

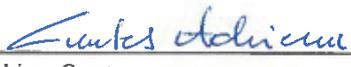
Revised Clinical Study Protocol

Drug Substance	budesonide/formoterol
Study Code	D589SC00001
Edition Number	4
Date	22 December 2016

**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 terbutaline Turbuhaler® 0.4 mg ‘as needed’ and with Pulmicort® (budesonide) Turbuhaler® 200 µg twice daily plus terbutaline Turbuhaler® 0.4 mg ‘as needed’**

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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	27 November 2014		
2	17 August 2015		
3	24 February 2016		
4	22 December 2016		
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1	10 December 2014		
2	8 May 2015		

Revised Clinical Study Protocol  
Drug Substance budesonide/formoterol  
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Date 22 December 2016

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

## PROTOCOL SYNOPSIS

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**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<sup>®</sup> (budesonide/formoterol) Turbuhaler<sup>®</sup> 160/4.5 µg ‘as needed’ compared with terbutaline Turbuhaler<sup>®</sup> 0.4 mg ‘as needed’ and with Pulmicort<sup>®</sup> (budesonide) Turbuhaler<sup>®</sup> 200 µg twice daily plus terbutaline Turbuhaler<sup>®</sup> 0.4 mg ‘as needed’**

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### International Co-ordinating Investigator

**Paul M. O’Byrne MB, FRCPC, FRSC**



### Study site(s) and number of patients planned

This study will recruit patients worldwide at approximately 265 sites. The target is to randomise 3750 male and female patients.

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

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### 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<sup>®</sup> (budesonide/formoterol) Turbuhaler<sup>®</sup> 160/4.5 µg ‘as needed’ compared with terbutaline Turbuhaler<sup>®</sup> 0.4 mg ‘as needed’ and with Pulmicort<sup>®</sup> (budesonide) Turbuhaler<sup>®</sup> 200 µg twice daily plus terbutaline Turbuhaler<sup>®</sup> 0.4 mg ‘as needed’.

## Objectives

<b>Primary Objective:</b>	<b>Outcome Measure:</b>
To demonstrate that Symbicort Turbuhaler 160/4.5 µg 'as needed' is superior to terbutaline Turbuhaler 0.4 mg 'as needed'	Evaluation of asthma control as measured by well-controlled asthma weeks as the primary variable

<b>Secondary Objectives:</b>	<b>Outcome Measure:</b>
To evaluate the relative efficacy of Symbicort Turbuhaler 160/4.5 µg 'as needed' and Pulmicort Turbuhaler 200 µg twice daily plus terbutaline Turbuhaler 0.4 mg 'as needed'	Evaluation of asthma control as measured by well-controlled asthma weeks as the primary variable
To evaluate the efficacy of Symbicort Turbuhaler 160/4.5 µg as compared to both: terbutaline Turbuhaler 0.4 mg '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 Time to first moderate or severe asthma exacerbation Average change from baseline in pre-dose Forced Expiratory Volume in one second Average change from baseline in Morning Peak Expiratory Flow Average change from baseline in Evening Peak Expiratory Flow Average change from baseline in number of inhalations of 'as needed' medication Average change from baseline in symptom score Percentage of Nighttime awakenings due to asthma Percentage of Symptom-free days Percentage of 'As needed' free days Percentage of Asthma control days Percentage of controller use days Time to asthma related discontinuation Poorly controlled asthma weeks Time to additional steroids for asthma Average change from baseline in Asthma Control Questionnaire 5-item version Average change from baseline in Asthma Quality of Life Questionnaire standard version

<b>Safety Objective:</b>	<b>Outcome Measure :</b>
To compare the safety of Symbicort Turbuhaler 160/4.5 µg ‘as needed’ with that of terbutaline Turbuhaler 0.4 mg ‘as needed’, and 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 inhaled short acting bronchodilator(s) ‘as needed’ (short acting β<sub>2</sub> 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 β<sub>2</sub> 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 short acting β<sub>2</sub> 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 β<sub>2</sub> agonist (Bricanyl) ‘as needed’ only. 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<sup>®</sup> 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<sup>®</sup>) administered two times daily

### **Comparators, dosage and mode of administration**

Terbutaline Turbuhaler<sup>®</sup> 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 Placebo for budesonide (powder for inhalation in a dry powder inhaler matching the Pulmicort Turbuhaler<sup>®</sup>) administered two times daily

Terbutaline Turbuhaler<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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 'well-controlled asthma weeks' (binary) will be analysed by a repeated measures logistic regression. 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 comparisons are:

1. Symbicort versus terbutaline (superiority, primary objective)
2. Symbicort versus Pulmicort plus terbutaline (non-inferiority)

Formally, the null and alternative hypothesis for comparison 1 is:

$$H_0: \text{odds-ratio (Symbicort vs terbutaline)} = 1$$

$$H_A: \text{odds-ratio (Symbicort vs terbutaline)} \neq 1$$

And for comparison 2:

$$H_0: \text{lower 95\% confidence limit of odds-ratio (Symbicort vs Pulmicort plus terbutaline)} < 0.8$$

$$H_A: \text{lower 95\% confidence limit of odds-ratio (Symbicort vs Pulmicort plus terbutaline)} \geq 0.8$$

#### Analysis of the secondary variables:

For all secondary variables stated below the following treatment comparisons will be made:

1. Symbicort versus terbutaline
2. Symbicort versus Pulmicort plus terbutaline

Time to first moderate-to-severe asthma exacerbation, time to first severe asthma exacerbation, time to the administration of additional steroids for asthma, and time to study

discontinuation 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 morning- and evening Peak Expiratory Flow, asthma symptom score, use of 'as needed' medication, awakening(s) due to asthma symptoms, symptom-free days, asthma-control days, 'as needed' - free days and the percentage of controller use days will be analysed by analysis of covariance.

Poorly controlled asthma weeks will be analysed in the same way as well controlled asthma weeks.

The total inhaled steroid load and the number of days with systemic glucocorticoids, respectively, will be presented descriptively by treatment.

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## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

<b>Abbreviation or special term</b>	<b>Explanation</b>
ACQ	Asthma Control Questionnaire (5-item Version)
AE	Adverse Event (See definition in Section 6.1)
'As needed'	Administered as needed in response to symptoms; similar to reliever or rescue medication
AQLQ(S)	Asthma Quality of Life Questionnaire (Standardised Version)
BID	Twice daily
CI	Confidence Interval
CHMP	Committee for Medicinal Products for Human Use (formerly: Committee for Proprietary Medicinal Products)
(e)CRF	Case Report Form (electronic/paper)
CSA	Clinical Study Agreement
CSR	Clinical Study Report
DAE	Discontinuation of Investigational Product due to Adverse Event
DMC	Data Management Centre
DPI	Dry Powder Inhaler
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
eDiary	Electronic Patient Diary
FEV <sub>1</sub>	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.
GRand	AstraZeneca Global Randomisation System
HRA	Health Research Associates
ICH	International Conference on Harmonisation
ICS	Inhaled corticosteroid

<b>Abbreviation or special term</b>	<b>Explanation</b>
International Co-ordinating Investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IP	Investigational Product
ISF	Investigator Study File
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
L	Litre
LABA	Long-acting $\beta_2$ agonist
LTRA	Leukotriene Receptor Antagonist
MID	Minimal Important Difference
MMRM	Mixed Model Repeated Measures
mL	Millilitre
OAE	Other Significant Adverse Event
PEF	Peak Expiratory Flow
PI	Principal Investigator
PN	Predicted Normal
SABA	Short-acting $\beta_2$ agonist
SAE	Serious Adverse Event (see definition in Section 6.2)
SAP	Statistical Analysis Plan
TUM	Turbuhaler Usage Monitor
VC	Vital Capacity
vs	Versus
WBDC	Web Based Data Capture
WCAW	Well Controlled Asthma Weeks

## 1. INTRODUCTION

### 1.1 Background and rationale for conducting this study

Asthma is a respiratory disease characterized by chronic inflammation and obstruction of the airways that 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  $\beta_2$ -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  $\beta_2$ -agonists alone, a controller medication is added, usually a low dose inhaled corticosteroid (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  $\beta_2$ -agonist for symptomatic improvement (Rabe et al 2004). Overuse of rapid-acting  $\beta_2$ -agonists often leads to delayed introduction of ICS: even if ICS is 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 with "as needed" administration of both the controller and the bronchodilator medications in response to symptoms.

Symbicort<sup>®</sup> is a fixed combination of the ICS budesonide and the rapid- and long-acting  $\beta_2$ -agonist formoterol (LABA). As formoterol has been shown to be as effective as short-acting  $\beta_2$ -agonists (SABA) for symptom relief (Chuchalin et al 2005), (Pauwels et al 2003b), (Tattersfield et al 2001), Symbicort<sup>®</sup> can also be used as a reliever medication (Palmqvist et al 2001). Such use of Symbicort<sup>®</sup> is approved for administration as Symbicort<sup>®</sup> Maintenance and Reliever Therapy (SMART) in moderate-to-severe asthma. According to the SMART concept, Symbicort<sup>®</sup> is taken as a regular maintenance treatment and 'as needed' in response to symptoms. Symbicort<sup>®</sup> SMART has been shown to reduce exacerbations and improve asthma control (O'Byrne et al 2005), (Scicchitano et al 2004), (Rabe et al 2006), (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 (Hahtela et al 2006, Papi et al 2007). In patients with mild intermittent asthma (i.e., requiring GINA step 1 treatment) and having signs of airway inflammation, Symbicort 'as needed' was more efficacious than Oxis (i.e., formoterol) 'as needed' in reducing fractional exhaled nitric oxide (FeNO) and improving lung function (Hahtela 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 (i.e., requiring GINA step 2 treatment), (Papi et al 2007).

When administered on an as-needed basis without daily maintenance medication, Symbicort<sup>®</sup> will provide both an anti-inflammatory and a reliever medication adapted to the patient's current asthma symptoms. Such an approach will address the need for a timely administration and adherence to ICS in asthma patients in need of GINA step 2 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 '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 (SABA and/or short acting anticholinergic agent) will be included in the study. The study will begin with a 2 to 4 week-long 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<sup>®</sup> Turbuhaler<sup>®</sup> in a new patient population, which will include both adult and adolescent patients.

