nurses think your problems are.

Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.

ID: _____

Date: _____/_____/_____ (dd/mm/yy)

Before completing the rest of the questionnaire:

Please select one box to show how you describe your current health:

Very good	Good	Fair	Poor	Very poor
☐	☐	☐	☐	☐

St. George's Respiratory Questionnaire
PART 1

Questions about how much chest trouble you have.

Please select **ONE** box for each question:

Question 1. I cough:

most days a week	☐ a
several days a week.....	☐ b
only with chest infections ..	☐ c
not at all.....	☐ d

Question 2. I bring up phlegm (sputum):

most days a week	☐ a
several days a week.....	☐ b
only with chest infections ..	☐ c
not at all.....	☐ d

Question 3. I have shortness of breath:

most days a week	☐ a
several days a week.....	☐ b
not at all.....	☐ c

Question 4. I have attacks of wheezing:

most days a week	☐ a
several days a week.....	☐ b
a few days a month.....	☐ c
only with chest infections ..	☐ d
not at all.....	☐ e

continued...

Question 5. How many attacks of chest trouble did you have during the last year?

3 or more attacks	☐ a
1 or 2 attacks	☐ b
none	☐ c

Question 6. How often do you have good days (with little chest trouble)?

no good days	☐ a
a few good days.....	☐ b
most day are good	☐ c
every day is good	☐ d

Question 7. If you have a wheeze, is it worse in the morning?

no.....	☐
yes	☐

continued...

St. George's Respiratory Questionnaire
PART 2

8. ***How would you describe your chest condition?***

Please select ***ONE***:

Causes me a lot of problems or is the most important problem I have ☐ a

Causes me a few problems ..... ☐ b

Causes no problem ..... ☐ c

9. ***Questions about what activities usually make you feel breathless.***

For each statement please select ***the box*** that applies to you **these days**:

	True	**False**	
Getting washed or dressed.....	☐	☐	a
Walking around the home.....	☐	☐	b
Walking outside on the level	☐	☐	c
Walking up a flight of stairs	☐	☐	d
Walking up hills.....	☐	☐	e

St. George's Respiratory Questionnaire
PART 2

10. ***Some more questions about your cough and breathlessness.***

For each statement please select ***the box*** that applies to you **these days**:

	True	False	
My cough hurts	☐	☐	a
My cough makes me tired	☐	☐	b
I am breathless when I talk	☐	☐	c
I am breathless when I bend over	☐	☐	d
My cough or breathing disturbs my sleep	☐	☐	e
I get exhausted easily	☐	☐	f

11. ***Questions about other effects that your chest trouble may have on you.***

For each statement please select ***the box*** that applies to you **these days**:

	True	False	
My cough or breathing is embarrassing in public	☐	☐	a
My chest trouble is a nuisance to my family, friends or neighbours	☐	☐	b
I get afraid or panic when I cannot get my breath	☐	☐	c
I feel that I am not in control of my chest problem	☐	☐	d
I have become frail or an invalid because of my chest	☐	☐	e
Exercise is not safe for me	☐	☐	f
Everything seems too much of an effort	☐	☐	g

continued...

St. George's Respiratory Questionnaire
PART 2

12. ***These are questions about how your activities might be affected by your breathing.***

For each statement please select ***the box*** that applies to you **because of your breathing**:

	True	False	
I take a long time to get washed or dressed	☐	☐	a
I cannot take a bath or shower, or I take a long time	☐	☐	b
I walk slower than other people, or I stop for rests	☐	☐	c
Jobs such as housework take a long time, or I have to stop for rests	☐	☐	d
If I walk up one flight of stairs, I have to go slowly or stop	☐	☐	e
If I hurry or walk fast, I have to stop or slow down	☐	☐	f
My breathing makes it difficult to do things such as walk up hills, carrying things up stairs, light gardening such as weeding, dance, play bowls or play golf	☐	☐	g
My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles per hour, play tennis or swim	☐	☐	h

13. ***We would like to know how your chest trouble <u>usually</u> affects your daily life.***

For each statement please select ***the box*** that applies to you **because of your breathing**:

	True	False	
I cannot play sports or games	☐	☐	a
I cannot go out for entertainment or recreation	☐	☐	b
I cannot go out of the house to do the shopping	☐	☐	c
I cannot do housework	☐	☐	d
I cannot move far from my bed or chair	☐	☐	e

St. George's Respiratory Questionnaire

14. ***How does your chest trouble affect you?***

Please select ***ONE***:

It does not stop me doing anything I would like to do ..... ☐ a

It stops me doing one or two things I would like to do ..... ☐ b

It stops me doing most of the things I would like to do ..... ☐ c

It stops me doing everything I would like to do ..... ☐ d

Thank you for filling in this questionnaire.

Before you finish, would you please check to see that you have answered all the questions.

Breathlessness, Cough and Sputum Scale

HOW MUCH DIFFICULTY DID YOU HAVE BREATHING TODAY?
0 = None – unaware of any difficulty 1 = Mild – noticeable during strenuous activity (e.g., running) 2 = Moderate – noticeable during light activity (e.g., bedmaking) 3 = Marked – noticeable when washing or dressing 4 = Severe – almost constant, present even when resting
HOW WAS YOUR COUGH TODAY?
0 = None – unaware of coughing 1 = Rare – cough now and then 2 = Occasional – less than hourly 3 = Frequent – one or more times an hour 4 = Almost constant – never free of cough or need to cough
HOW MUCH TROUBLE WAS YOUR SPUTUM TODAY? 0 = None – unaware of any difficulty 1 = Mild – rarely caused problem 2 = Moderate – noticeable as a problem 3 = Marked – caused a great deal of inconvenience 4 = Severe – an almost constant problem