AstraZeneca

Revised Clinical Study Protocol	
Drug Substance	Budesonide/formoterol
Study Code	D589SC00003
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A 52-week, double-blind, randomised, multi-centre, phase III, parallel-group study in patients 12 years and older with asthma, evaluating the efficacy and safety of Symbicort (budesonide/formoterol) Turbuhaler 160/4.5 µg 'as needed' compared with Pulmicort (budesonide) Turbuhaler 200 µg twice daily plus terbutaline Turbuhaler 0.4 mg 'as needed'

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

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

Amendment No.	Date of Amendment	Local Amendment No.	Date of local Amendment
1	31 October 2014		
2	17 August 2015		
3	15 February 2016		
4	12 October 2016		

Administrative change No.	Date of Administrative Change	Local Administrative change No.	Date of local Administrative Change
1	21 July 2014		
2	6 May 2015		

PROTOCOL SYNOPSIS

A 52-week, double-blind, randomised, multi-centre, phase III, parallel-group study in patients 12 years and older with asthma, evaluating the efficacy and safety of Symbicort (budesonide/formoterol) Turbuhaler 160/4.5 µg 'as needed' compared with Pulmicort (budesonide) Turbuhaler 200 µg twice daily plus terbutaline Turbuhaler 0.4 mg 'as needed'

International Co-ordinating Investigator

Eric D Bateman Prof, MB ChB, MD, FRCP, DCH

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South Africa

Study site(s) and number of patients planned

This study will recruit patients worldwide at approximately 330 sites in about 25 countries. The target is to randomise 4114 male and female patients. The sample size will be re-estimated based on blinded review during the study. The number of patients might be increased up to a maximum of 6171 patients.

Study period		Phase of development
Estimated date of first patient enrolled	QIII 2014	III
Estimated date of last patient completed	QII 2017	

Study design

This is a 52-week, double-blind, randomised, multi-centre, parallel-group, phase III study in patients 12 years and older with asthma, evaluating the efficacy and safety of Symbicort (budesonide/formoterol) Turbuhaler 160/4.5 µg 'as needed' compared with Pulmicort (budesonide) Turbuhaler 200 µg twice daily plus terbutaline Turbuhaler 0.4 mg 'as needed'.

Objectives

Primary Objective:	Outcome Measure:
To demonstrate that Symbicort Turbuhaler 160/4.5 µg 'as needed' is non-inferior to Pulmicort Turbuhaler 200 µg twice daily plus terbutaline Turbuhaler 0.4 mg 'as needed'.	Annual severe asthma exacerbation rate

Secondary Objective:	Outcome Measure :
To estimate the difference in efficacy between Symbicort Turbuhaler 160/4.5 µg 'as needed' and Pulmicort Turbuhaler 200 µg twice daily plus terbutaline Turbuhaler 0.4 mg 'as needed'	Secondary variables •Time to first severe asthma exacerbation •Average change from baseline in pre-dose FEV_1 •Time to study specific asthma related discontinuation •Average change from baseline in 'as needed' use • Change from baseline in percent of 'as needed' free days •Percentage of controller use days •Average change from baseline in Asthma Control Questionnaire (5-item version) - ACQ-5 score •Average change from baseline in Asthma Quality of Life Questionnaire Standardised Version - AQLQ(S) score

Safety Objective:	Outcome Measure :
To compare the safety of Symbicort Turbuhaler 160/4.5 µg 'as needed' with that of Pulmicort Turbuhaler 200 µg twice daily plus terbutaline Turbuhaler 0.4 mg 'as needed'	Adverse events (nature, incidence and severity); pulse, blood pressure and physical examination

Target patient population

The target population includes male and female patients who are ≥12 years old and who have a documented clinical diagnosis of asthma for at least 6 months prior to Visit 1. Patients who are either uncontrolled on an inhaled short acting bronchodilator(s) 'as needed' (short acting β2 agonist and/or short acting anticholinergic agent) or who are controlled on mono-maintenance therapy with either a low stable dose of an inhaled glucocorticosteroid or a leukotriene receptor antagonist in addition to 'as needed' use of inhaled short-acting bronchodilator (short acting β2 agonist and/or short acting anticholinergic agent) for the last 30 days before Visit 2 will be eligible for the study.

The patients should have reversible airway obstruction.

Patients should have used the short acting β2 agonist on at least 3 separate days during the last week of the run-in period.

Duration of treatment

This study starts with an enrolment visit (Visit 1) where informed consent is obtained and inclusion and exclusion criteria are reviewed. At Visit 2 patients will enter a 2-4 week run-in period during which all of them will be treated with a short acting β2 agonist (Bricanyl) 'as needed'. Eligible patients will be randomised at Visit 3 and enter a 52-week double-blind treatment period. Two weeks after the completion of study treatment a follow-up telephone contact will be performed. The total expected duration of the study for a patient will be 56-59 weeks.

Investigational product, dosage and mode of administration

Symbicort Turbuhaler 160/4.5 µg (budesonide 160 µg and formoterol fumarate dihydrate 4.5 µg per inhalation, powder for inhalation in a dry powder inhaler) used 'as needed' (to relieve asthma symptoms) in addition to Placebo for budesonide (powder for inhalation in a dry powder inhaler matching the Pulmicort Turbuhaler) administered two times daily.

Comparators, dosage and mode of administration

Terbutaline Turbuhaler 0.4 mg (terbutaline sulphate 0.4 mg per inhalation, powder for inhalation in a dry powder inhaler) used 'as needed' (to relieve asthma symptoms) in addition to Pulmicort Turbuhaler 200 µg (budesonide 200 µg per inhalation, powder for inhalation in a dry powder inhaler) administered two times daily.

Non-investigational medicinal product, dosage and mode of administration

Bricanyl Turbuhaler 0.5 mg (terbutaline sulphate 0.5 mg per inhalation, powder for inhalation in a dry powder inhaler) used 'as needed' during the run-in period and as a bronchodilator for the lung function measurements.

Statistical methods

Analysis of the primary variable:

The primary variable annual severe asthma exacerbation rate will be analysed by a negative binomial regression model. The analysis will be based on the efficacy analysis set which includes all randomised patients receiving any investigational product, irrespective of their protocol adherence and continued participation in the study. The planned treatment comparison will be Symbicort 'as needed' versus Pulmicort twice daily + terbutaline 'as needed' (non-inferiority, primary objective).

Formally, the null and alternative hypothesis is:

H_0: rate-ratio (Symbicort vs Pulmicort) ≥ 1.2

H_A: rate-ratio (Symbicort vs Pulmicort) < 1.2

If the upper 95% 1-sided confidence limit of the relative risk ratio is < 1.2 then non-inferiority can be declared.

If the criteria for the alternative hypothesis is met then superiority of Symbicort vs Pulmicort in terms of annual severe asthma exacerbation will be assessed.

Formally, the null and alternative hypothesis for superiority testing is:

H_0: rate-ratio (Symbicort vs Pulmicort) = 1
H_A: rate-ratio (Symbicort vs Pulmicort) ≠ 1

Analysis of the secondary variables:

For all secondary variables stated below the treatment difference between Symbicort 'as needed' and Pulmicort twice daily + terbutaline 'as needed' will be estimated.

Time to first severe asthma exacerbation and time to discontinuation of investigational product due to asthma related events will be analysed by a Cox proportional hazards model.

Forced Expiratory Volume in one second, Asthma Control Questionnaire 5 item version and Asthma Quality of Life Questionnaire (Standardised Version) will be analysed by a mixed model repeated measures analysis model.

The change from baseline in the use of 'as needed' medication, and the percentage of 'as needed'-free days will be analysed by analysis of covariance.

The percentage of controller use days will be analysed by analysis of covariance.

The total inhaled steroid load and the number of days with systemic glucocorticosteroids, respectively will be presented descriptively by treatment adjusted by the patients follow-up time.

TABLE OF CONTENTS PAGE

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
ACQ-5	Asthma Control Questionnaire (5-item Version)
AE	Adverse event
'As-needed'	Administered as needed in response to symptoms; similar to reliever or rescue medication
AQLQ(S)	Asthma Quality of Life Questionnaire (Standardised Version)
ATS/ERS	American Thoracic Society/European Respiratory Society
BID	Twice daily
(e)CRF	Case Report Form (electronic/paper)
CSA	Clinical Study Agreement
CSR	Clinical Study Report
DAE	Discontinuation of Investigational Product due to Adverse Event
DPI	Dry Powder Inhaler
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
EoT	End of Treatment
ePRO	Electronic Patient Reported Outcome
EQ-5D-5L	EuroQol Quality of Life Questionnaire
FEV_1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GCS	Glucocorticosteroid
GINA	Global Initiative for Asthma (GINA). Strategy for Asthma Management and Prevention 2012.
GMP	Good Manufacturing Practice
Grand	AstraZeneca Global Randomisation System
ICH	International Conference on Harmonisation
ICS	Inhaled glucocorticosteroid
ICU	Intensive Care Unit

Abbreviation or special term	Explanation
International Coordinating investigator	If a study is conducted in several countries the International Coordinating Investigator is the Investigator coordinating the investigators and/or activities internationally.
IP	Investigational Product
ISF	Investigator Study File
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
L	Litre
LABA	Long-acting β2 agonist
LTRA	Leukotriene Receptor Antagonist
mg	Milligramm
MID	Minimal important difference
ML	Millilitre
MMRM	Mixed Model Repeated Measures
OAE	Other Significant Adverse Event
PN	Predicted Normal
µg	Microgramm
SABA	Short-acting β2 agonist
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SMART	Symbicort Maintenance and Reliever Therapy
TUM	Turbuhaler Usage Monitor
ULN	Upper Limit of Normal
Vs	Versus
WBDC	Web Based Data Capture

1. INTRODUCTION

1.1 Background and rationale for conducting this study

Asthma is a respiratory disease characterized by chronic inflammation and largely reversible obstruction of the airways which vary over time. The main aim of asthma management is to achieve and maintain asthma control. For this purpose a stepwise treatment approach increasing in intensity is recommended (**GINA 2012**). Using a rapid-acting β2-agonist, commonly salbutamol or terbutaline, on an 'as needed' basis in response to symptoms is the first treatment step (GINA step 1). If asthma is not controlled on rapid-acting β2-agonists alone, a controller medication is added, usually a low dose inhaled glucocorticosteroid (ICS) taken regularly (GINA step 2). Thus adding a controller medication that addresses the underlying inflammation is important to improve asthma control and decrease the risk of severe asthma exacerbations in patients with mild asthma (**Pauwels et al 2003**).

Despite the availability of these conventional treatment regimens, many patients with mild asthma are still uncontrolled and are at risk of severe exacerbations. For example, severe exacerbations in mild asthma patients represent 30–40% of all asthma exacerbations requiring emergency consultation (**Dusser et al 2007**). Furthermore, some patients over-rely on their rapid-acting β2-agonist for symptomatic improvement (**Rabe et al 2004**). Overuse of rapid-acting β2-agonists often leads to delayed introduction of ICS: even if ICS are prescribed adherence to ICS treatment is low (**Horne et al 2006**). The purpose of the current study is to test the hypothesis that in patients in need of low dose ICS (GINA step 2), asthma control can be achieved by 'as needed' administration of both the controller and the bronchodilator medications in response to symptoms.

Symbicort is a fixed combination of the ICS budesonide and the rapid- and long-acting β2-agonist (LABA) formoterol. As formoterol has been shown to be as effective as short-acting β2-agonists (SABA) for symptom relief (**Chuchalin et al 2005**), (**Pauwels et al 2003b**), (**Tattersfield et al 2001**), Symbicort can also be used as a reliever medication in an acute asthma setting (**Palmqvist et al 2001**). Such use of Symbicort is approved for administration as Symbicort Maintenance and Reliever Therapy (SMART) in moderate-to-severe asthma. According to the SMART concept, Symbicort is taken as a regular maintenance treatment and 'as needed' in response to symptoms. Symbicort SMART has been shown to reduce exacerbations and improve asthma control (**O'Byrne et al 2005**), (**Scicchitano et al 2004**), (**Rabe et al 2004**), (**Vogelmeier et al 2005**), (**Atienza et al 2013**).

