Clinical Study Protocol

Drug Substance	Symbicort® pMDI
Study Code	D5896C00027
Edition Number	1
Date	

A 26 week, randomized, double-blind, parallel-group, active controlled, multicenter, multinational safety study evaluating the risk of serious asthma-related events during treatment with Symbicort®, a fixed combination of inhaled corticosteroid (ICS) (budesonide) and a long acting β_2-agonist (LABA) (formoterol) as compared to treatment with ICS (budesonide) alone in adult and adolescent (≥12 years of age) patients with asthma

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

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

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change

PROTOCOL SYNOPSIS

A 26 week, randomized, double-blind, parallel-group, active controlled, multicenter, multinational safety study evaluating the risk of serious asthma-related events during treatment with Symbicort®, a fixed combination of inhaled corticosteroid (ICS) (budesonide) and a long acting β_2-agonist (LABA) (formoterol) as compared to treatment with ICS (budesonide) alone in adult and adolescent (≥12 years of age) patients with asthma

International Co-ordinating Investigator

Study centre(s) and number of patients planned

Based on initial feasibility, this study is planned to be conducted at approximately 700 centres in approximately 25 countries. Each site is planned to recruit an estimated 12-20 patients. Eleven thousand seven hundred (11 700) male and female patients will be randomized, whereof 10 to 12% will be adolescents (from 12 years up to and including 17 years). To reach this goal, it is projected that about 16 000 patients will need to be enrolled. This study will recruit patients worldwide. A minimum of twenty percent of the patients will be recruited in the US.

Study period	Phase of development
Estimated date of first patient enrolled	III/IV
Estimated date of last patient completed	

Objectives

Primary:

To evaluate the risk of serious asthma related events during treatment with Symbicort® pMDI or budesonide pMDI alone over a 26-week treatment period in adult and adolescent patients with asthma.

Secondary:

To evaluate the efficacy of Symbicort pMDI compared to budesonide pMDI alone over a 26-week treatment period in adult and adolescent patients with asthma.

Exploratory objective

To collect and store deoxyribonucleic acid (DNA) samples for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to Symbicort and/or budesonide; and/or susceptibility to, progression of and prognosis of asthma.

All patients will be asked to participate in the exploratory genetic research. Participation is optional. If a patient declines to participate there will be no penalty or loss of benefit. The patient will not be excluded from any aspect of the main study.

Study design

This is a 26 week, randomized, double-blind, parallel-group, active-controlled, multi-centre, multinational study evaluating the risk of serious asthma-related events during long term treatment with Symbicort pMDI and budesonide pMDI.

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 1 year prior to Visit 1 who are either currently treated with ICS/LABA combination or not adequately controlled on a long-term asthma control medication or whose disease severity warrants initiation of treatment with ICS/LABA.

Patients should have experienced at least one, but not more than 4 exacerbations within the previous year but none within 4 weeks prior to Visit 2.

Investigational product, dosage and mode of administration

- Symbicort HFA pMDI, budesonide/formoterol, 80/4.5 μg x 2 actuations bid, for oral inhalation
- Symbicort HFA pMDI, budesonide/formoterol, 160/4.5 μg x 2 actuations bid, for oral inhalation

Comparator, dosage and mode of administration

- Budesonide HFA pMDI 80 µg x 2 actuations bid, for oral inhalation
- Budesonide HFA pMDI 160 µg x 2 actuations bid, for oral inhalation

Rescue Therapy (for oral inhalation)

Albuterol pMDI (US) administered as 90 µg x 2 actuations and salbutamol pMDI (outside US) 100 µg x 2 actuations, as needed, for relief of bronchospasm.

Duration of treatment

This study starts with information visit (Visit 1) where inclusion and exclusion criteria will be reviewed, informed consent obtained and concomitant medication reviewed. A patient who does not fulfil the study eligibility criteria may be re-screened (checked for eligibility criteria) after at least 4 weeks, but only once per calendar year. Eligible patients will be randomized at the following visit (Visit 2). Patients will then enter a 26 weeks double-blind period. All patients will be followed up for the full 26 weeks intended treatment period for the primary endpoint irrespective of early cessation of randomized treatment (Intention To Treat approach).

Outcome variables:

Primary outcome variables

The primary outcome variable is a composite safety endpoint of serious asthma events:

- Asthma-related deaths
- Asthma-related intubations
- Asthma-related hospitalizations

Other safety assessments are serious adverse events (SAEs) and discontinuation of treatment with investigational product due to adverse event (DAEs) and/or discontinuations due to asthma exacerbations.