The efficacy and safety of Symbicort 'as needed' will be compared with a commonly used SABA, terbutaline. In addition Symbicort 'as needed' will also be compared with Pulmicort<sup>®</sup> (budesonide) Turbuhaler<sup>®</sup> 200 µg twice daily plus terbutaline 'as needed' which is one of the current standard treatments for patients at GINA step 2. Symbicort (budesonide/formoterol) Turbuhaler 160/4.5 µg 'as needed' is the strength mostly used on 'as needed' basis with the Symbicort SMART concept. It is considered to provide adequate anti-inflammatory effect due to the budesonide component, and yet is safe to use as evidenced by Symbicort SMART data. The formoterol component of Symbicort<sup>®</sup> Turbuhaler<sup>®</sup> provides rapid and effective symptom relief.

During the treatment period of the study terbutaline will be provided in a Turbuhaler (dry powder inhaler - DPI) that is identical to the Symbicort<sup>®</sup> Turbuhaler<sup>®</sup> for blinding purposes. The dose of active substance in the terbutaline Turbuhaler (0.4 mg terbutaline per inhalation) is expressed as delivered dose that corresponds to 0.5 mg per inhalation in the commercially available product, Bricanyl<sup>®</sup> Turbuhaler<sup>®</sup> (expressed as metered dose). Bricanyl<sup>®</sup> Turbuhaler<sup>®</sup> will be used during the run in period (see Section 7.1 'Identity of investigational products').

Evaluating asthma control is important in patients with asthma, especially in patients with mild asthma. Well controlled asthma weeks (WCAW) are a well-known and well-accepted composite measure of asthma control (Bateman et al 2004). Therefore WCAW on the

randomised treatment has been chosen as the primary variable in the study. WCAW consists of several parameters including symptoms, nighttime awakenings, lung function and as needed use measured on a daily basis. In addition WCAW on randomised treatment take into consideration any additional asthma therapy received by the patients. Moderate and severe asthma exacerbations, another important aspect of asthma control, will be collected as secondary end-points.

Patients' recruitment will be balanced based on their pre-study treatment (i.e., patients who are uncontrolled on an inhaled short acting bronchodilator (SABA and/or short acting anticholinergic agent) 'as needed' 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 (SABA and/or short acting anticholinergic agent). Patients will be randomised to the three treatment arms in 1:1:1 proportion.

### **1.3 Benefit/risk and ethical assessment**

Symbicort, terbutaline Turbuhaler as well as Pulmicort 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 this study patients will be instructed to contact the investigator if using more than 12 as needed inhalations with Symbicort Turbuhaler per day. 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  $\beta_2$  agonists (SABAs). 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. The patients will be instructed to contact the investigator if using more than 12 as needed inhalations with terbutaline Turbuhaler per day.

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

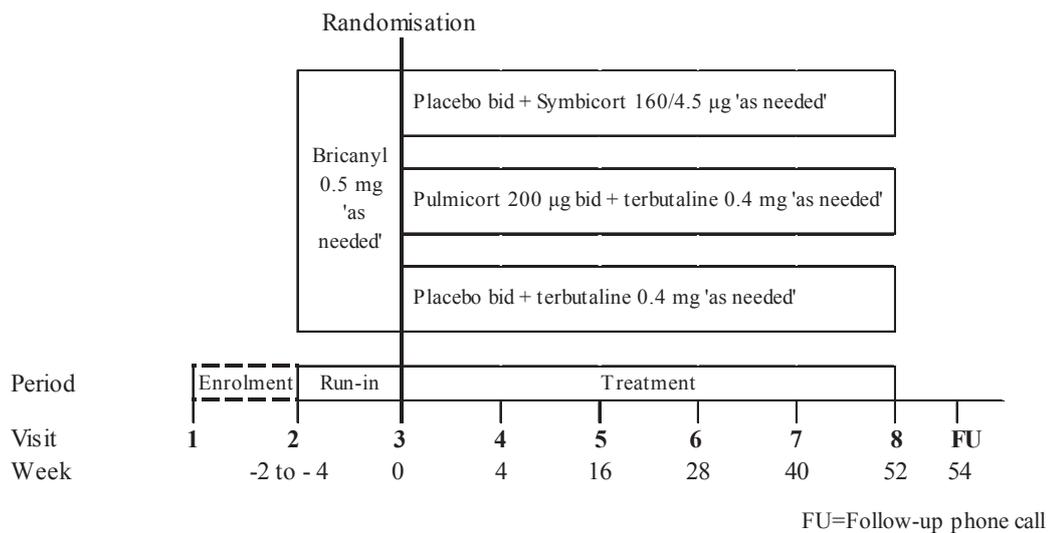
All patients will be thoroughly monitored during the course of the study with clinic visits at 4, 16, 28, 40 and 52 weeks of treatment and daily recording of Peak Expiratory Flow (PEF), asthma symptoms, use of maintenance and 'as needed' investigational product (IP) and nighttime awakenings. Furthermore there will be triggers in the electronic diary (eDiary) to generate alerts warning the patients for worsening of their asthma. Upon receiving such an

alert the patients will be asked to contact the investigators for a consultation. In addition the patients will be instructed to contact the investigator at any time they feel a need for medical assistance even without an alert. The investigators may prescribe additional glucocorticosteroid (GCS) treatment to patients having asthma exacerbations or poor long-term asthma control. Strict 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 superior to terbutaline Turbuhaler 0.4 mg ‘as needed’.	Evaluation of asthma control as measured by well-controlled asthma weeks as the primary variable.

### 2.2 Secondary objective

Secondary Objectives:	Outcome Measure:
To evaluate the relative efficacy of Symbicort Turbuhaler 160/4.5 µg ‘as needed’ and Pulmicort Turbuhaler 200 µg twice daily plus terbutaline Turbuhaler 0.4 mg ‘as needed’.	Evaluation of asthma control as measured by well-controlled asthma weeks as the primary variable
To evaluate the efficacy of Symbicort Turbuhaler 160/4.5 µg as compared to both: terbutaline Turbuhaler 0.4 mg ‘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 Time to first moderate or severe asthma exacerbation Average change from baseline in pre-dose FEV <sub>1</sub> Average change from baseline in Morning PEF Average change from baseline in Evening PEF Average change from baseline in number of inhalations of ‘as needed’ medication Average change from baseline in symptom score Percentage of Nighttime awakenings due to asthma Percentage of Symptom-free days Percentage of ‘As needed’ free days Percentage of Asthma control days Percentage of controller use days Time to asthma related discontinuation Poorly controlled asthma weeks Time to additional steroids for asthma Average change from baseline in Asthma Control Questionnaire (ACQ-5) Average change from baseline in Asthma Quality of Life Questionnaire; standard version (AQLQ(S))

## 2.3 Safety objective

Safety Objective:	Outcome Measure:
To compare the safety of Symbicort Turbuhaler 160/4.5 µg 'as needed' with that of terbutaline Turbuhaler 0.4 mg 'as needed', and 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 understand patient usage of study inhalers during the clinical study (particularly when and why study inhalers are used) from a qualitative patient-centred perspective.	Coded transcriptions of patient interviews (qualitative summary).
To understand: The patient experience of asthma control during the clinical study; Whether or not patients believe their asthma control has changed during their participation in the clinical study; What the term 'asthma control' means to the patient.	Coded transcriptions of patient interviews (qualitative summary).

The exploratory objectives outlined above are part of a qualitative sub-study that will be conducted in a sub-set of participating countries and sites. See [Appendix F](#) for an overview of the qualitative sub-study. Countries and sites not participating in the sub-study will not enrol any patients in the sub-study.

## 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.

In this study, both patients who are either uncontrolled on an inhaled short acting bronchodilator 'as needed' (SABA and/or short acting anticholinergic agent) or controlled on mono-maintenance therapy with either a low dose ICS or a LTRA in addition to 'as needed' use of inhaled short-acting bronchodilator (SABA and/or short acting anticholinergic agent), are eligible for enrolment and the proportion of these two groups should be approximately equal (see Section 3.5).

### 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  $\geq 12$  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 ( $\leq 400$   $\mu\text{g}$  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 only should have pre-bronchodilator  $\text{FEV}_1 \geq 60$  % of predicted normal (PN) and post-bronchodilator  $\text{FEV}_1 \geq 80$  % 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  $\text{FEV}_1 \geq 80$  % 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  $\text{FEV}_1 \geq 12\%$  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 within the last 12 months prior to Visit 3, with an increase in  $\text{FEV}_1 \geq 12\%$  and 200 ml relative to baseline after administration of a rapid acting  $\beta_2$ -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 and to complete the eDiary correctly. Morning and evening data must be recorded for at least 8 days (any 8) of the last 10 days of the run-in period

**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
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  $\beta$ -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  $\geq 10$  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  $\geq 6$  Bricanyl Turbuhaler ‘as needed’ inhalations per day, for a certain number of days depending on the actual length of run-in: for  $\geq 2$  days out of 14 days; for  $\geq 3$  days out of 15-21 days; for  $\geq 4$  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 handling 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 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 Sections 3.1 and 3.2
4. Re-assess patient eligibility at the start and end of the run-in period
5. 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 stratify patients, to assign enrolment and randomisation codes to the patients and to dispense investigational product (IP) at Visit 3 and at subsequent 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 using GRandom (AZ Global Randomisation system) using balanced blocks. Country and pre-study treatment groups will be used as stratification factors ensuring approximately equal number of patients per treatment group within each country and equal number of patients per treatment group for each pre-study treatment group, respectively. The randomisation codes will be loaded into the IVRS/IWRS database. As patients become eligible, they will be assigned to a treatment group in balanced blocks supplied to that country in accordance with the randomisation scheme. Randomisation codes will be assigned strictly sequentially as patients become eligible for randomisation.

The total study population should contain approximately equal number of patients in the two subgroups (previously treated with inhaled short-acting bronchodilator(s) (SABA and/or short acting anticholinergic agent) only and previously treated with additional low dose ICS/anti-inflammatory medication). This ratio will be monitored by the IVRS/IWRS and if one subgroup has completed the recruitment target it may only be possible to enrol patients belonging to the other group. In addition, 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 or having a large meal for at least 2 hours before the planned visits to the study site.