In mild asthma, initial studies where treatment was administered 'as needed' in response to symptoms, have shown promising results for Symbicort and similar combination products (**Haahtela et al 2006**, **Papi et al 2007**). In patients with mild intermittent asthma and having signs of airway inflammation, Symbicort 'as needed' was more efficacious than Oxis (ie formoterol) 'as needed' in reducing fractional exhaled nitric oxide (FeNO) and improving lung function (Haahtela et al 2006). Symptom-driven, 'as needed' use of a combination of a SABA (albuterol) and ICS (beclomethasone) in a single inhaler was equivalent to regular

treatment with inhaled ICS (beclomethasone) in controlling patients with mild persistent asthma (**Papi et al 2007**).

When administered on an 'as needed' basis without daily maintenance medication, Symbicort will provide both an anti-inflammatory medication and a reliever medication adapted to the patient's current asthma symptoms. Such an approach will address possible problems with timely administration and adherence to ICS in asthma patients in need of low dose ICS treatment. In addition this will be a simplified and convenient treatment regimen as the patients will use one inhaler only instead of two (1 for controller medication and 1 for 'as needed' use).

1.2 Rationale for study design, doses and control groups

The design of the study incorporates features that are consistent with the Committee for Medicinal Products for Human Use Asthma guideline (**CHMP 2013**). A randomised, double-blind, parallel-group design is standard in asthma clinical trials. Patients who are either uncontrolled on an inhaled short acting bronchodilator(s) 'as needed' (SABA and/or short acting anticholinergic agent) or controlled on mono-maintenance therapy with either a low dose ICS or a leukotriene receptor antagonist (LTRA) in addition to 'as needed' use of inhaled short-acting bronchodilator(s) (SABA and/or short acting anticholinergic agent) will be included in the study. The study will begin with a 2 to 4 weeks run in period in order to collect patients' baseline data and to ensure that the recruited patients are in need of GINA step 2 treatment. A 12-month treatment period has been chosen as this study investigates a new treatment regimen with Symbicort Turbuhaler in a new patient population, which will include both adult and adolescent patients.

Asthma exacerbations are relatively rare events and more so in mild asthma and thus a 12 month perspective is necessary owing to power considerations, and, secondly, as adherence to regular medications is an issue in mild asthma, a longer trial provides a longer period over which to observe patient behaviour which better approaches the intended long-term nature of the envisaged treatment, not achieved in a shorter controlled trial.

The efficacy and safety of Symbicort (budesonide/formoterol) Turbuhaler 160/4.5 µg 'as needed' will be compared with Pulmicort (budesonide) Turbuhaler 200 µg twice daily plus terbutaline Turbuhaler 0,4 mg 'as needed' which is one of the current standard treatments for patients at GINA step 2. Symbicort Turbuhaler 160/4.5 µg 'as needed' is the strength mostly used on an 'as needed' basis with the Symbicort SMART concept. This dose is considered adequate to provide an anti-inflammatory effect due to the budesonide component, and the formoterol component of Symbicort Turbuhaler provides rapid and effective symptom relief. Symbicort Turbuhaler is safe to use as evidenced by Symbicort SMART data.

During the study treatment terbutaline will be provided in a Turbuhaler (dry powder inhaler - DPI) that is identical to the Symbicort Turbuhaler for blinding purposes. Bricanyl Turbuhaler will be used during the run-in period.

Prevention of asthma exacerbations is a key goal of asthma management. It has been recognized that asthma exacerbations constitute the greatest risk to the patients, are a cause of anxiety to the patients and their families, and generate great cost for the society (**Reddel et al 2009**). Therefore severe asthma exacerbations have been chosen as the primary variable in this study. The study design includes clinic visits and additional phone contacts -or alternative method - to ensure that asthma exacerbation events are collected. A blinded sample size re-estimation will be done before the randomisation of the targeted 4114 patients. The pooled blinded event rate will be monitored during the trial to allow for the possibility of an increase in sample size up to a maximum of 6171 randomised patients.

1.3 Benefit/risk and ethical assessment

Symbicort Turbuhaler, terbutaline Turbuhaler and Pulmicort Turbuhaler are well known medications with efficacy and safety profiles established in numerous clinical studies and vast postmarketing experience.

Symbicort is effective as a reliever medication (**Palmqvist et al 2001**). In the Symbicort SMART program the patients have been allowed to use up to 12 inhalations per day (10 'as needed' inhalations in addition to their maintenance treatment) and the safety profile of Symbicort was no different from that of a fixed dose maintenance treatment. Furthermore a study in which patients took 10 inhalations of Symbicort Turbuhaler 160/4.5 µg per inhalation as an addition to a daily Symbicort maintenance dose of 640/18 µg revealed no new safety concerns compared to what was already known for ICS and LABA (**Ankerst et al 2003**) demonstrating that occasional high doses of Symbicort Turbuhaler are safe and well tolerated.

Terbutaline Turbuhaler is a well-known and frequently used short acting β2 agonist (SABA). It is widely acknowledged that terbutaline has a rapid onset of action within minutes of inhalation and a favourable safety profile (**Sears and Lötvall 2005**). The maximum dose to be allowed in the study is within the approved dose range in most countries.

In this study patients will be instructed to contact the investigator for reassessment if using more than 12 inhalations per day with blinded 'as needed' investigational product - Symbicort Turbuhaler or terbutaline Turbuhaler - during the treatment period.

Pulmicort which will be used as a maintenance treatment in the comparator arm is an effective and safe controller medication in asthma (**GINA 2012**).

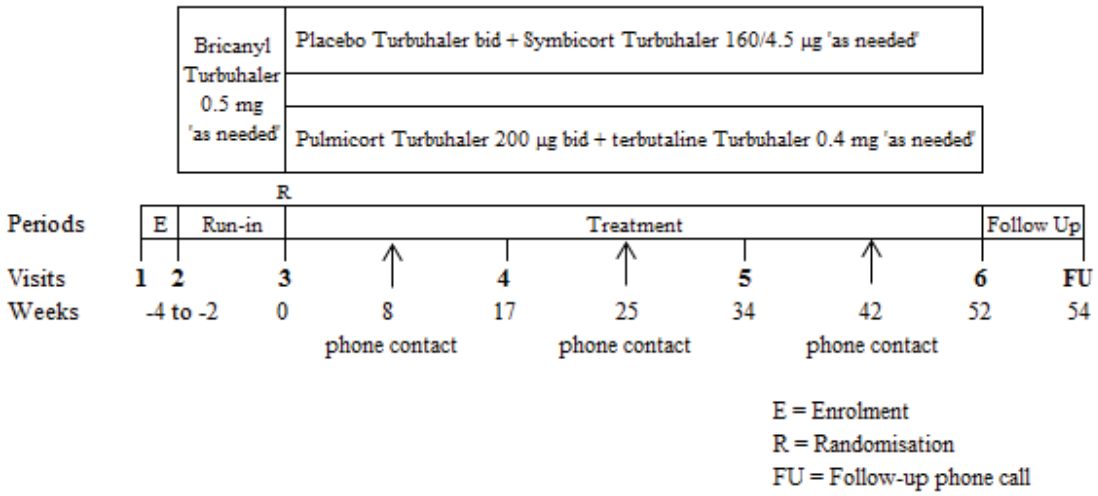
All patients will be monitored during the course of the study with clinic visits at 17, 34 and 52 weeks of treatment. In addition patients will be contacted by phone call (or other methods if needed) between site visits at weeks 8, 25 and 42, and asked if they have used any additional asthma treatment other than the randomised treatment since the last visit. The use of additional asthma treatment would be a trigger for the investigator to call the patient and ask for more information about the additional treatment and asthma worsening.

Patients who have discontinued Investigational Product (IP) prematurely will be followed up for severe asthma exacerbations and adverse events according to the original visit schedule (see Section 4.4).

Furthermore the patients will be instructed to contact the investigator at any time they feel a need for medical assistance. Study specific treatment discontinuation criteria are applied for an individual patient in case of severe asthma exacerbations, see Section 3.9. To conclude, the overall benefit/risk ratio is considered acceptable.

1.4 Study Design

Figure 1 Study flow chart



2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	Outcome Measure:
To demonstrate that Symbicort Turbuhaler 160/4.5 µg 'as needed' is non-inferior to Pulmicort Turbuhaler 200 µg twice daily plus terbutaline Turbuhaler 0.4 mg 'as needed'	Annual severe asthma exacerbation rate

2.2 Secondary objectives

Secondary Objective:	Outcome Measure :
To estimate the difference in efficacy between Symbicort Turbuhaler 160/4.5 µg 'as needed' and Pulmicort Turbuhaler 200 µg twice daily plus terbutaline Turbuhaler 0.4 mg 'as needed'	Secondary variables •Time to first severe asthma exacerbation •Average change from baseline in pre-dose FEV_1 •Time to study specific asthma related discontinuation •Average change from baseline in 'as needed' use • Change from baseline in percent of 'as needed' free days •Percentage of controller use days •Average change from baseline in Asthma Control Questionnaire (5-item version) - ACQ-5 score •Average change from baseline in Asthma Quality of Life Questionnaire Standardised Version - AQLQ(S) score

2.3 Safety objectives

Safety Objective:	Outcome Measure:
To compare the safety of Symbicort Turbuhaler 160/4.5 µg 'as needed' with that of Pulmicort Turbuhaler 200 µg twice daily plus terbutaline Turbuhaler 0.4 mg 'as needed'	Adverse events (nature, incidence and severity); pulse, blood pressure and physical examination

2.4 Exploratory objectives

Exploratory Objective:	Outcome Measure:
To compare health care resource utilization, indirect resource use and health related status associated with hospital admissions, health care visits and days lost from work/ school between treatment arms	• EuroQol five dimensional 5-level questionnaire (EQ-5D-5L) • Health Economics Questionnaire for resource utilisation

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

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

3.1 Inclusion criteria

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

1. Provision of informed consent prior to any study specific procedures. For patients under-age, signed informed consent from both the patient and the patient's parent/legal guardian is required

2. Outpatients of either gender aged ≥12 years at Visit 1

3. Diagnosis of asthma according to GINA criteria based on symptoms with a documented history of at least 6 months prior to Visit 1. Lung function and reversibility tests performed as part of Visit 2 and 3 can be used as a confirmation of asthma diagnosis according to GINA criteria if there is no measure of lung function available before Visit 1

4. Patients who are in need of GINA (2012) step 2 treatment:

   – uncontrolled on inhaled short-acting bronchodilator(s) 'as needed' (SABA and/or short acting anticholinergic agent) as judged by the investigator for the last 30 days before Visit 2, or

   – controlled on mono-maintenance therapy with low stable dose ICS (≤ 400 µg budesonide per day or corresponding dose of other ICS) (see Appendix E for conversion) or LTRA - in addition to 'as needed' use of inhaled short-acting bronchodilator(s) (SABA and/or short acting anticholinergic agent) as judged by the investigator for the last 30 days prior to Visit 2

5. Based on lung function tests (see Section 5.1.2) at Visit 2, patients pre-treated with

   – an inhaled short-acting bronchodilator(s) only should have pre-bronchodilator $FEV_1 \geq 60$ % of predicted normal (PN) and post-bronchodilator $FEV_1 \geq 80$ % of PN according to the European Respiratory Society (ERS) guidelines (Quanjer et al 2012)

   – low dose ICS or LTRA medication in addition to inhaled short-acting bronchodilator(s) should have pre-bronchodilator $FEV_1 \geq 80$ % PN according to the ERS guidelines

6. Reversible airway obstruction according to a reversibility test (see Section 5.1.2.2) performed at Visit 2 defined as an increase in $FEV_1 \geq 12\%$ and ≥200 ml relative to baseline, after inhalation of 1 mg Bricanyl Turbuhaler. The test can be repeated at Visit 3 in case the patients fail at Visit 2. If patients fail at both occasions, they can still be included if they have a documented historical reversibility test within the last 12 months prior to Visit 3, with an increase in $FEV_1 \geq 12\%$ and ≥200 ml relative to baseline after administration of a rapid acting β2-agonist.

For randomisation at Visit 3, patients should fulfil the following criteria:

7. Use of Bricanyl Turbuhaler 'as needed' due to asthma symptoms on at least 3 separate days during the last week of the run-in period

8. Ability to use Turbuhaler correctly.

3.2 Exclusion criteria

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

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

2. Previous randomisation in the present study or in the study D589SC00001 (SYGMA 1)

3. Participation in another clinical study with a non-biologic investigational product or new formulation of a marketed non-biologic drug during the last 30 days prior to Visit 1

4. Participation in another clinical trial with any marketed or investigational biologic drug within 4 months or 5 half-lives whichever is longer, prior to Visit 1

5. Any asthma worsening requiring change in asthma treatment other than inhaled short- acting bronchodilator(s) (SABA and/or short acting anticholinergic agent) within 30 days prior to Visit 1

6. Use of oral, rectal or parenteral GCS within 30 days and/or depot parenteral GCS within 12 weeks prior to Visit 1

7. Use of any β-blocking agent including eye-drops

8. Known or suspected hypersensitivity to study drugs or excipient

9. Smoker (current or previous) with a smoking history of ≥ 10 pack years

10. Medical history of life-threatening asthma including intubation and intensive care unit admission

11. Any significant disease or disorder (e.g., cardiovascular, pulmonary other than asthma, gastrointestinal, hepatic, renal, neurological, musculoskeletal, endocrine, metabolic, malignant, psychiatric, major physical impairment) which, in the opinion of the investigator, may either put the patient at risk because of participation in the study, or may influence the results of the study, or the patient's ability to participate in the study

12. Any clinically relevant abnormal findings in physical examination and/or vital signs at Visit 2, which, in the opinion of the investigator, may put the patient at risk if participating in the study

13. Pregnancy, breast-feeding or planned pregnancy during the study. Fertile women not using acceptable contraceptive measures, as judged by the investigator

14. Planned hospitalisation during the study

15. Suspected poor capability, as judged by the investigator, of following instructions of the study.

For randomisation at Visit 3, patients should not fulfil any of the following criteria:

16. Use of ≥ 6 Bricanyl Turbuhaler 'as needed' inhalations per day, for a certain number of days depending on the actual length of run-in: for ≥ 2 days out of 14 days; for ≥ 3 days out of 15-21 days; for ≥ 4 days out of 22 or more days of run-in

17. Any asthma worsening requiring change in asthma treatment other than inhaled short-acting bronchodilator(s) (SABA and/or short acting anticholinergic agent) from Visit 1 until Visit 2 and / or requiring any asthma treatment other than run-in study medication from Visit 2 until randomisation.

See procedures for withdrawal of incorrectly enrolled patients in Section 3.4.

3.3 Patient enrolment and randomisation

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

The Investigator(s) will:

1. Obtain signed informed consent from the potential patient or their guardian/legal representative before any study specific procedures are performed

2. Assign potential patient a unique enrolment number, beginning with 'E#'

3. Determine patient eligibility. See Section 3.1 and 3.2

4. Assign eligible patient unique randomisation code.

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

Randomisation codes will be assigned strictly sequentially as patients become eligible for randomisation.

3.4 Procedures for handling incorrectly enrolled or randomised patients

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

Where a patient does not meet all the eligibility criteria but is randomised in error, or incorrectly started on treatment, the Investigator should inform the AstraZeneca study physician immediately, and a discussion should occur between the AstraZeneca study physician and the investigator regarding whether to continue or discontinue the patient from treatment. The AstraZeneca study physician must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

An Interactive Voice or Web Response System (IVRS/IWRS) will be utilized to assign enrolment and randomisation codes to the patients and to dispense run-in study drug at Visit 2 and investigational product (IP) at Visit 3 and subsequent treatment visits. Detailed instructions regarding the use of the IVRS/IWRS will be provided in a manual.

The randomisation codes will be computer generated by AstraZeneca R&D or delegate using GRand (AZ Global Randomisation system). Randomisation will be made on site level. The randomisation codes will be loaded into the IVRS/IWRS database. As patients become eligible, they will be assigned to a treatment group in accordance with the randomisation scheme. Randomisation codes will be assigned strictly sequentially as patients become eligible for randomisation.

The study will aim to achieve approximately 10% proportion of adolescents among the randomised patients.

3.6 Methods for ensuring blinding

This study will be double blind. All packaging and labelling will be done in such a way as to ensure blinding. Symbicort and terbutaline Turbuhalers will be identical, and the Pulmicort and placebo Turbuhalers will be identical.

The following personnel will have access to the randomisation list:

- Personnel carrying out the packaging and labelling of investigational product (IP)
- Personnel generating the randomisation list.

Personnel other than the above involved in the conduct of the study will not have access to the information in the randomisation list. It will be kept in a secure location until the end of the study.

3.7 Methods for unblinding

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

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

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

3.8 Restrictions

Patients should avoid strenuous exercise for at least 30 minutes, smoking for at least 1 hour and having a large meal for at least 2 hours before the planned visits to the study site.

Patients should if possible avoid intake of 'as needed' IP 6 hours prior to a study site visit.

Restrictions regarding concomitant medication are described in Section 7.7.

3.9 Discontinuation of investigational product

Patients may be discontinued from IP in the following situations:

- Patients that are incorrectly randomised to the study
- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse Event
- Severe non-compliance with the study protocol
- Safety reason as judged by the investigator and/or AstraZeneca
- Pregnancy. IP should be discontinued immediately if a patient becomes pregnant during the course of the study. See section 6.6.1
- Development of any of the following study specific discontinuation criteria will necessitate discontinuation of IP (for definition of severe asthma exacerbation, see Section 5.1.1):

- A severe asthma exacerbation with a duration of more than 3 weeks
- Three severe asthma exacerbations within a period of 6 months

3.9.1 Procedures for discontinuation of a patient from investigational product

At any time, patients are free to discontinue administration of investigational product or withdraw from the study (ie investigational product and assessments, see Section 3.10), without prejudice to further treatment. A patient who decides to discontinue investigational product will always be asked about the reason(s) for this decision and the presence of any adverse events.

If possible, all patients who discontinue IP will be seen and Visit 6 / End of Treatment (EoT) assessments performed as soon as possible (see Table 1).

A follow-up phone contact will be performed 2 weeks +/-3 days after the last investigational product intake to follow adverse events. If the patient discontinues IP more than 2 weeks +/-3 days before a site visit, the information to be collected in the follow-up phone call can be collected at the visit instead (see Section 4.3).

After discontinuation of IP (ie before Visit 6) patients will be followed up for severe asthma exacerbations, concomitant medications and adverse events according to the original visit schedule including site visits and phone contacts. If it is not possible for the patient to visit the study site, the visit(s) may be performed via phone (see Section 4.4 for details).

All Turbuhaler Usage Monitor (TUM) devices and all investigational products should be returned by the patient. Discontinuation of the IP should be recorded in IVRS/IWRS.

If a patient discontinues IP due to a study specific discontinuation criteria this should always be recorded as 'Development of study specific discontinuation criteria' on the IP discontinuation form in the eCRF and record asthma deterioration as an AE (see Section 6.3.3).

If a patient is withdrawn from study, see Section 3.10.

3.10 Criteria for withdrawal

3.10.1 Enrolment failures

Enrolment failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be randomised. These patients should have the reason for study withdrawal recorded as 'Incorrect Enrolment' (ie patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for enrolment failures (not randomised patients).

The patient can be re-enrolled, due to the following reasons only:

- Enrolment failure due to technical reason (e.g., study equipment not working properly), if agreed with AstraZeneca Study Physician
- Enrolment failure due to inclusion criterion 5 not met at Visit 2 if according to investigator's clinical judgment patient is likely to demonstrate FEV_1 within the required ranges at a later occasion. Re-enrolment due to this reason can only be allowed once
- Enrolment failure due to inclusion criterion 6 not met for patients on inhaled short-acting bronchodilator(s) as needed who were screen-failed prior to approval of CSP Amendment 2 and who have documented historical reversibility. Re-enrolment due to this reason can only be allowed once

Re-enrolled patient should re-sign informed consent, and assent where applicable, at the re-enrolment Visit 1, and a new E-code will be assigned. All procedures for the enrolment/run-in period should be repeated.

Each re-enrolment must be documented in medical records at the study site and in the electronic Case Report Form (eCRF).

3.10.2 Withdrawal of the informed consent

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

A patient who withdraws consent will always be asked about the reason(s) for this decision and the presence of any adverse events (AE). The Investigator will follow up AEs outside of the clinical study. All TUMs and all investigational products should be returned by the patient.

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

3.11 Discontinuation of the study

In case early study termination would occur for any unforeseen reason, the following steps have to be taken:

Regardless of the reason for early study termination, all data available for the patient at the time of termination must be recorded in the eCRF.

The Sponsor will ensure that adequate consideration is given to the protection of the patients' interests.

4. STUDY PLAN AND TIMING OF PROCEDURES

Table 1 Study Plan detailing the procedures

	Enrolment	Run-in	Randomisation	Treatment						2 wks Follow-up	For details see Protocol Section
Visit	**1**	**2**	**3**	**Phone call**	**4**	**Phone call**	**5**	**Phone call**	**6/ EoT[a,b]**	**Phone call**	
Week		**-2 to -4**	**0**	**8**	**17**	**25**	**34**	**42**	**52**	**54**	
Visit window (days)	**0-7 days before Visit 2**	**14-28 days before Visit 3**		**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±3**	
Written Informed consent	X										3.3, 10.4
Allocation of enrolment code	X										4.1.1
Demography	X										4.1.1
Inclusion/exclusion criteria	X	X	X								3.1, 3.2
Medical/surgical history	X										4.1.1

	Enrol ment	**Run-in**	**Rando mi-sation**	**Treatment**						**2 wks Follow -up**	**For details see Protocol Section**
Visit	**1**	**2**	**3**	**Phone call**	**4**	**Phone call**	**5**	**Phone call**	**6/ EoT[a,b]**	**Phone call**	
Week		**-2 to -4**	**0**	**8**	**17**	**25**	**34**	**42**	**52**	**54**	
Visit window (days)	**0-7 days before Visit 2**	**14-28 days before Visit 3**		**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±3**	
Asthma history (including history of severe asthma exacerbations)	X										4.1.1
Smoking history	X										4.1.1
ACQ-5, AQLQ(S)		X	X		X		X		X		5.1.3, 5.1.4, 5.1.5
Health Care resource utilisation questionnaire, EQ-5D-5L			X		X		X		X		5.3.1
SAE/AEs[c]	X[c]	X[c]	X		X		X		X	X	6
Weight and height		X							X[d]		4.1.2

	Enrol ment	**Run-in**	**Rando mi-sation**	**Treatment**						**2 wks Follow -up**	**For details see Protocol Section**
Visit	**1**	**2**	**3**	**Phone call**	**4**	**Phone call**	**5**	**Phone call**	**6/ EoT[a,b]**	**Phone call**	
Week		**-2 to -4**	**0**	**8**	**17**	**25**	**34**	**42**	**52**	**54**	
Visit window (days)	**0-7 days before Visit 2**	**14-28 days before Visit 3**		**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±3**	
Physical examination		X							X		5.2.1
Vital signs (pulse and blood pressure)		X							X		5.2.2.1
Pregnancy test (if applicable)		X									4.1.2
Adjustment of current asthma medication		X									4.1.2

	Enrol ment	**Run-in**	**Rando mi-sation**	**Treatment**						**2 wks Follow -up**	**For details see Protocol Section**
Visit	**1**	**2**	**3**	**Phone call**	**4**	**Phone call**	**5**	**Phone call**	**6/ EoT[a,b]**	**Phone call**	
Week		**-2 to -4**	**0**	**8**	**17**	**25**	**34**	**42**	**52**	**54**	
Visit window (days)	**0-7 days before Visit 2**	**14-28 days before Visit 3**		**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±3**	
Patient training in how to use Turbuhaler (inhalation technique) and TUM; checking inhalation technique and re-training if needed		X	X		X		X				4.1.2
Bricanyl for run-in (dispense/return)		d	r								4.1.2, 7.2
Randomisation			X								3.3, 3.5
Lung function (FEV_1, FVC pre- and post-Bricanyl administration)		X	X		X		X		X		5.1.2, 7.2 for Bricanyl

	Enrol ment	Run-in	Rando mi- sation	Treatment						2 wks Follow -up	For details see Protocol Section
Visit	**1**	**2**	**3**	**Phone call**	**4**	**Phone call**	**5**	**Phone call**	**6/ EoT[a,b]**	**Phone call**	
Week		**-2 to -4**	**0**	**8**	**17**	**25**	**34**	**42**	**52**	**54**	
Visit window (days)	**0-7 days before Visit 2**	**14-28 days before Visit 3**		**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±3**	
Reversibility test[e]		X	X[e]								5.1.2.2, Inclusion criterion 6
Collection of severe asthma exacerbations				X[f]	X[f]	X[f]	X[f]	X[f]	X[f]		4.2
Concomitant medications		X	X		X		X		X		7.7
Investigational product (dispense/return/ check)			d		d/r/c		d/r/c		r/c		7

[a] After discontinuation of IP (ie before visit 6) patients will be followed up according to the original visit schedule including site visits and phone contacts. Only Severe asthma exacerbations, AEs and concomitant medications will be collected. If it is not possible for the patient to visit the study site, the visit(s) may be performed via phone. See section 4.4.