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

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:

- 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 duration of more than 3 weeks
  - Two severe asthma exacerbations within a period of 3 months
  - Three severe asthma exacerbations in total during the study.

### 3.9.1 Procedures for discontinuation of a patient from investigational product

Discontinuation of investigational product means that the patient has to be withdrawn from the study.

If possible, the patient will be seen and assessed by an Investigator; Visit 8 should be performed (see Table 1). Adverse events will be followed up (see Section 6).

Discontinuation of the IP should be recorded in IVRS/IWRS.

### 3.9.2 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' (i.e., 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<sub>1</sub> 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).

### **3.9.3 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) and the presence of any adverse events (AE). The Investigator will follow up AEs outside of the clinical study. The eDiary, Turbuhaler Usage Monitor (TUM) and all study drugs 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.

### **3.10 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 discontinuation must be recorded in the CRF.

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**

	Enrol- ment	Run-in	Rando- misation	Treatment						Follow- up	For details see Section
				4	5	6	7	8	TC		
<b>VISIT</b>	1	2	3	4	5	6	7	8	TC	Section	
<b>WEEK</b>		- 2 to - 4	0	4	16	28	40	52	54		
<b>Visit window (days)</b>	0 – 7 before Visit 2	14 – 28 before Visit 3		±3	±7	±7	±7	±7	±3	Re. Visits 1- 2: 4.1.2	
Informed consent	X									3.3	
Allocation of enrolment code (IVRS/TWRS)	X									4.1.1	
Demography (date of birth, gender, race)	X										
Inclusion/exclusion criteria	X	X	X							0, 3.2	
Medical, surgical history	X										
Asthma history (including history of severe asthma exacerbations)	X										
Smoking history	X									4.1.2	
Patient training in eDiary, Turbuhaler (inhalation technique), TUM and PEF meter use		X								4.1.2	
ACQ and AQLQ(S) at study site		X	X	only ACQ	X	X	X	X		5.1.5 5.1.6	
SAEs (from Visit 1) / AEs (from Visit 2)	X	X	X	X	X	X	X	X	X	6	

	Enrol- ment	Run-in	Rando- misation	Treatment						Follow- up	For details see Section
				4	5	6	7	8	TC		
<b>VISIT</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>	<b>8</b>	<b>TC</b>	<b>Section</b>	
<b>WEEK</b>		<b>- 2 to - 4</b>	<b>0</b>	<b>4</b>	<b>16</b>	<b>28</b>	<b>40</b>	<b>52</b>	<b>54</b>		
<b>Visit window (days)</b>	0 – 7 before Visit 2	14 – 28 before Visit 3		±3	±7	±7	±7	±7	±3	Re. Visits 1- 2: 4.1.2	
Weight and height (height only for adolescents at Visit 8)		X						X		4.1.2	
Physical examination		X						X		5.2.1	
Pulse and blood pressure		X						X		5.2.2.1	
Pregnancy test		X								4.1.2	
Adjustment of current asthma medication		X								4.1.2	
Randomisation			X							3.3, 3.5	
Bricanyl for run-in dispense / return		d	r							4.1.2, 7.2	
Lung function (FEV <sub>1</sub> , FVC pre- and post Bricanyl administration )		X	X	X	X	X	X	X		5.1.2, 7.2 for Bricanyl	
Reversibility test (calculated at Visit 2 and if needed, calculated at Visit 3 as well)		X	X							5.1.2.2 Inclusion 6	
Concomitant medication		X	X	X	X	X	X	X		7.7	
Investigational product (dispense/return/check)			d	d/r/c	d/r/c	d/r/c	d/r/c	r/c		7	
Intake of maintenance treatment morning dose			X	X	X	X	X			7.2	

	Enrol- ment	Run-in	Rando- misation	Treatment						Follow- up	For details see Section
				4	5	6	7	8	TC		
<b>VISIT</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>	<b>8</b>	<b>TC</b>	<b>Section</b>	
<b>WEEK</b>		<b>- 2 to - 4</b>	<b>0</b>	<b>4</b>	<b>16</b>	<b>28</b>	<b>40</b>	<b>52</b>	<b>54</b>		
<b>Visit window (days)</b>	0 – 7 before Visit 2	14 – 28 before Visit 3		±3	±7	±7	±7	±7	±3	Re. Visits 1- 2: 4.1.2	
Review of PEF, asthma symptoms, nighttime awakenings, maintenance and 'as needed' IP intake and Turbuhaler user technique; re-training of patient if needed <sup>b</sup>			X <sup>b</sup>	X <sup>b</sup>	X <sup>b</sup>	X <sup>b</sup>	X <sup>b</sup>	X <sup>b</sup>		5.1.3 For TUM see 5.1.8	
Review of patient's compliance with eDiary			X	X	X	X	X	X			
Hand over the 'Participant Letter' to patient <sup>c</sup>				X <sup>c</sup>							
Informed consent (qualitative sub-study) <sup>a</sup>								X <sup>a</sup>			

<sup>a</sup> Obtaining informed consent of patients into the qualitative sub-study is only applicable to the subset of sites selected to participate. Informed consent into the sub-study is to be obtained before any interview-related activities. Informed consent can occur at any time at Visit 4 (Week 4) or later, however, the qualitative patient interview conducted with the patient should occur between Week 12 and Week 50 for each patient who has elected to participate. The exact time point of the interview will be determined by Health Research Associates (Contract Research Organization). Refer to [Appendix F](#).

<sup>b</sup> Training Turbuhalers can be used only until the expiry date of 31 March 2017

<sup>c</sup> Participant Letter is to be handed over by site staff to patient at one of the site visits between Visit 4 and Visit 7

## **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](#).

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

Patients will sign informed consent for the study at enrolment and will then receive an enrolment code, allocated by IVRS/IWRS. Serious Adverse event recording will start at enrolment after signing the informed consent.

Patients will continue taking their prescribed medication until Visit 2 and will be informed by the investigator about medication restrictions applicable before Visit 2 (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 week run-in period.

Patients will be asked to stop their prescribed asthma medication (including maintenance treatment with ICS or LTRA) used at the time of study entry and during the enrolment period in accordance with [Section 7.7](#). All patients will receive Bricanyl Turbuhaler for 'as needed' use during the run-in period.

At Visit 2 instructions will be given to the patients on how to use the Turbuhaler (inhalation technique), the TUM, the eDiary and the PEF meter. 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 patient will practice inhalation technique with a training device, as many times as judged necessary by the supervising study personnel. Patients will complete ACQ and AQLQ questionnaires. Patients will be asked to fill in the eDiary twice daily during the run-in period. PEF (morning and evening measurements), asthma symptoms and nighttime awakenings due to asthma will be recorded. To verify eligibility, lung function measurement including reversibility test will be performed by spirometry.

Height will be measured in cm (without shoes) and weight in kg (light clothes and without shoes).

Pregnancy test by urine dipstick should be performed for female patients aged  $\leq 60$  years.

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

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

During the run-in period, the patients and investigators will get an alert if the patients fulfil exclusion criterion 16. The patients will be instructed to contact their investigators. The investigators should discontinue these patients from the study.

## 4.2 Treatment period

At Visit 3 investigator should check eligibility before randomisation.

Descriptions of the procedures for this period are included in the Study Plan, see [Table 1](#).

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

Additional treatment for patients experiencing deterioration of asthma or having long-term poor asthma control will be allowed. The conditions and detailed procedures are described in Section 5.1.1.

## 4.3 Follow-up period

A follow-up telephone contact will be performed 2 weeks after the last investigational product administration, i.e., 2 weeks after Visit 8 or if the patient is withdrawn from the study, 2 weeks after the last visit.

At the follow-up telephone call, the investigator will check for adverse events.

## 5. STUDY ASSESSMENTS

The Rave Web Based Data Capture (WBDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the electronic Case Report Forms (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 electronic Case Report Forms. A copy of the completed electronic Case Report Forms will be archived at the study site.

## **5.1 Efficacy assessments**

### **5.1.1 Asthma exacerbations**

In this study asthma exacerbations are defined as deterioration in asthma that is associated with a medical intervention. 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 (from diary data) or which happens acutely ( $\leq 24$  h) (from clinic data) 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 steroids for at least 3 days<sup>1</sup>
- Inpatient hospitalization
- Emergency room visit<sup>2</sup> due to asthma that required systemic steroids.

<sup>1</sup> An injection of depot glucocorticosteroids due to asthma worsening is considered equivalent to at least 3 days of systemic glucocorticosteroids

<sup>2</sup> Emergency room visit or other urgent unscheduled health care visit

A moderate exacerbation is defined as:  
a deterioration of asthma requiring a change in treatment i.e., initiation of prescribed ICS treatment (inhaled budesonide 200 µg twice daily), to avoid progression of the worsening of asthma to a severe exacerbation.

The start and end date of each asthma exacerbation will be recorded in the eCRF at the site visits. For severe exacerbations the start date is defined as the first day of hospitalisation/- emergency room treatment or the first day of systemic (i.e. 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. For moderate exacerbations the start date is defined as the first day of additional prescribed ICS treatment (inhaled budesonide 200 µg twice daily) and the end date is defined as the last day of this treatment.

Additional hospitalisations/emergency room treatments and systemic GCS treatments occurring during a severe asthma exacerbation should not be regarded as a new exacerbation.

For a 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.

For a moderate asthma exacerbation to be counted as a separate event, it must be preceded by at least seven days in which no criteria for severe or moderate exacerbations are fulfilled.

If a patient has a severe asthma exacerbation with a duration of more than 3 weeks or 2 severe asthma exacerbations during 3 months or 3 severe asthma exacerbations during the study, he/she should discontinue the study participation and the reason should be recorded as ‘Study specific discontinuation criteria met’ on the termination form in the eCRF.

For the purpose of reporting in this study, asthma exacerbations should be distinguished from long term poor asthma control. Exacerbations are acute deteriorations of asthma as defined above. Chronic loss of asthma control (i.e. without evidence of an acute asthma deterioration), which does not meet exacerbation criteria but requires additional ICS treatment is to be reported as long term poor asthma control.