[b] EoT is end of treatment visit.

[c] Serious adverse events will be collected from time of signing Informed consent. Adverse events will be collected from visit 2.

[d] Height only for adolescents.

[e] Reversibility test will be performed at Visit 2. The test can be repeated at Visit 3 in case the patients fail to meet inclusion criterion no. 6 at Visit 2. See section 3.1 for inclusion criteria.

[f] Severe asthma exacerbations will be collected from visit 3 through the entire study.

4.1 Enrolment and run-in periods

4.1.1 Enrolment procedures at Visit 1

Procedures will be performed according to the Study Plan, see Table 1.

Patients will obtain information regarding the study and sign informed consent for the study before any study related procedures are initiated.

Consented patients will be assessed to ensure that they meet eligibility criteria. Patients who do not meet these criteria must not be enrolled in the study.

Eligible patients will receive an enrolment code, allocated by IVRS/IWRS.

Demography, medical, surgical and asthma history including previous asthma exacerbations and smoking history will be checked.

For the evaluation of smoking history, pack years will be calculated as follows:

10 pack years = 1 pack (20 cigarettes) per day for 10 years or 2 pack (40 cigarettes) per day for 5 years or ½ pack (10 cigarettes) per day for 20 years	1 cigar = 5 cigarettes 1 cigarillo = 2 cigarettes 50 g pipe tobacco = 65 cigarettes Hand rolled cigarettes can be calculated as cigarettes or pipe tobacco.

All serious adverse events occurring after signing the informed consent will be reported.

Patients will continue taking their prescribed medication until Visit 2 and will be informed about medication restrictions applicable before Visit 2 by the investigator (see section 7.7.1).

4.1.2 Run-in procedures at Visit 2

Visit 2 can be performed within 7 days after Visit 1.

Visit 1 and Visit 2 can be performed on the same day only in cases where the patient has not taken any medication which could affect the lung function measurements (see details in Section 7.7.1, Table 2).

Procedures will be performed according to the Study Plan, see Table 1.

Patients who fulfil the inclusion and none of the exclusion criteria (Visit 2) will enter a 2-4 weeks run-in period.

From Visit 2 all adverse events will be collected (see Section 6 for details).

Height will be measured in cm (without shoes) and weight in kg (light clothes and without shoes). Physical examination will be performed and pulse and blood pressure will also be measured.

Pregnancy test by urine dipstick should be performed for female patients aged ≤60 years.

Patients will be asked to stop their prescribed asthma medication (including maintenance treatment with ICS and LTRA) used at the time of study entry and during the enrolment period in accordance with Section 7.7.

At Visit 2 patients will complete ACQ-5 and AQLQ(S) questionnaires using the electronic Patient Reported Outcome (ePRO) device after receiving detailed information.

Instructions will be given to the patients on how to use the Turbuhaler (inhalation technique) and the TUM device. Before taking the first dose of run-in medication the patient will be instructed by the study personnel how to take the medication. In order to inhale properly according to instructions the patients will practice inhalation technique with a training device, as many times as judged necessary by the supervising study personnel.

All patients will receive Bricanyl Turbuhaler for 'as needed' use during the run-in period.

Spirometry – including reversibility test – will preferably be performed between 7 am and 11 am to measure lung function and verify eligibility of the patient (see Section 5.1.2 for details).

Concomitant medications will be checked.

Patients will be instructed to contact their investigator immediately for reassessment if they need to take more than 12 inhalations per day from the run-in medication (white label with blue bar Turbuhaler).

4.2 Treatment period

At Visit 3 investigator should check eligibility of the patient before randomisation.

Length of run-in period is flexible from 2 to 4 weeks. Assessment of the Bricanyl 'as needed' use criterion is allowed more than once during run-in. If inclusion criterion 7 is not fulfilled after at least 2 weeks of run-in AND patient has not used Bricanyl Turbuhaler above the limits described in exclusion criterion 16, investigator can re-schedule Visit 3. Downloading the Turbuhaler Usage Monitor (TUM) data to check inclusion criterion 7 and exclusion criterion 16 should be the first procedure during this visit. Patient can remain in run-in period for maximum 4 weeks.

For timing of visits appointment for spirometry procedure (± 1 hour related to spirometry procedure at Visit 2) has to be taken into account (see Section 5.1.2 for details).

Treatment visits will take place at 17, 34 and 52 weeks of treatment after randomisation.

Description of the procedures for this period is included in the Study Plan, see Table 1.

The patient should take the first dose of maintenance IP at the study site.

Patients should bring the study medication to site and take the morning dose of maintenance IP at the study site after study procedures are completed. Patient's inhalation technique will be checked by the study personnel at each visit. Patient will be re-trained on how to use the Turbuhaler and TUM if needed.

Patients will be instructed to contact their investigator immediately for reassessment if they need to take more than 12 inhalations per day with blinded 'as needed' investigational product - Symbicort Turbuhaler or terbutaline Turbuhaler - during the treatment period.

At randomisation and each treatment visit, the patients will complete ACQ-5, AQLQ(S) and EQ-5D-5L questionnaires as the first activity. Information on health care resource utilization will be collected.

Thereafter, spirometry will be performed within the requested time window (see Section 5.1.2).

In addition patients will be contacted by phone call (or other methods if needed) preferably by the study nurse between site visits at weeks 8, 25 and 42 (Figure 1), and be asked if he/she since the last study visit

- has taken any additional asthma treatment other than the study medication and
- has had any asthma worsening that led to hospitalisation or emergency room visit or to a doctor's consultation.

If the answer is "yes" the investigator will call the patient and ask for more detailed information in order to collect and document any additional asthma medication and/or severe asthma exacerbation events.

Investigators should make all efforts to collect severe asthma exacerbation data and verify the information given by the patient to the greatest possible extent using medical records and other source data.

4.3 Follow-up

A follow-up telephone contact will be performed 2 weeks +/- 3 days after the last investigational product intake. At the follow-up telephone call, the investigator will check for adverse events ongoing at the end of study treatment or occurred after last treatment visit.

In the event of discontinuation of IP, the procedure described in Section 3.9.1 will be followed. Patients will be treated according to local medical practice.

4.4 Follow-up in case of discontinuation of IP

After discontinuation of IP (ie before Visit 6) patients will be followed up for severe asthma exacerbations, concomitant medications and adverse events according to the original visit schedule including site visits and phone contacts. Patients will be treated according to local medical practice. Only Severe asthma exacerbations, AEs and concomitant medications will be documented and entered into the eCRF. No more study specific procedures will be required for the purpose of this study.

If it is not possible for the patient to visit the study site, the visit(s) may be performed via phone.

5. STUDY ASSESSMENTS

The Rave Web Based Data Capture (WBDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the electronic Case Report Form (eCRF) as specified in the study protocol and in accordance with the instructions provided.

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

5.1 Efficacy assessments

5.1.1 Severe asthma exacerbation

In this study severe asthma exacerbation is defined as deterioration of asthma that is associated with a medical intervention as described below. Deterioration of asthma defined as worsening of asthma symptoms, increased use of 'as needed' medication, or deterioration of lung function which lasts for two or more days or which happens acutely (≤24 h) will be recorded in the eCRF by the investigator.

A severe exacerbation is defined as a deterioration of asthma requiring any of the following:

- Use of systemic glucocorticosteroids for at least 3 days[1]
- Inpatient hospitalization
- Emergency room visit[2] due to asthma that required systemic glucocorticosteroids.

[1] An injection of depot glucocorticosteroids due to asthma worsening is considered equivalent to at least 3 days of systemic glucocorticosteroids

[2] Emergency room visit or other urgent unscheduled health care visit

The start and end date of each severe asthma exacerbation will be recorded in the eCRF. For severe exacerbations the start date is defined as the first day of hospitalisation / emergency room treatment or the first day of systemic (ie not inhaled) GCS treatment. The end date is defined as the last day of hospitalisation/emergency room treatment or the last day of systemic GCS treatment. If the same asthma exacerbation includes both hospitalisation/emergency room treatment and systemic GCS treatment, the start and end dates are the first and last day that either of the criteria was fulfilled.

Additional hospitalisations/emergency room treatments and systemic GCS treatments occurring during a severe asthma exacerbation should not be regarded as a new exacerbation. For severe asthma exacerbation to be counted as a separate event, it must be preceded by at least seven days in which no criteria for severe exacerbations are fulfilled.

If a patient has a severe asthma exacerbation with a duration of more than 3 weeks or 3 severe asthma exacerbations during 6 months, patient should discontinue IP and the reason should be recorded as 'Development of study specific discontinuation criteria' on the IP discontinuation form.

5.1.2 Lung function measurement by spirometry (FEV_1, FVC) at the study site

Equipment and conditions

Spirometry will be performed by the Investigator or authorized delegate according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines (**Miller et al 2005**). The study site personnel who will be performing the testing should be properly certified / trained.

The spirometer must meet ATS/ERS recommendations (**Miller et al 2005**). The monitor/vendor is responsible for checking that the spirometer in use meets these recommendations. It should be serviced once a year or according to the manufacturer's instruction at an authorised facility. All service measures and repairs must be documented.

Due to diurnal variation of lung function it is important that all spirometry assessments at Visits 3, 4, 5 and 6 are performed ±1 hour in relation to the time of spirometry at Visit 2 and preferably after 7 am and no later than 11 am.

The spirometry should be conducted with the same spirometer within patients and for all patients at each site. Preferably, the same study personnel should test the patient's lung function throughout the study to reach optimal performance and to enhance reproducibility. The patient should rest at least 15 minutes prior to the test. For repeated measurements e.g., to assess best of 3, a short pause (1 minute) between measurements is recommended.

The measurements are to be made with the patient seated in an upright position (preferably), or if not comfortable standing position is also acceptable. The same position should be used for all spirometry measures during the entire study. The head must not be tilted during measurements. During the breathing manoeuvres, the thorax should be able to move freely; hence tight clothing should be loosened.

A nose-clip should be used for the manoeuvre. Mouthpieces of the same dimension and shape should be used throughout the study. Spirometry should be performed using a calibrated spirometer and values are expressed at Body Temperature and ambient Pressure Saturated with water vapour.

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 study site. Instead of using a 3 L syringe, a 1 L can be used 3 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 ISF along with a signed and dated copy (if the calibration reports are not on archive-quality paper). If a calibration report cannot be printed, the results should be documented in writing in the Investigator Study File (ISF).

FEV_1 and FVC

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

At least 3 technically satisfactory forced vital capacity (FVC) manoeuvres should be performed. The difference between highest and second highest FVC and FEV_1, respectively, should not be more than 150 mL. A maximum of 8 manoeuvres should be performed in attempting to meet reproducibility criteria. If the reproducibility criteria cannot be met within 8 manoeuvres, the highest FEV_1 value should be recorded, and a comment should be entered on the printout.

FEV_1 values will be taken from the FVC curves. After examining the data from all acceptable curves, the highest FEV_1 value and the highest FVC value should be recorded, even if the 2 values do not come from the same curve.

Signed and dated copies of the 3 best manoeuvres printouts must be kept in the ISF for source data verification. The printouts must be marked with study code, enrolment code, date and time of measurements, visit number and patient initials.

5.1.2.1 Pre-bronchodilator and post-bronchodilator FEV_1 and FVC including reversibility testing and calculation of predicted normal values (PN)

Pre-bronchodilator and post-bronchodilator FEV_1 and FVC expressed in liters (L) will be performed at Visits 2 to 6.

The assessment will be performed as follows:

- Pre-bronchodilator FEV_1 measurement
- Inhalation of Bricanyl Turbuhaler 2 x 0.5 mg

- Wait 15 to 30 minutes
- Post-bronchodilator FEV_1 measurement.

At Visit 2 these measurements are performed for inclusion verification and characterisation of the patient population. Thus at this visit pre-bronchodilator and post-bronchodilator FEV_1 PN will be calculated. FEV_1 PN value will be based on the reference values from European Respiratory Society (ERS) guidelines for adult and adolescent patients (**Quanjer et al 2012**).

At Visits 3 to 6 the purpose of the assessment is to get pre-bronchodilator and post-bronchodilator values of FEV_1 and FVC as part of the evaluation of lung function

5.1.2.2 Reversibility test

To fulfil the reversibility inclusion criterion at Visit 2 the increase in FEV_1 relative to baseline must be ≥12% and ≥200 ml 15-30 minutes after inhalation of 2 x 0.5 mg Bricanyl Turbuhaler.

The reversibility is calculated as follows:

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

The investigator should record the pre- and post-bronchodilator FEV_1 in the eCRF and the calculation will be performed by the eCRF.

If the reversibility inclusion criterion is not met at Visit 2, the reversibility test may be repeated at Visit 3. If patients on low dose ICS or LTRA fail at both occasions, they can still be included if they have a documented historical reversibility within the last 12 months prior to Visit 3, see also inclusion criterion 6, Section 3.1.

5.1.3 Asthma Control Questionnaire (5-item Version)

The ACQ was developed by Juniper (**Juniper et al 1999**). The ACQ includes 7 items covering all the criteria (symptoms, FEV_1, and SABA used as rescue medication) deemed necessary by international guidelines committees for determining the adequacy of asthma control. The ACQ has undergone rigorous validation and has been shown to have strong evaluative and discriminative measurement properties (**Juniper et al 1999**). In this study, the FEV_1 and SABA use questions will be excluded, and patients will be responding to the five symptom questions (ACQ-5). It has been shown that exclusion of the questions for SABA use and/or the FEV_1 does not alter the validity and the measurement properties of the questionnaire (**Juniper et al 2001**). Linguistically validated translations of the ACQ-5 into the local languages will be used. The original North American English version is included in Appendix C.

The ACQ-5 will be self-administered using ePRO device during site visits as indicated in Table 1. The questions take approximately 2 to 3 minutes to complete.

Patients who are not fluent in the local language will not perform the ACQ-5 assessments, but they can still participate in the study. The assessment of ACQ-5 will only be performed in countries where validated translations are available.

5.1.4 Asthma Quality of Life Questionnaire (Standardised Version)

The AQLQ has been developed by Juniper (**Juniper et al 1992**) and includes 32 questions in 4 domains: activity limitation, symptoms, emotional function and exposure to environmental stimuli. A feature of the AQLQ is that patients themselves select 5 of the 11 activity questions. The standardised version of the AQLQ, the AQLQ(S), in which 5 generic activities replace the 5 patient-specific activities of the AQLQ (**Juniper et al 1999**) will be used in this study. The AQLQ(S) is more appropriate than AQLQ for long-term clinical studies, when patients' activities and priorities may change over time. The AQLQ(S) evaluates the impact of asthma on patients every day functioning and wellbeing. The AQLQ(S) has been validated for use from the age of 12 years (**Juniper et al 2005**). Linguistically validated translations of AQLQ(S) into the local languages will be used. The North American English version is included in Appendix D.

The AQLQ(S) will be self-administered using ePRO device during site visits as indicated in Table 1. The questionnaire takes approximately 15 minutes to complete. The patient needs to be able to read and to be fluent in the local language to be able to answer the questions.

Patients who are not fluent in the local language will not perform the AQLQ(S) assessments, but they can still participate in the study. The assessment of AQLQ(S) will only be performed in countries where validated translations are available.

5.1.5 Administration of patient reported outcome questionnaires

The questionnaires (ACQ-5 and AQLQ[S]) should be completed using ePRO device at the scheduled visits before any other study-related procedures are performed to avoid biased responses. At Visit 2 only, the questionnaires can be completed following the lung function measurements. At Visit 2 instructions will be provided to each patient in the local language, how to complete the questionnaires.

The patient should be informed about the purpose and importance of completing the questionnaires and be given adequate time to complete all items. It is important to administer the questionnaires according to the guidelines for standardised administration. The questions should be completed in a quiet place without influence from family, friends, or study personnel. Family, friends, or study personnel should never help the patient to choose an answer, interpret, or rephrase the questions for the patient.

5.1.6 Turbuhaler Usage Monitor (TUM)

The Turbuhaler Usage Monitor (TUM, a SmartTurbo™ version manufactured by Nexus6 Ltd, New Zealand) is a battery powered electronic data logger designed to be attached to a Turbuhaler (DPI). The TUM contains an internal electronic clock and calendar that logs

through a microprocessor the date and time when the Turbuhaler base grip is rotated back and forth.

TUM devices will be used for the Turbuhalers containing 'as needed' and maintenance investigational product, and for Bricanyl Turbuhaler used during the run-in period as well (see also Section 7 for details).

The colour of the main body of all the TUMs will be white. The colour of the locking ring of the TUM will be:

- white for the 'as needed' study medication and the Bricanyl Turbuhaler
- brown for the maintenance study medication

Patients will be informed about the TUM at Visit 2 and will receive written user instructions (see Section 4.1.2).

5.2 Safety assessments

5.2.1 Physical examination

A physical examination will be performed at Visit 2 and Visit 6 and include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, head and neck (including head, ears, eyes, nose and throat). The examination at Visit 2 is regarded as baseline data. Physical examination will also be performed in case of discontinuation of IP (see Section 3.9.1). For reporting of AEs based on examinations, see Section 6.3.6.

5.2.2 Vital signs

For reporting of AEs based on vital signs, see Section 6.3.6.

5.2.2.1 Pulse and blood pressure

Blood pressure and pulse rate measurements will be performed at Visit 2 and Visit 6. The measurements at Visit 2 are regarded as baseline data. Blood pressure and pulse rate will also be measured in case of discontinuation of IP (see also Section 3.9.1).

Pulse rate (beats/min) will be measured over 30 seconds in a sitting position, after 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

5.3 Health Economics

Information on health care resource utilization as well as health related quality of life (EQ-5D-5L) will be collected at randomisation and at each treatment visits to enable health technology assessment, health economic analysis and health economic modelling.

5.3.1 Health care resource utilisation

At baseline (Visit 3, Randomisation) and at subsequent treatment visits until Visit 6 / EoT the patient will be asked questions about asthma-related health care resource use events since last visit as well as asthma-related sickness absence, time-off work or education.

The patient will be asked about health care resource use in terms of use of ambulance services; emergency room visits; hospital admissions to general or intensive care; ambulatory-setting or home consultations with specialists, primary care physicians or other healthcare professionals; and telephone consultations with physicians or nurse.

For patients in paid employment, they will also be asked how much time they have taken as sickness absence due to their asthma.

For patients in education, they will also be asked how much time they have taken as sickness absence due to their asthma.

5.3.1.1 Methods of assessment EQ-5D-5L

The EQ-5D is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (**The EuroQol Group 1990**).

The EQ-5D is applicable to a wide range of health conditions and treatment. It provides a simple descriptive profile and a single index value for health status that can be used in economic evaluation of health care. There are two versions of EQ-5D – a three level version (EQ-5D-3L) and a five level version (EQ-5D-5L). The EQ-5D-5L will be used in this trial, see Appendix F. The EQ-5D-5L consists of 2 pages - the EQ-5D descriptive system and the EQ Visual Analogue Scale (VAS). The descriptive system comprises five dimensions, mobility, self-care, usual activity, pain/discomfort and anxiety/depression. Each dimension has five levels (response options): no problems, slight problems, moderate problems, severe problems and extreme problems. The EQ VAS records the respondent´s self-rated health on a 20 cm vertical visual analogue scale with endpoints labelled “the best health you can imagine” and “the worst health you can imagine”

This instrument is extensively validated and is available in several languages that facilitate its use in multinational studies. The translations into local languages have been performed according to a linguistic validation process.

The EQ-5D-5L will be self-administered using the paper version. The questions will be assessed at baseline (Randomisation Visit 3) and at subsequent treatment visits until Visit 6 / EoT. The 5 questions will take approximately 5 minutes to answer. The patients need to be able to read and to be fluent in the local language to be able to answer the questions.

5.3.1.2 Administration of EQ-5D-5L questionnaire

The EQ-5D-5L should be given to patients as detailed in the Study Plan (see Table 1), before assessments, prior to administration of study drug, and before imparting any news about the

status of their disease. Patients should be allowed to complete the paper questionnaire in their own time, and without any help from relatives or clinic staff. The patient can receive help from a study nurse in reading the instructions and questions. However, under no circumstances should help in interpreting the questions or in selecting responses be provided.

The appropriate module of eCRF will be completed by the clinic staff to detail if a questionnaire has been completed at each EQ-5D-5L visit, and if not, the reason will be recorded. Each centre must allocate responsibility for the EQ-5D-5L questionnaire to a specific individual (ie a Research Nurse). The AstraZeneca Study Team will provide training for relevant personnel in the administration of the EQ-5D-5L questionnaire. Investigator or delegate will transfer the patient´s data from the paper copy to the eCRF. It is also important that the significance and relevance of the data are explained carefully to participating patients so that they are motivated to comply with data collection (**The EuroQol Group 1990**).

Patients who are not fluent in the local language will not perform the EQ-5D-5L assessments, but they can still participate in the study. The assessment of EQ-5D-5L will only be performed in countries where validated translations are available.

5.4 Pharmacokinetics

Pharmacokinetic samples will not be taken during the study.

5.5 Pharmacodynamics

Pharmacodynamic samples will not be taken during the study.

5.6 Pharmacogenetics

Pharmacogenetic samples will not be taken during the study.

5.7 Biomarker analysis

Biological samples will not be taken during the study.

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

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

6.1 Definition of adverse events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical

studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

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

6.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (ie run-in, treatment, wash out, 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/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.

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

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

Adverse Events will be collected from Visit 2 throughout the entire treatment period and during the follow-up period until the last telephone follow-up, or the last contact.

SAEs will be recorded from the time of informed consent.

6.3.2 Follow-up of unresolved adverse events

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

6.3.3 Symptoms of the disease under study

Asthma symptoms or signs, such as wheeze, cough, chest tightness, dyspnoea, breathlessness and phlegm, will be recorded as AEs only when:

- The sign or symptom meets Serious Adverse Event criteria, see Section 6.2 for definition
- The patient discontinues IP 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 asthma history (defined as within 1 year of Visit 1) as judged by the investigator.

If a patient discontinues IP due to a study specific discontinuation criterion this should always be recorded as 'Development of study specific discontinuation criteria' on the IP discontinuation form in the eCRF. In addition, the investigator has to report asthma deterioration as an AE leading to discontinuation with investigational product (DAE)/AE on the AE form.

6.3.4 Variables

The following variables will be collected for each AE;

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

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- 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
- Description of AE.

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

Maximum intensity refers to the complete course of the AE. The patient (parents/legal guardians) will be asked to assess the maximum intensity of the reported AEs according to the following scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities).

6.3.5 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. 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.

6.3.6 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or care provider or reported in response to the open question from the study personnel: *‘Have you / your child had any health problems since the previous visit/you were last asked?’*, or revealed by observation will be collected and

recorded in the eCRF. The question will be put to each patient (or parent/legal guardian) in local language from Visit 2 to the last follow-up telephone contact. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.3.7 Adverse events based on examinations and tests

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

If deterioration in a vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated vital sign will be considered as additional information. In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

6.3.8 Hy's Law

Cases where any lab samples that are collected from a patient show an Aspartate Aminotransferase or Alanine Aminotransferase ≥3xUpper Limit of Normal (ULN) or total bilirubin ≥2xULN may need to be reported as SAEs according to handling of cases representing Hy's Law. In such case, the investigator should contact the AstraZeneca Study Physician.

6.4 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 eCRF.

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

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

For fatal or life-threatening 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 ie immediately but **no later than 24 hours** of when he or she becomes aware of it.

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

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

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

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

6.5 Overdose

Background

The risks associated with overdosage of Symbicort are considered to be small, as the safety margins for inhaled budesonide and formoterol are substantial. Administration of a Symbicort Turbuhaler dose of 1600/45 µg over one hour on top of maintenance treatment with daily doses of 640 µg budesonide and 18 µg formoterol in asthma 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.

In high-dose formoterol studies where terbutaline was given as an active comparator, a terbutaline dose up to 10 mg over three hours in adult patients with acute bronchoconstriction raised no safety concerns.

Symptoms

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

Treatment suggestions

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

Procedures for reporting

For the purpose of this study, an accidental or deliberate intake of blinded treatment of more than 20 inhalations (> 3200/90 µg Symbicort or 8 mg terbutaline delivered dose) during one day is defined as an overdose and must be reported as such as described below:

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

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

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

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

6.6 Pregnancy

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

6.6.1 Maternal exposure

If a patient 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 methods, 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 investigational product. 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 patient was discontinued from the study.