#### Additional treatment with prescribed inhaled budesonide 200 µg twice daily

Based on the investigator’s individual assessment of the patient, additional treatment with prescribed inhaled budesonide can be added to the blinded maintenance treatment, see Section 7.7.2:

- During any severe exacerbation for at least 2 weeks
- In case of a moderate exacerbation for at least 2 weeks
- In case of a long-term poor asthma control for at least 4 weeks, see Section 7.7.2

After 2 and 4 weeks respectively of such an additional treatment, the investigator should evaluate the patient and step down to the blinded maintenance treatment if possible. After two occasions of additional budesonide treatment either for a moderate exacerbation or for long-term poorly controlled asthma, the investigator should consider continuing with the additional budesonide for the rest of the study.

### **5.1.2 Lung function measurement by spirometry (FEV1, 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, 6, 7, and 8 are performed  $\pm 1$  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 min.) 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 measure 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 data should be performed at body temperature, barometric pressure and saturated with water vapour (BTPS), using a calibrated spirometer.

Calibration should be in accordance with each trademark specification. If nothing else is specified, calibration should be performed every day when a patient visits the 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  $\pm 3\%$  of the reading or  $\pm 0.05$  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<sub>1</sub> 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<sub>1</sub>, separately, 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<sub>1</sub> value should be recorded, and a comment should be entered on the printout.

FEV<sub>1</sub> values will be taken from the FVC curves. After examining the data from all acceptable curves, the highest FEV<sub>1</sub> 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<sub>1</sub> and FVC including reversibility testing and calculation of predicted normal values (PN)**

Pre-bronchodilator and post-bronchodilator FEV<sub>1</sub> and FVC expressed in liters (L) will be performed at Visits 2 to 8.

The assessment will be performed as follows:

1. Pre-bronchodilator FEV<sub>1</sub> measurement
2. Inhalation of Bricanyl Turbuhaler 2 x 0.5 mg
3. Wait 15 to 30 minutes
4. Post-bronchodilator FEV<sub>1</sub> 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<sub>1</sub> PN will be calculated. FEV<sub>1</sub> 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 8 the purpose of the assessment is to get pre-bronchodilator and post-bronchodilator values of FEV<sub>1</sub> 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<sub>1</sub> relative to baseline must be  $\geq 12\%$  and 200 ml 15-30 minutes after inhalation of 2 x 0.5 mg Bricanyl Turbuhaler.

The reversibility is calculated as follows:

$$\text{Reversibility} = \frac{FEV_{1(after)} - FEV_{1(before)}}{FEV_{1(before)}} \times 100$$

The investigator should record the pre- and post-bronchodilator FEV<sub>1</sub> 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 in addition to inhaled short-acting bronchodilator(s) 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 Recorded electronic diary variables

Patients will complete an electronic diary (eDiary) and measure PEF with a handheld PEF meter (Vitalograph ASMA-1) twice daily during the run-in and the treatment periods. At Visit 2, all patients will be carefully instructed and trained in how to complete the eDiary and how to handle the devices (eDiary, PEF meter and Turbuhaler Usage Monitor (TUM See section 5.1.8). The patients must understand and be willing to complete the eDiary twice daily. Patients will also be instructed how and where to request help if problems should occur.

The patients will be informed that the recordings made electronically in the eDiary cannot be retrospectively or prospectively entered. The recordings must be completed within a defined time window.

The eDiary will be completed twice each day from the evening of Visit 2 until the morning of Visit 8. The following will be recorded:

- Morning and evening PEF (transferred from PEF meter)
- Asthma symptoms (entered by patient)
- Nights with awakenings due to asthma symptoms (entered by patient)
- Use of 'as needed' and randomised maintenance treatment (transferred from TUM)  
See section 5.1.8.

#### PEF measurement

Measurements of morning and evening PEF will be performed during the entire run-in and treatment period (Visit 2 to Visit 8).

The patients will be requested to perform 3 manoeuvres twice daily (morning and evening), where the highest reading will be recorded. The measurements should be made while standing. The measurements should be performed before the maintenance IP administration upon rising in the morning and at bedtime in the evening.

#### Asthma symptoms

Asthma symptoms during nighttime and daytime will be recorded by the patient each morning and evening in the eDiary, from Visit 2 to Visit 8, according to the following scoring system:

0 = no asthma symptoms

1 = you are aware of your asthma symptoms but you can easily tolerate the symptoms

2 = your asthma is causing you enough discomfort to cause problems with normal activities (or with sleep)

3 = you are unable to do your normal activities (or to sleep) because of your asthma

Daytime is defined as the time period between the morning lung function assessment (upon rising in the morning) and the evening lung function assessment.

Nighttime is defined as the time period between the evening lung function assessment (at bedtime) and the morning lung function assessment.

#### Nighttime awakenings due to asthma symptoms

Each morning the patient will record in the eDiary whether he/she woke up during the night due to asthma symptoms by a “yes” or “no” response.

#### Use of ‘as needed’ and randomised maintenance treatment

The use of ‘as needed’ treatment between the morning and evening assessments will be regarded as daytime use. The use of ‘as needed’ treatment between the evening and morning assessments will be regarded as nighttime use.

Randomised maintenance treatment is taken regularly twice a day in the morning and in the evening.

The number of times the grip of the Turbuhaler is turned back and forth as well as the timing will be recorded by the TUM as data about the use of these treatments.

#### **5.1.4 Triggers of patient alerts in the eDiary**

Triggers in the eDiary will alert patients to signs of worsening of asthma and prompt them to contact the investigator.

The alerts will be triggered if one or both of the following criteria are fulfilled:

1. Decrease in morning PEF >20% on at least two consecutive days, compared with baseline (last 10 days of run-in)
2. Increase in total daily asthma symptom score of  $\geq 3$  units (the sum of morning and evening score) compared with baseline (last 10 days of run-in) on at least two consecutive days.

The patient will be instructed to contact the investigator as soon as possible when an alert appears in the eDiary. Investigator’s judgement regarding the need for a patient visit has to be documented in the medical records. If judged necessary, the investigator will arrange for a visit as soon as possible (if this coincides with the visit window for a scheduled study visit, the scheduled assessments may be performed). Additional asthma treatment could be prescribed by the investigator during such a visit after having the patient’s status assessed (for additional

treatments due to asthma exacerbations, see Section 5.1.1). Any action taken during such a visit will be recorded in the eCRF.

Even in the absence of eDiary triggers, patients experiencing worsening of asthma during the study should always be instructed to contact the investigator who should act according to medical judgment.

### **5.1.5 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<sub>1</sub>, 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<sub>1</sub> 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<sub>1</sub> 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 will be self-administered at clinical visits within the eDiary at the time points indicated in Table 1. The questions take approximately 2 to 3 minutes to complete.

### **5.1.6 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 within the eDiary at the time points 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.

### **5.1.7 Administration of patient reported outcome questionnaires**

The questionnaires (ACQ and AQLQ[S]) should be completed in the eDiary 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, all patients will be carefully instructed and trained in how to complete the eDiary. Written instructions will be provided to each patient in the local language.

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.

### **5.1.8 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.

The TUM will be applicable for the ‘as needed’ and maintenance study medication Turbuhalers, as well as the Bricanyl Turbuhaler used during the run-in phase (see Turbuhalers described in Section 7).

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 (see Section 4.1.2) and receive written user instructions.

## **5.2 Safety assessments**

### **5.2.1 Physical examination**

A physical examination will be performed at Visit 2 and Visit 8 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 premature discontinuation from the study (see also Section 3.9.1 Procedures for withdrawal). 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 8. The measurements at Visit 2 are regarded as baseline data. Blood pressure and pulse rate will also be measured in case of withdrawal from study (see also Section 3.9.3 Procedures for withdrawal).

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 Other Assessments**

Pharmacokinetic samples will not be taken during the study.

### **5.3.1 Qualitative Sub-study**

A patient interview will be conducted as part of a qualitative sub-study at a subset of sites in selected countries. Patients will be consented separately for the qualitative sub-study and once informed consent is obtained each patient will complete an interview over the telephone with a trained interviewer. Refer to [Appendix F](#) for additional information on the design and conduct of the sub-study.

## **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 is 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 (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/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 treatment period and including the follow-up period until the last telephone follow-up, or the last contact.

SAEs will be recorded from the time of informed consent.

### **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 is serious according to definitions, see Section 6.2 and/or
- The patient discontinues the study due to the sign or symptom and/or
- The sign or symptom is new to the patient or not consistent with the patient's pre-existing asthma history (defined as within 1 year of Visit 1) as judged by the investigator.

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

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 labs that are collected from a patient show an AST or ALT  $\geq 3 \times \text{ULN}$ \* or total bilirubin  $\geq 2 \times \text{ULN}$  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.

\* AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, ULN: Upper Limit of Normal

## 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 i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

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

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day i.e., immediately but **no later than 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 Web Based Data Capture (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 IB 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**

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 glucocorticoid effects may appear if used chronically in excessive doses.

There is limited clinical experience regarding overdosage with inhaled formoterol. An overdose would likely lead to effects that are typical of  $\beta_2$ -agonists such as tremor, headache and palpitations. Symptoms and signs reported with formoterol from isolated cases are tachycardia, hyperglycaemia, hypokalaemia, prolonged QT<sub>c</sub>-interval, arrhythmia, nausea and vomiting.

Experience with other  $\beta_2$ -agonists has shown that overdoses may also cause restlessness, irritability, excitation, somnolence, convulsions and hyper- or hypotension. Metabolic effects may include acidosis and in serious cases, possibly rhabdomyolysis and renal failure.

### **Treatment suggestions**

Normally, an overdose with Symbicort 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  $\mu$ g 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 measures, as judged by the investigator, should not be included in the study.

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

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the 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 1 day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

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

The same timelines apply when outcome information is available.

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

### **6.6.2 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 medicinal 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)**

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 from Visit 2 and will be used as ‘as needed’ medication during the run-in period. Bricanyl Turbuhaler will have blue grip and blue label. 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.

The Bricanyl Turbuhaler will also be used for the post-bronchodilator FEV<sub>1</sub> and FVC measurements at Visits 2-8.