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

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

The same timelines apply when outcome information is available.

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

6.6.2 Paternal exposure

There is no restriction on fathering children or donating sperm during the study.

6.7 Management of IP related toxicities

Treatment related toxicity is not expected from budesonide/formoterol, when used as directed. For overdose, see Section 6.5.

6.8 Study governance and oversight

6.8.1 Independent adjudication committee for fatal events

An independent external adjudication committee will be constituted to provide an independent, external and unbiased assessment of fatal events reported during the study in order to determine whether the death may have been related to asthma. The committee will operate in accordance with an Adjudication Committee Charter, which will also provide detail on specific information the committee requires to enable the adjudication.

Following adjudication a notification will be sent to the AstraZeneca senior medical officer in order to decide whether a Data Safety Monitoring Board should be appointed for further review of safety data in the studies.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

Investigational product	Dosage form and strength	Manufacturer
Symbicort Turbuhaler 160/4.5 µg (Budesonide / formoterol fumarate dihydrate 160/4.5 µg)	Budesonide / formoterol fumarate dehydrate powder for inhalation, 160 µg budesonide and 4.5 µg formoterol per inhalation, 120 doses	AstraZeneca
Terbutaline Turbuhaler 0.4 mg (terbutaline sulphate 0.4mg)	Terbutaline sulphate powder for inhalation, 0.4 mg terbutaline per inhalation, 120 doses	AstraZeneca
Pulmicort Turbuhaler 200 µg (budesonide 200 µg)	Budesonide powder for inhalation, 200 µg per inhalation, 200 doses	AstraZeneca
Placebo for budesonide (Placebo Turbuhaler)	Placebo powder for inhalation, 200 doses	AstraZeneca

Budesonide/formoterol, terbutaline, budesonide and placebo for budesonide will all be dispensed as inhalers (Turbuhaler). Budesonide/formoterol, terbutaline and placebo for budesonide inhalers contain lactose as part of the filling material whereas the budesonide inhaler and the Bricanyl Turbuhaler do not.

The terbutaline Turbuhaler 0.4 mg corresponds to Bricanyl Turbuhaler 0.5 mg with regards to the dose delivered. The terbutaline Turbuhaler 0.4 mg dose is expressed as delivered dose whereas the Bricanyl Turbuhaler 0.5 mg dose is expressed as metered dose. The terbutaline Turbuhaler 0.4 mg product is a clinical trial product that is blinded against the Symbicort Turbuhaler.

The budesonide dose in Pulmicort Turbuhaler, 200 µg expressed as metered dose, corresponds to the budesonide dose in Symbicort Turbuhaler, 160 µg expressed as delivered dose.

7.1.1 Non-investigational product for run-in and for post-bronchodilator lung function measurements

Additional study drug	Dosage form and strength	Manufacturer
Bricanyl Turbuhaler 0.5 mg	Terbutaline sulphate powder for inhalation, 0.5 mg terbutaline per inhalation, 100 doses	AstraZeneca

Bricanyl is a non-investigational medicinal product since it is used only ‘as needed’ during the run-in period and as a bronchodilator during the lung function measurements.

7.2 Dose and treatment regimens

Priming of the Turbuhaler

All Turbuhaler inhalers need to be primed before their initial use. The priming should **only** be executed once per Turbuhaler (priming should **not** be repeated even if the inhaler is not used regularly). The Investigator will prime the Bricanyl Turbuhaler at Visit 2 **before** attaching a

TUM and giving it to the patient. At subsequent visits this procedure should be repeated for all Turbuhalers. Instructions on how to use the Turbuhaler will be provided in local language to the patients.

The priming procedure:

Remove cover. Hold the inhaler in an upright position and turn the grip as far as possible in both directions. Perform this step twice. The first dose can now be loaded.

Run-in period (Visit 2 to Visit 3)

At Visit 2 an empty Turbuhaler will be used for training purpose. The training Turbuhaler should be kept at the study site and should not be taken home by the patients. The training Turbuhaler will be labelled with an English label only.

Bricanyl Turbuhaler will be dispensed at Visit 2 and will be used as 'as needed' medication during the run-in period. Bricanyl Turbuhaler will have blue grip and a white label with a blue bar. Patients will be instructed to use Bricanyl Turbuhaler whenever needed to relieve asthma symptoms but not for prophylactic reasons. In addition, those patients who are treated with low-dose ICS or LTRA at study entry will be asked to stop taking these medications at Visit 2.

Bricanyl Turbuhaler will also be used for the post-bronchodilator FEV_1 and FVC measurements at Visits 2 to 6.

Treatment period (Visits 3 to 6)

At Visit 3 patients will be randomised to one of the 2 treatment groups with IP:

- Maintenance Placebo BID (twice daily) + Symbicort 160/4.5 µg 'as needed'
- Maintenance Pulmicort 200 µg BID + terbutaline 0.4 mg 'as needed'

At Visit 3 all randomised patients will receive maintenance study drug containing either Pulmicort or placebo as well as 'as needed' study drug, containing either Symbicort or terbutaline.

To avoid confusion, the maintenance Turbuhalers and the Turbuhalers for 'as needed' treatment will have labels with different colours and the Turbuhaler grip will have different colours for the two different treatments. The maintenance Turbuhaler will have brown grip and a white label with a yellow bar. During the treatment period the Turbuhaler for 'as needed' treatment will have white grip and white label with a grey bar. The patients will be instructed to take one inhalation from the inhaler with the brown grip every morning upon rising and every evening before going to bed. Patients will further be instructed to take one inhalation from the inhaler with the white grip whenever needed to relieve asthma symptoms but not for prophylactic use.

The patient should take the first dose of maintenance IP (morning dose) at the study site.

During the treatment period, the patients are allowed to use up to 12 inhalations of the 'as needed' medication during one single day. If a patient needs more than 12 inhalations of the 'as needed' medication in one single day, the patient will be instructed to contact the investigator for reassessment of condition.

7.3 Labelling

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

7.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label on the Turbuhaler specifies the appropriate storage.

7.5 Compliance

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

Indication of study drug intake will be captured by TUM (see Section 5.1.6).

7.6 Accountability

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

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

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

Study Drug is destroyed once there are satisfactory records of product accountability by the Monitor and the Study Leader has given authorisation. The destruction of used and unused Study Drugs should preferably be done at the study site. If destruction at the study site is not possible, the study site personnel should work with the Monitor to ensure Study Drugs are destroyed at a site approved by the local regulatory authority and in accordance with local regulations. A Certificate of Destruction should be filed.

7.7 Concomitant and other treatments

7.7.1 Prohibited Medications

In order not to affect the reversibility test at Visit 2 and / or at Visit 3, patients should not have received the medications listed in Table 2 within the given time limits prior to the visit. Asthma medication before study start is defined by inclusion criterion 4 not by Table 2.

Table 2 Medications which may affect the reversibility test at Visit 2 and/or at Visit 3

	Not allowed before Visit	Time limit prior to Visit
1.*	Inhaled disodium cromoglycate or inhaled nedocromil sodium	6 hours
2.*	Inhaled short-acting anticholinergics	6 hours
3.	Inhaled SABAs	6 hours
4.*	Inhaled long-acting β2-agonists (LABA) formoterol salmeterol oladaterol indacaterol	 24 hours 24 hours 48 hours 72 hours
5.*	Oral β2-agonists as follows: short-acting depot long-acting	 6 hours 24 hours 48 hours
6.*	Transdermal β2-agonists	24 hours
7.*	Leukotriene receptor antagonist or 5-lipoxygenase inhibitors	48 hours
8.*	Xanthines: once daily twice daily	 24 hours 12 hours
9.*	Inhaled anticholinergics: acledinium tiotropium glycopyrrolate	 24 hours 48 hours 48 hours
10.*	Medications containing ephedrine	24 hours

* Not allowed during run-in

Table 3 Medications Not allowed during the run-in period and while on IP

	Not allowed during the run-in period and while on IP - For exceptions see section 7.7.2
1.	Oral, parenteral or rectal GCS
2.	Any ICS other than study medication
3.	Any β2-agonist other than the study medication
4.	Inhaled disodium cromoglycate or inhaled nedocromil sodium
5.	Leukotriene receptor antagonists or 5-lipoxygenase inhibitors
6.	Xanthines

	Not allowed during the run-in period and while on IP - For exceptions see section 7.7.2
7.	Inhaled anticholinergics
8.	Phosphodiesterase inhibitors
9.	Omalizumab or any other monoclonal or polyclonal therapy for any reason
10.	Beta-adrenergic blockers including eye-drops
11.	Systemic treatment with potent CYP3A4 inhibitors (e.g., ketoconazole, itraconazol and ritonavir)

7.7.2 Concomitant asthma treatment

Severe asthma exacerbation treatment: oral or parenteral GCS are allowed in case of a suspected severe asthma exacerbation. During a severe asthma exacerbation, treatment with the concomitant medications included in Number 2-7 (Table 3) is also allowed.

Other allowed asthma-related medications:

- Mucolytics and expectorants not containing bronchodilators
- Patients on allergen-specific immunotherapy (desensitization) must have been on a maintenance regimen for at least 4 weeks prior to Visit 2 and remain on a maintenance regimen during the study. Patients should not begin allergen-specific immunotherapy during the course of the study
- Topical, nasal or ocular formulations of GCS, disodium chromoglycate and/or nedocromil sodium.

7.7.3 Other concomitant treatment

Medications other than that described above, which are considered necessary for the patient's safety and well being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF.

7.8 Post Study Access to Study Treatment

After discontinuation of IP patients will receive asthma medication prescribed according to the investigator's judgment and local medical practice.

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

All personnel involved with the analysis of the study will remain blinded until database lock.

Analyses will be performed by AstraZeneca or its representatives.

A comprehensive Statistical Analysis Plan (SAP) will be prepared prior to first patient randomised and any subsequent amendments will be documented, with final amendments completed prior to unblinding of the data.

8.2 Sample size estimate

The study is powered to assess the primary objective of comparing Symbicort Turbuhaler 'as-needed' versus Pulmicort Turbuhaler bid plus terbutaline Turbuhaler assuming that Symbicort Turbuhaler will be superior to Pulmicort Turbuhaler with regard to the annual severe asthma exacerbation rate.

Based on a subset of patients from the START study a retrospective estimation of severe exacerbation rate was 0.12 events per patient-year in the Pulmicort group (based on Poisson regression). There was no sign of over-dispersion, hence the shape parameter is assumed to be 0. The GOAL study (**Bateman et al 2004**) indicated a similar exacerbation rate in the steroid naïve sub-population 0.12 for patients treated with Fluticasone while for patients pre-study treated with low-dose steroid the exacerbation rate was 0.17 for patients treated with Fluticasone.

The number of patients required for the analyses is estimated to be 4114 overall (2057/treatment group). This was based on the following assumptions using a negative binomial model (**Keene ON et al 2007**):

- alpha 5%
- power 90%
- exacerbation rate of 0.16 in the Pulmicort treatment group
- 25% risk reduction in Symbicort vs Pulmicort
- no over-dispersion (shape parameter=0)

Based on these assumptions 3704 patients (1852 per arm) would be required. Accounting for a 10% drop-out give a total sample size of 4114 patients (2057 per arm).

Sample size re-estimation:

Because of lacking phase II data on Symbicort 'as-needed' use in the target population there are uncertainties about the assumed exacerbation rates as well as the dispersion parameter. To account for that uncertainty the overall exacerbation rate will be monitored during study in a blinded fashion and allow for an increase of the sample size by a maximum of 50% ie up to a total of 6171 patients.

The exacerbation rate and shape parameter will be estimated using the maximum likelihood approach as proposed by (**Friede and Schmidli, 2010**). If results of the blinded reviews indicate that the projected power falls to below 85%, the sample size may be increased. Since

this monitoring of the exacerbation rate will be performed in a blinded fashion, no adjustment for the type I error is needed. The reviews will be based on pooled, blinded data and will not use any treatment information. The blinding will be strictly maintained and not be affected by the reviews in any way.

Decision to change the primary objective from a superiority to non-inferiority hypothesis

In September 2016, the decision was made to change the primary objective to assess whether Symbicort Turbuhaler will be non-inferior to Pulmicort Turbuhaler with regard to the annual severe asthma exacerbation rate. Assuming a 25% exacerbation risk reduction in Symbicort vs Pulmicort, 0.14 exacerbation rate and no overdispersion, a total sample size of 4114 will produce over 90% power to determine if Symbicort Turbuhaler is non-inferior to Pulmicort Turbuhaler with regard to the annual severe asthma exacerbation rate when the non-inferiority limit is set to 120% at the 5% (one-sided) significance level.

8.3 Definitions of analysis sets

8.3.1 Full analysis set

All patients randomised and receiving any investigational product will be included in the full analysis set, irrespective of their protocol adherence and continued participation in the study. Patients will be analysed according to their randomised treatment.

The efficacy analysis set will be based on the 'full analysis set' in line with the ICH E9 guideline.

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

8.3.2 All patients analysis set

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

8.3.3 Safety analysis set

All patients receiving any investigational product will be included in the safety analysis population. Patients will be classified according to the treatment they actually received. Erroneously treated patients (e.g., those randomised to treatment A but actually given treatment B) will be accounted for in the actual treatment group. The classification of patients will be finalised prior to database lock and documented in the Statistical Analysis Plan. All safety summaries will be based on this analysis set.

8.4 Outcome measures for analyses

8.4.1 Derivation of efficacy variables

The primary analysis will include data from the randomisation visit until the subject terminates the use of IP. Sensitivity analysis will include all data regardless of whether or not the subject terminated the use of IP.

8.4.1.1 Derivation of annual severe asthma exacerbation rate (primary variable)

The total number of severe asthma exacerbations will be calculated for each patient during the randomised treatment period according to the following principle:

For the production of summary statistics, the annual exacerbation rate per patient is calculated, and standardized using data from the double-blind treatment period according to the formula described below:

*Annual Exacerbation Rate = Number of Exacerbations*365.25 / (Date of Visit6/EoT – Date of Randomisation (Visit 3) + 1)*

8.4.1.2 Derivation of time to first severe asthma exacerbation

Time to first severe asthma exacerbation (see Section 8.5.2) will be calculated as the time from randomisation until the start date of the first severe asthma exacerbation ie:

Start Date of first severe asthma exacerbation – Date of Randomisation (Visit 3) +1

Patients not having any severe asthma exacerbation will be considered as censored at the date of their last visit or, for patients discontinuing IP, the day when it was decided that the patient should discontinue the IP.

Maximum follow-up time for a patient is approximately 52 weeks; defined as the time from randomisation to the date of Visit 6/EoT. For a patient lost to follow-up, this will be defined as the time from randomisation to the time point after which an exacerbation could not be assessed.

8.4.1.3 Derivation of total inhaled steroid load and number of days with systemic GCS treatment

Total inhaled steroid load during the randomised treatment period will be calculated for each patient as the sum of the cumulative doses of maintenance ICS (budesonide), ‘as needed’ ICS as part of Symbicort (budesonide). Data on IP will be recorded via the TUM.

The number of days with systemic GCS will be recorded via the appropriate CRF module.

8.4.1.4 Derivation of ‘as-needed’ use

‘As-needed’-use during the randomised treatment period will be calculated as the cumulative doses of ‘as-needed’ medication divided by the follow-up time (number of days).

For Symbicort treatment arm 'as needed' will be Symbicort, while for the Pulmicort treatment arm 'as needed' will be terbutaline.

Change from baseline will be calculated for each patient, where baseline is defined as the 'as-needed' use 10 days prior to randomisation during run-in.

'As-needed' use will be captured via the TUM device and measures the number of turns of the inhaler.

'As-needed' use (as recorded by the TUM) for the day- and night time period will be derived in the following way:

- Start of the daytime period is defined as the time when the patient takes their morning maintenance dose (between 04:00-11:59:59). If the patient takes their morning maintenance dose before or after this time interval, or if there is no recorded morning maintenance dose the start of the daytime period will be set to the average of the recorded morning maintenance doses (between 04:00-11:59:59) across the trial for that patient. The end of the daytime period will be set to the second prior to the start of the night-time period.

- Start of the night-time period is defined as the time when the patient takes their evening maintenance dose (between 18:00-23:59:59). If the patient takes their evening maintenance dose before or after this time interval, or if there is no recorded evening maintenance dose the start of the night-time period will be set to the average of the recorded evening maintenance doses (between 18:00-23:59:59) across the trial for that patient. The end of the night-time period will be set to the second prior to the start of the daytime period.

For analysis where full days are assessed they are a day followed by a night.

8.4.1.5 Derivation of controller-use days

'Controller'-use during the randomised treatment period will be calculated as the cumulative days when any controller medication (containing ICS) was taken divided by the follow-up time (number of days).

For Symbicort treatment arm controller will be the 'as needed' use, while for the Pulmicort treatment arm this will be the maintenance use. This will be derived from the TUM.

8.4.1.6 Derivation of percent 'as-needed'-free days

An 'as needed'-free day is defined as a day and night with no use of 'as needed' medication. Percent 'as-needed' free days will then be calculated as the number of days during the randomised treatment period with no record in the TUM device of 'as-needed' medication divided by the follow-up time (days). Change from baseline will then be calculated for each patient, where baseline is defined as the 'as-needed' free days 10 days prior to randomisation during run-in.

8.4.1.7 Derivation of time to asthma related discontinuation

Study specific asthma related discontinuation criteria are given by:

- A severe asthma exacerbation with a duration for more than 3 weeks
- Three severe asthma exacerbations during 6 months

Time to discontinuation due to any of the specified asthma related events will be calculated as:

Date of discontinuation due to any of the specified asthma related events – Date of Randomisation (Visit 3) + 1

Patients not discontinuing the IP due to asthma related events will be considered as censored at the date of their last visit or, for patients discontinuing the IP, the day when it was decided that the patient should discontinue IP for whatever reason.

8.4.1.8 Derivation of lung function variables

Change from baseline (Visit 3) to Visits 4, 5 and 6 will be calculated for each patient for the following lung function variables:

- Pre- and post-bronchodilator FEV1 (L)
- Pre- and post-bronchodilator FEV1 % of predicted normal
- Pre- and post-bronchodilator FVC (L)

If the baseline measurement is missing, the last non-missing value before Visit 3 will be used as baseline instead.

Percent predicted of normal for pre- and post-bronchodilator FEV_1 will be calculated according to **Quanjer et al 2012**.

8.4.2 Derivation of patient reported outcome variables

8.4.2.1 Derivation of ACQ-5

All 5 symptom questions are assessed on a 7-point scale from 0 to 6 where 0 represents good control and 6 represents poor control. The overall score is the mean of the 5 items. At least 4 out of the 5 symptom items are needed to provide an ACQ score.

The minimal important difference (MID) has been defined as “the minimal change in score which clinicians consider to be clinically important and which would mandate, in the absence of troublesome side effects and undue cost, a change in the patient’s management”. For the ACQ, it has been estimated to be a change in score of 0.5 (**Juniper et al 2005 /2**).

Baseline is defined as the ACQ-5 assessment at Visit 3. In case of a missing value the Visit 2 value will be used instead.

Based on MID the following variables will be derived:

- Patients improved (end of treatment – baseline) ≤-0.5
- Patients unchanged (end of treatment – baseline) within (-0.5; 0.5)
- Patients worsened (end of treatment – baseline) ≥0.5.

In addition, an asthma control variable based on ACQ-5 will be derived as:

- If the ACQ-5 value at the last visit (or last available value) is less than 0.75 the patient would be considered to be 'in control'. Otherwise 'not in control'.

8.4.2.2 Standardised Asthma Quality of Life Questionnaire (AQLQ(S))

AQLQ(S) consists of 32 questions all assessed on a 7-point Likert scale from 1 to 7, with higher values indicating better health-related quality of life. Domain scores as well as the overall scores are calculated from the unweighted arithmetic means of the individual question scores. Differences between the follow-up visits and the baseline measure (Visit 3) for each of the domains and the overall scores will be calculated. In addition the difference between the patients last measurements and baseline will be calculated. For overall health-related quality of life and for each of the domains, the MID has been determined to be a change in score of 0.5 (**Juniper et al 1994**).

Baseline is defined as the assessment at Visit 3. In case of a missing value the Visit 2 value will be used instead.

Based on MID the following variables will be derived:

- Patients improved (end of treatment – baseline) ≥0.5
- Patients unchanged (end of treatment – baseline) within (-0.5; 0.5)
- Patients worsened (end of treatment – baseline) ≤-0.5.

8.4.3 Derivation of safety variables

8.4.3.1 Vital signs

Change from baseline (Visit 2) to week 52 (Visit 6 / EoT) in pulse and blood pressure will be calculated for each patient.

8.4.3.2 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. A similar review of vital signs data will be performed for identification of OAEs.

8.5 Methods for statistical analyses

All tests will be 2-sided and at 5% level of significance unless otherwise stated. No adjustment will be made for multiplicity.

For all repeated measures analyses, missing at random (MAR) will be assumed.

In addition the analyses described below, all variables will be summarised descriptively, as appropriate.

8.5.1 Analysis of the primary variable

The primary variable annual severe asthma exacerbation rate will be analysed by a negative binomial regression model. The response variable in the model will be the number of severe asthma exacerbations over the treatment period. The model will include treatment, pre-study treatment group and region as factors. The logarithm of the follow-up time will be used as an offset variable. From the negative binomial model the annual severe asthma exacerbation rates will be estimated and treatments effects will be expressed as the rate ratio along with its corresponding one-sided 95% non-inferiority interval (interval from point estimate to UCL) and two-sided 95% confidence interval. The planned treatment comparison will be:

- Symbicort vs Pulmicort (non-inferiority, primary objective)

Formally, the null and alternative hypothesis is:

H_0: rate-ratio (Symbicort vs Pulmicort) ≥ 1.2

H_A: rate-ratio (Symbicort vs Pulmicort) < 1.2

If the upper 95% 1-sided confidence limit of the relative risk ratio is < 1.2 then non-inferiority can be declared.

If the criteria for the alternative hypothesis is met then superiority of Symbicort vs Pulmicort in terms of annual severe asthma exacerbation will be assessed.

Formally, the null and alternative hypothesis for superiority testing is:

H_0: rate-ratio (Symbicort vs Pulmicort) $= 1$
H_A: rate-ratio (Symbicort vs Pulmicort) $\neq 1$

8.5.2 Analysis of the secondary and other variables

For all secondary variables stated below Symbicort vs Pulmicort will be compared.

Exacerbations: Time to first severe asthma exacerbation will be analysed by a Cox proportional hazards model with treatment, pre-study treatment group and region as factors. The hazard ratio and its corresponding 95% confidence interval will be estimated from the model.

Pre-dose FEV_1: The treatment effect for change from baseline (Visit 3) in pre-dose FEV_1, will be estimated using a mixed model repeated measures (MMRM) analysis. FEV_1 data from visits 4, 5 and 6 will be included in the model, with terms for treatment, pre-study treatment group, region, visit and treatment*visit. Baseline FEV_1 (Visit 3) will be included as a covariate. Visit will be fitted as a categorical variable, and the variance-covariance matrix will be assumed to be unstructured. If the procedure does not converge then a compound symmetric variance-covariance matrix will be used instead.

This model will be used to give an overall assessment of the treatment effect as well as 95% confidence intervals.

Summary statistics will be presented for change from baseline across all the time points in the trial for pre- and post-dose FEV_1 (L) and FVC, respectively by treatment.

Steroid load: The total inhaled steroid load and the number of days with systemic GCS, respectively will be presented descriptively by treatment adjusted by the patients follow-up time.

'As-needed' use: The change from baseline in 'as-needed' use will be analysed by analysis of covariance (ANCOVA) with treatment, pre-study treatment group and region as factors, and the 'as-needed' use value during run-in as a continuous covariate. Least squared means by treatment and differences in least squared means (between treatments) along with corresponding 95% confidence intervals will be estimated.

More details of eg graphical presentations of pattern of use will be provided in the SAP. It will include summaries of day time and night time use.

Percent 'as needed'-free days: The change from baseline in percent 'as needed'-free days will all be analysed in the same way as 'as-needed' use described above.

Controller-use days: The percentage of controller use days will be analysed by analysis of covariance (ANCOVA) with treatment, pre-study treatment group and region as factors. Least squared means by treatment and differences in least squared means (between treatments) along with corresponding 95% confidence intervals will be estimated.

Discontinuation due to asthma related events: Time to discontinuation due to asthma related events will be analysed by Cox proportional hazards model with treatment, pre-study treatment group and region as factors. The hazard ratio and its corresponding 95% confidence interval will be estimated from the model.