### **Treatment period (Visits 3 to 8)**

At Visit 3 patients will be randomised to one of the 3 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’
- Maintenance Placebo 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 yellow label. During the treatment period the Turbuhaler for ‘as needed’ treatment will

have white grip and white label. 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 '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 inhaler 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 5.1.8). The eDiary will facilitate patient compliance.

### **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 also account for all study drugs dispensed to and returned from the patient.

Study site personnel will account for all study drugs received at the site, unused study drugs and drugs 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 Medication

In order not to affect the reversibility test at Visit 2 and/or at Visit3, patients should not have received the medications listed in Table 2 below 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**

	<u>Not</u> allowed before Visit 2	Time limit prior to Visit 2
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 $\beta_2$ -agonists (LABA) formoterol salmeterol oladaterol indacaterol	24 hours 24 hours 48 hours 72 hours
5.*	Oral $\beta_2$ -agonists as follows: short-acting depot long-acting	6 hours 24 hours 48 hours
6.*	Transdermal $\beta_2$ -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 from Visit 2 to Visit 8**

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<b><u>Not allowed from Visit 2 to Visit 8</u></b>	
1.	Oral, parenteral or rectal GCS
2.	Any ICS other than study medication
3.	Any $\beta_2$ -agonist other than the study medication
4.	Inhaled disodium cromoglycate or inhaled nedocromil sodium
5.	Leukotriene receptor antagonists or 5-lipoxygenase inhibitors
6.	Xanthines
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)

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For exceptions see [Section 7.7.2](#) below.

### **7.7.2 Concomitant asthma treatment**

Severe asthma exacerbation treatment: Oral or parenteral GCS are allowed in case of a suspected severe asthma exacerbation, see Section 5.1.1. During a severe asthma exacerbation, treatment with the concomitant medications included in Number 2-7 ([Table 3](#)) is also allowed.

Moderate asthma exacerbation treatment: Addition of prescribed ICS (budesonide 200  $\mu\text{g}$  bid) to the blinded maintenance treatment is allowed in case of a moderate asthma exacerbation, see Section 5.1.1.

Long-term poor asthma control treatment: Addition of prescribed ICS (budesonide 200  $\mu\text{g}$  bid) to the blinded maintenance treatment is allowed in case of long-term poor asthma control, see Section 5.1.1.

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 cromoglycate and/or nedocromil sodium

### **7.7.2.1 Prescribed inhaled budesonide 200 µg BID**

Budesonide 200 µg (metered dose) BID as additional ICS treatment in case of exacerbation or long term poor asthma control is not regarded as an investigational product. It shall be prescribed by the investigator and reimbursed (to the prescribing investigator, patient, site institution or vendor, as appropriate) by AstraZeneca as permitted by local regulations, to maintain oversight and access to this concomitant medication.

The administration of prescribed ICS should be recorded in the appropriate section of the eCRF.

### **7.7.3 Other concomitant treatment**

Medication other than that described above, which is 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 completion of study treatment 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 and protocol violators identified.

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**

In this section the following brief terms are used to describe the three treatment arms:

<b>Treatment arm</b>	<b>Brief term used</b>
Maintenance Placebo BID (twice daily) + Symbicort 160/4.5 µg 'as needed'	Symbicort
Maintenance Pulmicort 200 µg BID + terbutaline 0.4 mg 'as needed'	Pulmicort plus terbutaline
Maintenance Placebo BID + terbutaline 0.4 mg 'as needed'	terbutaline

The study is powered to assess both the primary objective of comparing Symbicort versus (vs) terbutaline and the secondary objective to estimate the relative efficacy of Symbicort vs Pulmicort plus terbutaline in the overall population and pre-study treatment groups. The estimation of relative efficacy between the 2 treatments will be done as described in the “EMA reflection paper on the need for active control in therapeutic areas where the use of placebo is deemed ethical.” (EMA 2010). It is planned to estimate the relative efficacy of Symbicort and to conclude that Symbicort is non-inferior to Pulmicort plus terbutaline if the lower limit of the 95% confidence interval of the relative efficacy is  $\geq 0.8$  (assessed using an odds ratio).

This number ( $\geq 0.8$ ) is based on the assumption that this study will show similar efficacy between Symbicort and Pulmicort plus terbutaline for the primary endpoint, well controlled asthma weeks. Moreover, it has been assumed both treatments will demonstrate superiority to terbutaline. There is limited data regarding the relative efficacy of Symbicort vs Pulmicort plus terbutaline. In the assessment of benefit/risk, the potential risk of a lower efficacy will be assessed in the context of any benefits on other variables including effects on exacerbations and potentially reduced steroid load.

Thus, after demonstration of superiority vs terbutaline, relative efficacy will be evaluated. The relative efficacy of Symbicort vs Pulmicort plus terbutaline will be estimated as the odds ratio of well-controlled weeks on the Symbicort arm as compared to Pulmicort plus terbutaline arm.

The number of patients required for the analyses was estimated to be 3750 overall (625/treatment group/pre-study treatment group). This was based on the following assumptions:

- The treatment effect of Pulmicort plus terbutaline vs terbutaline is an odds ratio of 1.39 (based on results from post-hoc analyses of study SD-037-0345, data on file)
- Symbicort as has the same level of efficacy as Pulmicort plus terbutaline
- Data will follow a similar pattern to that observed in study SD-037-0345, which was performed in a similar patient population.

Simulations were performed on the pattern of data observed in the study SD-037-0345. The sample size of 3750 patients gives:

- Overall,  $>95\%$  power to detect a difference between Symbicort and terbutaline
- Overall 90% power to achieve non-inferiority of Symbicort vs Pulmicort plus terbutaline with a pre-defined NI limit of 0.8 - i.e., the lower 95% confidence interval of the odds ratio for Symbicort compared to Pulmicort plus terbutaline is  $\geq 0.8$ .

Since it is also important to estimate the treatment effects within each of the strata (defined by pre-study treatment) the sample size assessments were also done assuming that 1875 were recruited in each group and this gives:

- 80% power to detect a difference between Symbicort and terbutaline
- 80% power to achieve non-inferiority of Symbicort vs Pulmicort plus terbutaline with a pre-defined NI limit of 0.78 - i.e., the lower 95% confidence interval of the odds ratio for Symbicort compared to Pulmicort plus terbutaline is  $\geq 0.78$ .

### **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.

#### **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**

##### **8.4.1.1 Derivation of well-controlled asthma weeks (primary variable)**

###### Well-controlled asthma weeks

A well-controlled asthma week is defined as the fulfilment of both conditions below:

- Two or more of the following criteria are fulfilled:
  - No more than 2 days with a daily asthma symptom score  $>1$

- No more than 2 days of ‘as needed’ medication use, up to a maximum of 4 occasions per week (multiple occasions per day should be regarded as separate occasions)
- Morning PEF  $\geq 80\%$  of PN every day
- Both of the following criteria are fulfilled:
  - No nighttime awakenings due to asthma
  - No additional inhaled and/or systemic glucocorticosteroid treatment due to asthma.

For each patient and study week, the binary variable well-controlled asthma week will be derived. In addition, for each week the percent of patients with well-controlled asthma week will also be derived.

It is required that the eDiary has to be completed on at least 5 days in a week to be a well-controlled asthma week.

#### **8.4.1.2 Derivation of time to first moderate, severe and moderate-to-severe asthma exacerbation**

Time to first moderate, severe and moderate-to-severe asthma exacerbation (see Section 5.1.1) will be calculated as the time from randomisation until the start date of the first asthma exacerbation (moderate or severe) i.e.:

$$\textit{Start Date of first asthma exacerbation} - \textit{Date of Randomisation} + 1$$

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

Maximum follow-up time for a patient is approximately 52 weeks; defined as the time from randomisation to the date of Visit 8. 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 the number of moderate, severe and moderate-to-severe asthma exacerbations**

The total number of moderate, severe, and moderate-to-severe asthma exacerbations (see Section 5.1.1), respectively will be calculated for each patient during the 52-week 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 52-week double-blind treatment period according to the formula described below:

$$\text{Annual Exacerbation Rate} = \text{Number of Exacerbations} * 365.25 / (\text{Follow-up date} - \text{Visit 3 date} + 1)$$

#### **8.4.1.4 Derivation of time to administration of additional steroids for asthma**

Time to administration of additional steroids for asthma will be calculated as the time from randomisation until the start date of administration of additional steroids for asthma i.e.:

$$\text{Start Date of administration of additional steroids} - \text{Date of Randomisation} + 1$$

Patients not receiving additional steroids will be considered as censored at the date of their last visit or, for patients discontinuing the study, the day when it was decided that the patient should discontinue the study.

Maximum follow-up time for a patient is approximately 52 weeks; defined as the time from randomisation to the date of Visit 8.

#### **8.4.1.5 Derivation of total inhaled steroid load and number of days with systemic GCS treatment**

Total inhaled steroid load during the randomised 52 week 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), and prescribed inhaled budesonide. Data on IP will be recorded via the TUM, while prescribed inhaled budesonide will be collected via the appropriate CRF module.

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

#### **8.4.1.6 Derivation of controller use days**

Controller use days during the randomised treatment period will be calculated as the cumulative days when any controller medication containing ICS (including Pulmicort, Symbicort and any other inhaled corticosteroid) was taken divided by the follow-up time (number of days).

Controller use will be defined as the 'as needed' use for the Symbicort treatment arm, the maintenance use for the Pulmicort treatment arm, and any additional prescribed inhaled corticosteroid which is applicable for all treatment arms. Data on IP will be recorded via the TUM, while prescribed inhaled corticosteroid will be collected via the appropriate CRF module.

#### **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 duration for more than 3 weeks
- Two severe asthma exacerbations during 3 months
- Three severe asthma exacerbations in total during the study

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

*Date of study termination due to any asthma related event – Date of Randomisation + 1*

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

#### **8.4.1.8 Derivation of lung function variables**

Change from baseline (Visit 3) to Visits 4, 5, 6, 7 and 8 will be calculated for each patient for the following lung function variables:

- Pre- and post-bronchodilator FEV<sub>1</sub> (L)
- Pre- and post-bronchodilator FEV<sub>1</sub> % 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<sub>1</sub> will be calculated according to [Quanjer et al 2012](#).

#### **8.4.1.9 Derivation of electronic diary variables**

The following variables will be derived for the electronic diary variables:

- Morning and evening PEF
- ‘As needed’ medication (nighttime, daytime and total)
- Asthma symptom score (nighttime, daytime and total)
- Nights with awakening(s) due to asthma symptoms

Change from baseline will be calculated for each patient as defined by the change in all post-randomisation observations to baseline, where baseline is defined as the mean of the measurements 10 days prior to randomisation during run-in.

#### Symptom-free days

A symptom-free day is defined as the fulfilment of both of the following criteria:

- A day and night with no asthma symptoms (i.e.: asthma symptom score=0)
- A night with no awakenings due to asthma symptoms

#### 'As needed'-free days

An 'as needed'-free day is defined as a day and night with no use of 'as needed' medication.

#### Asthma-control days

An asthma control day is defined as the fulfilment of all of the following criteria:

- A day and night with no asthma symptoms (i.e., asthma symptom score=0)
- A night with no awakenings due to asthma symptoms
- A day and night with no use of 'as needed' medication

#### Well-controlled asthma weeks (see definition in Section 8.4.1.1)

#### Poorly controlled asthma weeks

A poorly controlled asthma week is defined as the fulfilment of one of the following conditions:

- Two or more consecutive days with awakenings due to asthma on both nights
- A recorded use of 'as needed' medication for symptom relief of at least 3 occasions per day, for at least 2 consecutive days
- Additional systemic GCS treatment required for severe exacerbation

#### Partly controlled asthma weeks

A partly controlled asthma week is defined as, if the patient does not fulfil neither the criteria of a well-controlled asthma week nor of a poorly controlled asthma week.

## **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)  $\leq -0.5$
- Patients unchanged (end of treatment – baseline) within (-0.5; 0.5)
- Patients worsened (end of treatment – baseline)  $\geq 0.5$ .

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)  $\geq 0.5$
- Patients unchanged (end of treatment – baseline) within (-0.5; 0.5)
- Patients worsened (end of treatment – baseline)  $\leq -0.5$ .

### **8.4.3 Derivation of safety variables**

#### **8.4.3.1 Vital signs**

Change from baseline (Visit 2) to week 52 (Visit 8) 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.
- 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 well-controlled asthma weeks (binary) will be analysed by a repeated measures logistic regression model with treatment, pre-study treatment, region as fixed effects, study week as a categorical variable, and patient as a random effect.

Exchangeable structure of the correlation matrix will be used in the model i.e., correlations between all time points assumed equal. The statistical inference will be based on the estimated odds-ratio (treatment A vs treatment B) and corresponding 95% confidence interval averaged over the whole randomised treatment period. The planned treatment comparisons are:

1. Symbicort vs terbutaline (superiority, primary objective)
2. Symbicort vs Pulmicort plus terbutaline (non-inferiority)

Formally, the null and alternative hypothesis for comparison 1 is:

$$H_0: \text{odds-ratio (Symbicort vs terbutaline)} = 1$$

$$H_A: \text{odds-ratio (Symbicort vs terbutaline)} \neq 1$$

Hence, the odds of a well-controlled asthma week on Symbicort must be greater than the odds of a well-controlled asthma week on terbutaline in order to declare superiority.

And for comparison 2:

$H_0$ : lower 95% confidence limit of odds-ratio (Symbicort vs Pulmicort plus terbutaline)  $< 0.8$

$H_A$ : lower 95% confidence limit of odds-ratio (Symbicort vs Pulmicort plus terbutaline)  $\geq 0.8$

Hence, the odds of a well-controlled asthma week on Symbicort must be  $\geq 0.8$  of the odds of a well-controlled asthma week on Pulmicort plus terbutaline in order to declare non-inferiority. The selection of 0.8 of the non-inferiority margin is detailed in section 8.2 of the protocol.

The two hypotheses will be tested sequentially. If the comparison 1 fails, no formal statistical inference will be made for comparison 2.

An important consideration when interpreting the results of the comparison of Symbicort to Pulmicort plus terbutaline is the extent to which the primary endpoint is driven by 'as needed' medication use. A key component of the primary endpoint is the use of 'as needed medication' which is confounded with the different treatment regimes. In particular the use of Pulmicort maintenance treatment may result in a higher proportion of well controlled asthma weeks, due to less 'as needed' medication use, even if overall asthma control is truly similar to Symbicort as needed treatment (as all Symbicort use is counted as 'as needed medication'). Several supportive analyses will be conducted, including analysis of the individual components of the primary endpoint, adjusting the as needed threshold in the primary endpoint and thoroughly describing the pattern of as needed use. The aim is to look for consistency of the treatment effect, across the analyses and secondary endpoints to aid interpretation. More details of the analyses will be given in the SAP.

**Missing data:** If not all elements of the electronic diary are available, then the available data will be used to derive the presence or absence of a well controlled asthma week whenever possible, if the data are indeterminate then the week will be recorded as missing. Sensitivity analyses to explore the potential impact of any missing data will be defined in the SAP.

### **8.5.2 Analysis of the secondary variables**

For all secondary variables stated below the following treatment comparisons will be made:

1. Symbicort vs terbutaline
2. Symbicort vs Pulmicort plus terbutaline

The two hypotheses will be tested sequentially for each secondary endpoint if the primary endpoint is significant. If the comparison 1 fails, no formal statistical inference will be made for comparison 2.

**Exacerbations:** The number of moderate-to-severe and severe asthma exacerbations will be analysed by a negative binomial regression model. The response variable in the model will be the number of moderate-to-severe and severe asthma exacerbations over the 52-week treatment period, respectively. The model will include covariates of treatment, pre-study treatment 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 moderate-to-severe and severe exacerbation rates will be estimated and treatments effects will be expressed as the rate ratio along with its corresponding 95% confidence intervals.

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

**Additional steroids for asthma:** Time to the administration of additional steroids for asthma will be analysed by a Cox proportional hazards model with treatment, pre-study treatment and region as factors. The hazard ratio and its corresponding 95% confidence interval will be estimated from the model.

**Steroid load:** The total inhaled steroid load and the number of days with systemic GCS, respectively will be presented descriptively by treatment.

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

**FEV<sub>1</sub>:** The treatment effect for change from baseline (Visit 3) in FEV<sub>1</sub>, will be estimated using a mixed model repeated measures (MMRM) analysis. FEV<sub>1</sub> data from visits 4, 5, 6, 7 and 8 will be included in the model, with terms for treatment, pre-study treatment, region, visit and treatment\*visit. Baseline FEV<sub>1</sub> (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 FEV<sub>1</sub> (L) by treatment.

**PRO variables:** ACQ-5 and AQLQ will be analysed in the same way as FEV<sub>1</sub> using MMRM analysis. In addition, change from baseline to the end of treatment will also be analysed from the model.

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 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.

**Electronic diary variables:** The change in the mean morning PEF during run-in period to the mean value of available data during the randomised treatment period will be analysed by analysis of covariance (ANCOVA) with treatment, pre-study treatment and region as factors, and the mean PEF 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.

The change from baseline in evening PEF, asthma symptom score (day, night and total), use of 'as needed' medication (day, night and total), awakening(s) due to asthma symptoms, symptom-free days, asthma-control days, and 'as needed'-free days will all be analysed in the same way as described for morning PEF above.

Poorly controlled asthma weeks will be analysed in the same way as well-controlled asthma weeks (see Section 8.5.1).

Well-controlled asthma weeks, partly controlled asthma weeks and poorly controlled asthma weeks will be jointly depicted graphically by week and treatment.

### **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 Sensitivity analysis**

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

### **8.5.5 Analysis methods for 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.

### **8.5.6 Analysis methods for exploratory variables**

The exploratory variables will be analysed from qualitative interviews with patients who participated in the sub-study. Due to the qualitative nature of the data and the analysis, the results will be presented in a separate report (i.e. not in the clinical study report) and the data (i.e. transcriptions) will not be entered into the study database. Refer to [Appendix F](#).

## **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 electronic PRO (eDiary) system(s) utilised.

The investigator and study site staff should 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 (e.g., clinic charts).

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

### **9.2.1 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 II in 2014 and to end by Quarter III 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.

## **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 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., eDiary, 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, 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/Institutional Review Boards (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 coordinating Investigator and AstraZeneca.

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

## **11. LIST OF REFERENCES**

### **Ankerst et al 2003**

Ankerst J, Persson G, Weibull E. Tolerability of high dose of budesonide/formoterol in a single inhaler in patients with asthma. *Pulm Pharmacol Ther* 2003;13(3):147-51.

### **Atienza et al 2013**

Atienza T, Aquino T, Fernández M, Boonsawat W, Kawai M, Kudo T et al. Budesonide/formoterol maintenance and reliever therapy via Turbuhaler versus fixed-dose budesonide/formoterol plus terbutaline in patients with asthma: phase III study results. *Respirology* 2013 Feb;18(2):354-63.

**Bateman et al 2004**

Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels R, et al (2004) Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control (GOAL) Study. *Am J Respir Crit Care Med*, 170:836-44.

**Chuchalin et al 2005**

Chuchalin A, Kasl M, Bengtsson T, Nihlen U, Rosenborg J. Formoterol used as needed in patients with intermittent or mild persistent asthma. *Respir Med* 2005;99:461-70.

**CHMP 2013**

The European Agency for the Evaluation of Medicinal Products. Note for guidance on the clinical investigation of medicinal products in the treatment of asthma. CHMP/EWP/2922/01, Rev.1, June 2013.

**Dusser et al 2007**

Dusser D, Montani D, Chanez P, de Blic J, Delacourt C, Deschildre A et al. Mild asthma: an expert review on epidemiology, clinical characteristics and treatment recommendations. *Allergy* 2007;62:591-604.

**EMA 2010**

European Medicines Agency. Reflection paper on the need for active control in therapeutic areas where use of placebo is deemed ethical and one or more established medicines are available. November 2010.

**GINA 2012**

Global Initiative for Asthma (GINA). Strategy for Asthma Management and Prevention 2012.