PRO variables: ACQ-5 and AQLQ(S) will be analysed in the same way as FEV_1 using MMRM analysis. In addition, change from baseline to the end of treatment will be analysed using analysis of covariance with treatment, pre-study treatment group and region as factors and baseline as a continuous variable.

Responder variables based on MID for ACQ-5 and AQLQ(S) will be analysed using a logistic regression model with treatment, region and pre-study treatment group as factors, and baseline as a covariate. From the logistic regression model treatment effects will be estimated by odds-ratio and its corresponding 95% confidence interval.

The responder variable ACQ-5 <0.75 at the end of treatment will be analyzed using a logistic regression model with treatment, region and pre-study treatment as factors, and baseline as a covariate. From the logistic regression model treatment effects will be estimated by odds-ratio and its corresponding 95% confidence interval.

Safety variables: AEs will be summarized by means of count summaries. AEs will be listed for each patient and summarized by System Organ Class and Preferred Term assigned to the event by MedDRA. Other safety variables will be summarized as appropriate. Further details will be provided in the SAP.

8.5.3 Subgroup analysis

The assessment of treatment effect will also be investigated in the 2 subgroups as defined by pre-study treatment to assess the consistency of the treatment effect. This will be done for each of the primary and secondary variables by including a pre-study treatment*treatment interaction term in the models.

8.5.4 Blinded sample size re-estimation

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

8.5.5 Sensitivity analysis

Sensitivity analyses of the primary and key secondary variables will be carried out and will be specified in the SAP.

For the primary variable a sensitivity analysis will be performed including all data for patients who discontinue IP but remain in the study.

The primary analysis assumes that data are missing at random. Different missing data assumptions will be explored if possible.

8.5.6 Exploratory analysis

8.5.7 Analyses related to exploratory objective

Descriptive reporting of the resource utilization data and health related quality of life data based on the EQ-5D-5L will be carried out in the CSR. The data will be combined with economic data collected independently of the study to construct comparative health economic analyses between treatment groups. The economic analyses and cost-effectiveness analyses that include data external to the study will be reported in a separate health economic report and will not be included in the CSR.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site personnel

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

The investigator and study site staff should preferably have prior experience in performing spirometry.

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

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

9.2 Monitoring of the study

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

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

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

9.2.1 Source data

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

9.2.2 Study agreements

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

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

9.2.3 Archiving of study documents

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

9.3 Study timetable and end of study

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

The study is expected to start in Quarter 3 in 2014 and to end by Quarter 2 in 2017.

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

9.4 Data management by Cognizant Data Management Centre

Data management will be performed by Cognizant Data Management Centre staff according to the Data Management Plan. Adverse events and medical/surgical history will be classified according to the terminology of the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. Classification coding will be performed by the Medical Coding Team at the AstraZeneca Data Management Centre.

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

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

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

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

Serious Adverse Event (SAE) Reconciliation

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

Management of external data

Data Management determines the format of the data to be received from external vendors and coordinates the flow of data to the clinical database. Data Management will ensure that the data collection tool (e.g., ePRO, TUM and IVRS etc) will be tested and validated. External data reconciliation will be done with the clinical database as applicable.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

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

10.2 Patient data protection

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

10.3 Ethics and regulatory review

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

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

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

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

Before enrolment of any patient 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.

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

10.4 Informed consent

The Principal Investigator(s) at each site will:

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

10.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the International 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 10.3.

If a protocol amendment requires a change to a site's Informed Consent Form, AstraZeneca and the site'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.

10.6 Audits and inspections

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

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AstraZeneca

Clinical Study Protocol Appendix B

Drug Substance	budesonide/formoterol
Study Code	D589SC00003
Edition Number	1
Date	17 June 2014

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 hospitalisation
- 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.

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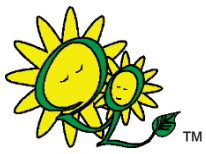
Clinical Study Protocol Appendix C	
Drug Substance	budesonide/formoterol
Study Code	D589SC00003
Edition Number	1
Date	17 June 2014

Appendix C
Asthma Control Questionnaire (5-item version)

ASTHMA CONTROL QUESTIONNAIRE (ACQ)

(SYMPTOMS ONLY)



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DECEMBER 2002

Please answer questions 1 - 5.

Circle the number of the response that best describes how you have been during the past week.

1. On average, during the past week, how often were you **woken by your asthma** during the night?

0 Never
1 Hardly ever
2 A few times
3 Several times
4 Many times
5 A great many times
6 Unable to sleep because of asthma

2. On average, during the past week, how **bad were your asthma symptoms when you woke up** in the morning?

0 No symptoms
1 Very mild symptoms
2 Mild symptoms
3 Moderate symptoms
4 Quite severe symptoms
5 Severe symptoms
6 Very severe symptoms

3. In general, during the past week, how **limited were you in your activities** because of your asthma?

0 Not limited at all
1 Very slightly limited
2 Slightly limited
3 Moderately limited
4 Very limited
5 Extremely limited
6 Totally limited

4. In general, during the past week, how much **shortness of breath** did you experience because of your asthma?

0 None
1 A very little
2 A little
3 A moderate amount
4 Quite a lot
5 A great deal
6 A very great deal

5. In general, during the past week, how much of the time did you **wheeze?**

0 Not at all
1 Hardly any of the time
2 A little of the time
3 A moderate amount of the time
4 A lot of the time
5 Most of the time
6 All the time

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Clinical Study Protocol Appendix D	
Drug Substance	budesonide/formoterol
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Appendix D
Asthma Quality of Life Questionnaire with Standardised Activities (AQLQ(S)) self administered ≥ 12 years of age

ASTHMA QUALITY OF LIFE QUESTIONNAIRE WITH STANDARDISED ACTIVITIES (AQLQ(S))

SELF-ADMINISTERED

(≥12 years)

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APRIL 2008

Modified September 2010
AQLQ(S) ≥12 years SA North American English Version

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S) PATIENT ID: _____

SELF-ADMINISTERED DATE: _____

Please complete **all** questions by circling the number that best describes how you have been during the **last 2 weeks as a result of your asthma.**

HOW **LIMITED** HAVE YOU BEEN **DURING THE LAST 2 WEEKS** IN THESE ACTIVITIES **AS A RESULT OF YOUR ASTHMA**?

	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at all Limited
1. STRENUOUS ACTIVITIES (such as hurrying, exercising, running up stairs, sports)	1	2	3	4	5	6	7
2. MODERATE ACTIVITIES (such as walking, housework, gardening, shopping, climbing stairs)	1	2	3	4	5	6	7
3. SOCIAL ACTIVITIES (such as talking, playing with pets/children, visiting friends/relatives)	1	2	3	4	5	6	7
4. WORK/SCHOOL-RELATED ACTIVITIES* (tasks you have to do at work/in school)	1	2	3	4	5	6	7
5. SLEEPING	1	2	3	4	5	6	7

*If you are not employed or self-employed, these should be tasks you have to do most days.

HOW MUCH **DISCOMFORT OR DISTRESS** HAVE YOU FELT **DURING THE LAST 2 WEEKS**?

	A Very Great Deal	A Great Deal	A Good Deal	Moderate Amount	Some	Very Little	None
6. How much discomfort or distress have you felt over the last 2 weeks as a result of CHEST TIGHTNESS?	1	2	3	4	5	6	7

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
7. Feel CONCERNED ABOUT HAVING ASTHMA?	1	2	3	4	5	6	7
8. Feel SHORT OF BREATH as a result of your asthma?	1	2	3	4	5	6	7
9. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO CIGARETTE SMOKE?	1	2	3	4	5	6	7
10. Experience a WHEEZE in your chest?	1	2	3	4	5	6	7
11. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF CIGARETTE SMOKE?	1	2	3	4	5	6	7

HOW MUCH **DISCOMFORT OR DISTRESS** HAVE YOU FELT **DURING THE LAST 2 WEEKS**?

	A Very Great Deal	A Great Deal	A Good Deal	Moderate Amount	Some	Very Little	None
12. How much discomfort or distress have you felt over the last 2 weeks as a result of COUGHING?	1	2	3	4	5	6	7

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
13. Feel FRUSTRATED as a result of your asthma?	1	2	3	4	5	6	7
14. Experience a feeling of CHEST HEAVINESS?	1	2	3	4	5	6	7

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
15. Feel CONCERNED ABOUT THE NEED TO USE MEDICATION for your asthma?	1	2	3	4	5	6	7
16. Feel the need to CLEAR YOUR THROAT?	1	2	3	4	5	6	7
17. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO DUST?	1	2	3	4	5	6	7
18. Experience DIFFICULTY BREATHING OUT as a result of your asthma?	1	2	3	4	5	6	7
19. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF DUST?	1	2	3	4	5	6	7
20. WAKE UP IN THE MORNING WITH ASTHMA SYMPTOMS?	1	2	3	4	5	6	7
21. Feel AFRAID OF NOT HAVING YOUR ASTHMA MEDICATION AVAILABLE?	1	2	3	4	5	6	7
22. Feel bothered by HEAVY BREATHING?	1	2	3	4	5	6	7
23. Experience asthma symptoms as a RESULT OF THE WEATHER OR AIR POLLUTION OUTSIDE?	1	2	3	4	5	6	7
24. Were you WOKEN AT NIGHT by your asthma?	1	2	3	4	5	6	7
25. AVOID OR LIMIT GOING OUTSIDE BECAUSE OF THE WEATHER OR AIR POLLUTION?	1	2	3	4	5	6	7

IN GENERAL, **HOW MUCH OF THE TIME DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
26. Experience asthma symptoms as a RESULT OF BEING EXPOSED TO STRONG SMELLS OR PERFUME?	1	2	3	4	5	6	7
27. Feel AFRAID OF GETTING OUT OF BREATH?	1	2	3	4	5	6	7
28. Feel you had to AVOID A SITUATION OR ENVIRONMENT BECAUSE OF STRONG SMELLS OR PERFUME?	1	2	3	4	5	6	7
29. Has your asthma INTERFERED WITH GETTING A GOOD NIGHT'S SLEEP?	1	2	3	4	5	6	7
30. Have a feeling of FIGHTING FOR AIR?	1	2	3	4	5	6	7

HOW LIMITED HAVE YOU BEEN **DURING THE LAST 2 WEEKS**?

	Severely Limited Most Not Done	Very Limited	Moderately Limited Several Not Done	Slightly Limited	Very Slightly Limited Very Few Not Done	Hardly Limited At All	Not Limited Have Done All Activities
31. Think of the OVERALL RANGE OF ACTIVITIES that you would have liked to have done during the last 2 weeks. How much has your range of activities been limited by your asthma?	1	2	3	4	5	6	7

HOW LIMITED HAVE YOU BEEN **DURING THE LAST 2 WEEKS**?

	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at all Limited
32. Overall, among ALL THE ACTIVITIES that you have done during the last 2 weeks, how limited have you been by your asthma?	1	2	3	4	5	6	7

DOMAIN CODE:

Symptoms: 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 29, 30
Activity Limitation: 1, 2, 3, 4, 5, 11, 19, 25, 28, 31, 32
Emotional Function: 7, 13, 15, 21, 27
Environmental Stimuli: 9, 17, 23, 26

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Clinical Study Protocol Appendix E	
Drug Substance	Budesonide/formoterol
Study Code	D589SC00003
Edition Number	2
Date	17 August 2015

Appendix E
Inhaled Glucocorticosteroids Equivalence Table

INHALED GLUCOCORTICOSTEROIDS EQUIVALENCE TABLE

Asthma Therapy	**Total Daily Dose (µg/day)**
Inhaled Glucocorticosteroid	**Low**
Beclomethasone dipropionate (non HFA propellant)	200 to 500
Beclomethasone HFA*	100 to 250
Ciclesonide	80 to 160
Triamcinolone acetonide	400 to 1000
Flunisolide	500 to 1000
Fluticasone propionate	100 to 250
Budesonide	200 to 400
Mometasone furoate	200

* For some HFA beclomethasone products dose ranges related to non-HFA beclomethasone may apply depending on formulation. Formulations with smaller particles size have greater lung disposition. The manufacturer's information should be reviewed in order to determine patient's eligibility with regard to ICS daily dose.

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Clinical Study Protocol Appendix F	
Drug Substance	budesonide/formoterol
Study Code	D589SC00003
Edition Number	1
Date	17 June 2014

Appendix F
EQ-5D-5L Health Questionnaire

Health Questionnaire

English version for the UK

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

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

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

ANXIETY / DEPRESSION

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

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

YOUR HEALTH TODAY = ☐