**Haahtela et al 2006**

Haahtela T, Tamminen K, Malmberg LP, Zetterstrom O, Karjalainen J, Yla-Outinen H, et al. Formoterol as needed with or without budesonide in patients with intermittent asthma and raised NO levels in exhaled air: A SOMA study. *Eur Respir J* 2006;28(4):748-55.

**Horne et al 2006**

Horne R. Compliance, adherence and concordance: Implications for asthma treatment. *Chest* 2006;130(1 suppl):65-72.

**Juniper et al 1992**

Juniper EF, Guyatt GH, Epstein RS, Ferrie PJ, Jaeschke R, Hiller TK. Evaluation of impairment of health-related quality of life in asthma: development of a questionnaire for use in clinical trials. *Thorax* 1992;47:76-83.

**Juniper et al 1994**

Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific quality of life questionnaire. *J Clin Epidemiol* 1994;47:81-7.

**Juniper et al 1999**

Juniper EF, Buist AS, Cox FM, Ferrie PJ, King DR. Validation of a standardized version of the Asthma Quality of Life Questionnaire. *Chest* 1999;115:1265-70.

**Juniper et al 2001**

Juniper EF, O'Byrne PM, Roberts JN. Measuring asthma control in group studies: do we need airway calibre and rescue  $\beta_2$ -agonist use? *Respir Med* 2001;95:319-23.

**Juniper et al 2005**

Juniper EF, Svensson K, Mörk AC, Ståhl E. Modification of the asthma quality of life questionnaire (standardised) for patients 12 years and older. *Health Qual Life Outcomes* 2005;3:58.

**Juniper et al 2005 /2**

Juniper EF, Svensson K, Mörk A-C, Ståhl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respiratory Medicine* 2005; 99:553-558.

**Miller et al 2005**

Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A et al. Standardisation of Spirometry. *Eur Respir J* 2005;26:319-38.

**O'Byrne et al 2005**

O'Byrne PM, Bisgaard H, Godard PP, Pistolesi M, Palmqvist M, Zhu Y et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. *Am J Respir Crit Care Med*. 2005;171:129-36.

**Palmqvist et al 2001**

Palmqvist M, Arvidsson P, Beckman O, Peterson S, Lötvall J. Onset of bronchodilation of budesonide/formoterol vs. salmeterol/fluticasone in single inhalers. *Pulm Pharm Ther* 2001;14:29-34.

**Papi et al 2007**

Papi A, Canonica GW, Maestrelli P, Paggiaro P, Olivieri D, Pozzi E, et al; BEST Study Group. Rescue Use of Beclomethasone and Albuterol in a Single Inhaler for Mild Asthma. *N Engl J Med* 2007; 356:2040-2052.

**Pauwels et al 2003**

Pauwels RA, Pedersen S, Busse WW, Tan WC, ChenYZ, Ohlsson SV et al, on behalf of the START Investigators Group. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. *Lancet* 2003;361:1071-6.

**Pauwels et al 2003b**

Pauwels RA, Sears M, Campell M, Villasante C, Huang S, Lindh A. Formoterol as relief medication in asthma: a worldwide safety and effectiveness trial. *Eur Resp J* 2003;22:787-94.

**Quanjer et al 2012**

Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012;40(6):1324-43.

**Rabe et al 2004**

Rabe KF, Adachi M, Lai CK, Soriano JB, Vermeire PA, Weiss KB et al. Worldwide severity and control of asthma in children and adults: the global asthma insights and reality surveys. *J Allergy Clin Immunol* 2004;114(1):40-7.

**Rabe et al 2006**

Rabe KF, Atienza T, Magyar P, Larsson P, Jorup C, Lalloo UG. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. *Lancet* 2006;368:744-53.

**Scicchitano et al 2004**

Scicchitano R, Aalbers R, Ukena D, Manjra A, Fouquert L, Centanni S et al. Efficacy and safety of budesonide/formoterol single inhaler therapy vs a higher dose of budesonide in moderate to severe asthma. *Curr Med Res Opin* 2004;20:1403-18.

**Sears and Lötvall 2005**

Sears MR, Lötvall J. Past, present and future -  $\beta_2$  adrenoceptor agonists in asthma management. *Resp Med* 2005;99(2):152-70.

**Tattersfield et al 2001**

Tattersfield AE, Löfdahl CG, Postma DS, Eivindson A, Schreurs AG, Rasidakis A, et al. Comparison of formoterol and terbutaline for as-needed treatment of asthma: a randomised trial. *Lancet* 2001;357:257-61.

**Vogelmeier et al 2005**

Vogelmeier C, D'Urzo A, Pauwels R, Merino JM, Jaspal M, Boutet S et al. Budesonide/formoterol maintenance and reliever therapy: an effective asthma treatment option? *Eur Respir J* 2005;26:819-28.



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**Clinical Study Protocol Appendix B**

Drug Substance	budesonide/formoterol
Study Code	D589SC00001
Edition Number	1
Date	17 January 2014

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**Appendix B**  
**Additional Safety Information**

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## **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	D589SC00001
Edition Number	1
Date	17 January 2014

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**Appendix C**  
**Asthma Control Questionnaire (5-item version)**

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# ASTHMA CONTROL QUESTIONNAIRE

(SYMPTOMS ONLY)

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QOL TECHNOLOGIES Ltd.



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**December 2002**

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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 <b>woken by your asthma</b> during the night?               | 0 Never<br>1 Hardly ever<br>2 A few times<br>3 Several times<br>4 Many times<br>5 A great many times<br>6 Unable to sleep because of asthma                          |
| 2. On average, during the past week, how <b>bad were your asthma symptoms when you woke up</b> in the morning?      | 0 No symptoms<br>1 Very mild symptoms<br>2 Mild symptoms<br>3 Moderate symptoms<br>4 Quite severe symptoms<br>5 Severe symptoms<br>6 Very severe symptoms            |
| 3. In general, during the past week, how <b>limited were you in your activities</b> because of your asthma?         | 0 Not limited at all<br>1 Very slightly limited<br>2 Slightly limited<br>3 Moderately limited<br>4 Very limited<br>5 Extremely limited<br>6 Totally limited          |
| 4. In general, during the past week, how much <b>shortness of breath</b> did you experience because of your asthma? | 0 None<br>1 A very little<br>2 A little<br>3 A moderate amount<br>4 Quite a lot<br>5 A great deal<br>6 A very great deal   |
| 5. In general, during the past week, how much of the time did you <b>wheeze</b> ?                                   | 0 Not at all<br>1 Hardly any of the time<br>2 A little of the time<br>3 A moderate amount of the time<br>4 A lot of the time<br>5 Most of the time<br>6 All the time |



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**Clinical Study Protocol Appendix D**

Drug Substance	budesonide/formoterol
Study Code	D589SC00001
Edition Number	2
Date	16 December 2014

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**Appendix D**  
**Asthma Quality of Life Questionnaire with Standardised Activities**  
**(AQLQ(S)) self administered  $\geq 12$  years of age**

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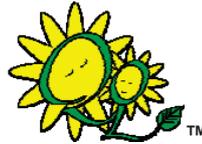
# ASTHMA QUALITY OF LIFE QUESTIONNAIRE WITH STANDARDISED ACTIVITIES (AQLQ(S))

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**SELF-ADMINISTERED**  
(≥12 years)

© 1998  
QOL TECHNOLOGIES LTD.



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**APRIL 2008**

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S)

PATIENT ID: \_\_\_\_\_

SELF-ADMINISTERED

DATE: \_\_\_\_\_

Page 1 of 5

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

ASTHMA QUALITY OF LIFE QUESTIONNAIRE (S)

PATIENT ID: \_\_\_\_\_

SELF-ADMINISTERED

DATE: \_\_\_\_\_

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 <b>CONCERNED ABOUT HAVING ASTHMA?</b>	1	2	3	4	5	6	7
8. Feel <b>SHORT OF BREATH</b> as a result of your asthma?	1	2	3	4	5	6	7
9. Experience asthma symptoms as a <b>RESULT OF BEING EXPOSED TO CIGARETTE SMOKE?</b>	1	2	3	4	5	6	7
10. Experience a <b>WHEEZE</b> in your chest?	1	2	3	4	5	6	7
11. Feel you had to <b>AVOID A SITUATION OR ENVIRONMENT BECAUSE OF CIGARETTE SMOKE?</b>	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 <b>COUGHING?</b>	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 <b>FRUSTRATED</b> as a result of your asthma?	1	2	3	4	5	6	7
14. Experience a feeling of <b>CHEST HEAVINESS?</b>	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	D589SC00001
Edition Number	2
Date	17 August 2015

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**Appendix E**  
**Inhaled Glucocorticosteroids Equivalence Table**

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### Inhaled Glucocorticosteroids Equivalence Table

<b>Asthma Therapy</b>	<b>Total Daily Dose (µg/day)</b>
<b>Inhaled Glucocorticosteroid</b>	<b>Low</b>
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	D589SC00001
Edition Number	1
Date	24 February 2016

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**Appendix F**  
**Sub-study with Qualitative Interviews**

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## 1. INTRODUCTION

In the primary study for D589SC00001, the efficacy and safety of Symbicort<sup>®</sup> (budesonide/formoterol) Turbuhaler<sup>®</sup> 160/4.5 µg ‘as needed’ compared with terbutaline Turbuhaler<sup>®</sup> 0.4 mg ‘as needed’ and with Pulmicort<sup>®</sup> (budesonide) Turbuhaler<sup>®</sup> 200 µg twice daily plus terbutaline Turbuhaler<sup>®</sup> 0.4 mg ‘as needed’ is evaluated. The primary endpoint in clinical study D589SC00001 is well controlled asthma weeks (WCAW), a well-recognized composite score (Bateman et al 2004) that was based on then-current guideline definitions of asthma control. This composite score included the frequency of use of ‘as needed’ medication, and at the time of development of the composite score, this medication was usually a short-acting bronchodilator. Although there have been some changes over time, guidelines at the time clinical study D589SC00001 was planned (Reddel et al 2009; GINA 2012) and current guidelines (GINA 2015) also include use of ‘as needed’ medication in the assessment of current asthma control. Asthma control is now accepted as having two domains: current control (also called symptom control) and future risk (e.g. of exacerbations). The guidelines’ approach is that higher use of ‘as needed’ medication is a flag that the patient needs anti-inflammatory treatment (or needs more treatment), to both reduce the burden of symptoms and to reduce their future risk of exacerbations. This is supported by the association between higher ‘as needed’ medication use and higher risk of asthma exacerbations, and by the reduction in ‘as-needed’ medication use after patients are commenced on regular anti-inflammatory treatment such as inhaled corticosteroids (ICS).

However, guideline developers have not specifically evaluated their criteria for assessment of current asthma control when the ‘as needed’ bronchodilator is long-acting (as well as fast-onset), nor when it also includes ICS. The latter issue is particularly important for the context of an ‘as needed’ budesonide/formoterol regimen, when the patient’s anti-inflammatory treatment is delivered as part of their reliever medication rather than as a separate inhaler prescribed for regular use. The inclusion of ‘as needed’ medication use in the assessment of asthma control may not be applicable to this regimen in the same way as when the ‘as needed’ medication only contains a bronchodilator. For example, the level of symptoms that would influence a patient to take a dose of an ‘as needed’ medication containing ICS vs one containing only a bronchodilator may be different, and the relationship between frequency of ‘as needed’ medication use and risk of exacerbations may also differ for these two regimens.

Therefore, this qualitative patient interview sub-study with a subset of patients participating in the primary study D589SC00001 will aim to provide a deeper understanding of study inhaler use and patient perception of asthma control.

## **2. SUB-STUDY OBJECTIVES**

The objective of this sub-study is to understand patient usage of study inhalers during the clinical study (particularly when and why study inhalers are used) from a qualitative patient-centred perspective.

The additional objectives are to:

- Understand the patient experience of asthma control during the clinical study
- Understand whether or not patients believe their asthma control has changed during their participation in the clinical study
- Understand what the term ‘asthma control’ means to the patient

## **3. SUB-STUDY PLAN AND PROCEDURES**

### **3.1 Study Design**

This is a qualitative patient interview study, where telephone interviews will be conducted by trained interviewers in the native language of the country using a semi-structured interview guide. A subset of patients participating in the primary study for D589SC00001 will be recruited to participate in the qualitative interviews. Participation in the qualitative part is optional.

In qualitative research, sample size estimation is based on projections of the number of patients needed to reach saturation of concept (i.e. the point in the data collection process after which no further relevant information is being obtained). An initial set of 80 patients overall is planned to be recruited for a first round of interviews. After this initial round of interviews, an evaluation of saturation will be performed. If saturation is not achieved then further interviews (in rounds of 5 patients) will be conducted on an iterative basis until saturation is reached. It is expected no more than 120 patients will be enrolled.

### **3.2 Study Sample**

Patients from the primary D589SC00001 study will be recruited to participate in this qualitative study, and enrolment criteria will be tied to the ongoing clinical study. The primary D589SC00001 study has three blinded arms, and since it cannot be known ahead of time, or during the study, what groups these patients will fall into, a sufficient sample size is needed to ensure coverage of patients from all three arms.

Recruitment will be monitored across study sites to prevent clustering around key demographic variables and to ensure a good distribution of age-groups and gender are included. Therefore, other variables such as type of pre-study treatment status (previously treated with inhaled short-acting bronchodilator(s) (SABA and/or short acting anticholinergic agent) only and previously treated with additional low dose ICS/LTRA) and amount of time in study (e.g. 3-5 months; 6-8 months; 9-11 months) will be asked when the patient is enrolled in the interview study in order to ensure there is at least some of each group present in the sample. These latter variables will be described, but will not constitute defined recruitment quotas.

### **3.2.1 Inclusion Criteria**

For inclusion in this sub-study, patients must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol and:

1. Provision of signed and dated written informed consent for the qualitative sub study. Informed consent is to be obtained before any interview-related activities. Participation in the sub-study is optional (and not required for participation in the primary D589SC00001 study).
2. Have been randomised and are currently receiving investigational product, irrespective of their protocol adherence.

### **3.2.2 Exclusion Criteria**

Exclusion from this qualitative research may be for any of the exclusion criteria specified in the main study or any of the following:

1. Not fluent in native language of the country of enrolment

## **3.3 Recruitment**

Staff at enrolling sites will be asked to work with an interviewer at Health Research Associates (known as HRA, a Contract Research Organization) assigned to their site in order to identify, recruit, consent patients for interviews and assist with communications and scheduling of the patients to be interviewed from their sites. Staff will be provided with a script for describing the topic of the qualitative study to potential interviewees, in order to avoid prompting patients about specific issues. Once the patient agrees to the interview, their contact information (name and phone number) will be provided to the HRA interviewer, who will contact the patient and schedule a time at the patient's convenience to complete a telephone interview. Patients enrolled in the sub-study may choose to discontinue participation at any point prior to or during the qualitative interview. Site staff should gauge patient interest in participating in the sub-study starting at Visit 4 (Week 4). Patients may consent to participate in the sub-study as early as Visit 4 (Week 4), however the interview

conducted by HRA with the patient should occur at study Week 12 or later, but not exceeding Week 50. Once a patient has signed the informed consent (or assent, in the case of an adolescent patient), then the site staff should contact their assigned HRA interviewer (alternatively, HRA will contact site staff regularly to discuss enrolment and potential patients for the sub-study). The HRA interviewer will ensure the patient is still on study treatment at the time of the interview.

### **3.4 Conduct of Interviews**

All interviews will be conducted in the native language of the country of enrolment using an interview guide and audio recorded, with permission obtained through the informed consent process. Each patient will be interviewed only once and interviews will last approximately 40 minutes each. A closing statement at the end of the interview will emphasise that nothing which has been discussed is intended to change the patient's use of their study inhalers. English transcript files will be provided to AstraZeneca after final analysis has been performed.

### **3.5 Interviewers**

Interviewers are experienced in qualitative research, possessing interviewing skills and will all be trained specifically to the needs of this study and monitored by HRA. All interviewers will be bilingual in the native language and English.

### **3.6 Ethics**

Each patient will be given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. The patient will be provided with the information and consent form and allowed to read it, with opportunity to ask any questions. In the case of adolescent patients their guardian/legal representative will sign the consent form on their behalf. The investigator will ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File. A copy of the signed Informed Consent Form is to be provided to the patient and/or their guardian/legal representative. The investigator should ensure the patient is notified they are free to discontinue from the sub-study at any time.

This appendix detailing the sub-study along with the Informed Consent Form and Interview Guide should be approved by an Ethics Committee and the national Regulatory Authority, including the final version of the separate Informed Consent Form and any other written information and/or materials to be provided to the patients. AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

### **3.7 Adverse Event Reporting**

The patient's participation in the sub-study will occur within his/her participation in the main protocol, therefore, the Principal Investigator remains responsible for ensuring that all staff involved in the study is familiar with the content of section 6 of the protocol on Safety Reporting and Medical Management. If during an interview the patient reports an adverse event, serious adverse event, overdose, or pregnancy, then the interviewer will collect the relevant information after the end of the qualitative interview and report it to the investigator and site staff. In the case of a serious adverse event, overdose, or pregnancy it must be reported within 24 hours for follow-up. The site investigator and site staff will be responsible for checking to see if this AE has already been reported yet or not, and for official reporting in the same manner as for the primary D589SC00001 study. HRA will ensure all interviewers are adequately trained to complete the appropriate form and submit it to the site.

## **4. ANALYSIS AND REPORTING**

### **4.1 Analysis of Interviews**

All data will be confidential and the patient identifiers used will conform to applicable regulations, so as to preserve patient confidentiality (e.g., to ensure matching between the audio recording and the subsequent transcript). Data from the audio recordings of the interviews will be transcribed to paper and used for exploratory descriptive analysis using a number of qualitative techniques particular to this methodology (Ericsson 1980; Campanelli 1991).

The primary means of analysis will aim at identifying relevant concepts and themes that will provide an understanding of the patient's use of study inhalers, reasons for the patterns of their usage behaviours, their perception of asthma control, their experience of asthma control during the study, and whether they believe their asthma control has changed. To accomplish this, a coding framework will be developed and expanded during the coding process. An experienced coding team will be trained to the coding framework for this project, and English versions of all transcripts will be coded. Coded concepts will be grouped by similar content and organized against specific themes and study questions. Primary analysis of the qualitative data from the interviews will be by randomisation group.

### **4.2 Reporting**

Due to the qualitative nature of the data and the analysis, the results will be presented in a separate report (i.e., not in the clinical study report) and the data (i.e., transcriptions) will not be entered into the study database. The de-identified English transcripts will be sent to AstraZeneca at the conclusion of the primary study for D589SC00001 (after database lock). The recorded voice files will remain at HRA in a secure database.

Copies of the interview transcripts will be stored at HRA in locked files until they are packaged for storage in an off-site archive facility, where they will remain for a period of 15 years and then be destroyed. Electronic files are all stored on password protected computers with routine back up onto a secure, firewalled server system. Individual files are password protected when shipped outside the secured server system. The voice files from the audio recordings are placed on a secure file transfer protocol server where they can be accessed by password by the transcription vendor.

## **5. LIST OF REFERENCES**

### **Bateman et al 2004**

Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels R, et al (2004) Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control (GOAL) Study. *Am J Respir Crit Care Med*, 170:836-44.

### **Campanelli 1991**

Campanelli PC, Martin EA, Rothgeb JM. The use of respondent and interviewer debriefing studies as a way to study response error in survey data. *The Statistician*. 1991;40:253-264.

### **Ericsson 1980**

Ericsson KA, Simon HA. Verbal reports as data. *Psychological Review*. 1980; 87: 215-250.

### **GINA 2012**

Global Initiative for Asthma (GINA). Strategy for Asthma Management and Prevention 2012.

### **GINA 2015**

Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention, Updated 2015.

### **Reddel et al 2009**

Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al (2009) An Official American Thoracic Society/European Respiratory Society Statement: Asthma Control and Exacerbations, Standardizing Endpoints for Clinical Asthma Trials and Clinical Practice. *Am J Respir Crit Care Med*, 180:59-99.