Primary efficacy variable

- Asthma exacerbations, defined as a deterioration of asthma requiring systemic corticosteroids (tablets, suspension, or injection) for at least 3 days or an inpatient hospitalization or emergency room visit due to asthma that required systemic corticosteroids

Secondary efficacy variables

- Healthcare utilization for asthma: Telephone contact with study doctor, Telephone contact with other physician or healthcare provider, Unscheduled or unplanned visit to study doctor (including home visits), Unscheduled or unplanned visit to other

physician or healthcare provider (including home visits), Emergency department or hospital (<24 hrs), Hospital admission or Emergency Department (≥24 hrs)

- Days (a part of a day will be counted as a full day) of school or work missed due to asthma
- Rescue medication use
- Asthma symptoms
- Asthma symptoms leading to activity limitations
- Nights with awakening(s) due to asthma
- Assessment of current asthma control by Asthma Control Questionnaire (ACQ) at clinic visits

This study will be conducted under the supervision of a Joint Oversight/Steering Committee (JOSC) and an independent Joint Data Monitoring Committee (JDMC). The composition and scope of these committees will be described in their respective charters. Both committees will be shared with other LABA Sponsor companies planning studies with the same objective.

In addition to the two committees mentioned above, each LABA Sponsor Company will have a independent Trial Data Monitoring Committee (TDMC) whose main role is to monitor possible events that will trigger a meeting of the joint DMC. The chair from each LABA Sponsor Company's TDMC will be members in the JDMC. The composition and detailed scope of the TDMC will be described in a charter.

Statistical methods

For the time to event variables, a Cox proportional hazards model with terms for randomized treatment and strata for incoming control/asthma treatment will be used to compare Symbicort and budesonide. Hazard ratios and 95% confidence intervals will be provided. Patients who complete the 26-week follow-up period without experiencing any event as defined by the component in the primary endpoint will be censored at 26 weeks. Any patients without an event who are lost to follow-up prior to 26 weeks will be censored at the time of the last assessment of the status of the components of the primary endpoint. For the primary endpoint the following hypothesis will be tested at the 2.5%, 1-sided significance level,

- H_0: Hazard ratio ≥2.0 versus H_1: Hazard ratio <2.0

If the null hypothesis is rejected then a 2.0-fold increase in risk is ruled out.

A subsidiary analysis, excluding events occurring 7 days after the last dose of randomized treatment for discontinued patients, will be performed in the same manner as the primary analysis.

A formal interim analysis will be performed once half of the required number of primary endpoint events has been achieved. Consideration will be given to early stopping, if the p-value for the HR is extreme, $p \leq 0.0001$ (1-sided), z-value ≥ 3.7, using the Haybittle-Peto rule so that the alpha level in the final analysis is largely unaltered at 0.0249 1-sided.

SAEs and DAEs will be summarized and evaluated descriptively.

Sample size

The incidence rate on ICS alone, based on Symbicort studies with a similar population, SD-039-0668 and SD-039-0673, is estimated to be 15 events per 1000 per treatment years. To rule out 2 fold increase in the event rate with ICS/LABA combination versus ICS alone, equating to an increase from 1.5% to 3.0% per year, or from 0.75% to 1.5% per 6 months, 87 events are required. Assuming a 6-month study, an approximate linear incidence rate over time, and using 90% power, this requires a total of 11664 patients to be randomized.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this clinical study protocol.

Abbreviation or special term	Explanation
ACM	Actuation Counter Module
ACQ	Asthma Control Questionnaire (ACQ6 will be used, see Section 6.3.2)
AE	Adverse Event (see definition in Section 6.4.1)
ANCOVA	Analysis of covariance
ATS	American Thoracic Society
Bid	Twice daily
DMC	Data Management Centre
CYP	Cytochrome P
DAE	Discontinuation of investigational product due to adverse event
eCRF	electronic Case Report Form
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
EoT	End of Treatment
ER	Emergency Room
Event Adjudication Package	All available relevant data and documentation of an event; eCRF, ePRO responses, clinical summaries, diagnostic tests, death certificates, autopsy reports
FDA	(United States) Food and Drug Administration
GCP	Good Clinical Practice
HFA	Hydrofluoralkane
HFA-227	Propellant HFA-227
IB	Investigators' brochure
ICH	International Conference on Harmonisation
ICS	Inhaled glucocorticosteroids
International Co-ordinating Investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the investigator co-ordinating the investigators and/or activities internationally
IP	Investigational Product
IRB	Institutional Review Board
IVRS	Interactive Voice Response System (ePRO)

Abbreviation or special term	Explanation
IVRS/IWRS	Interactive Voice Response System/Interactive Web Response System (handle and distribute Investigational Product)
JAC	Joint Adjudication Committee (responsible for adjudication of all the primary safety endpoints: deaths, intubations and hospitalizations and assess for asthma relatedness)
JAC Charter	A brief overview of the adjudication methodology and procedures
JAC Operations Manual	Details the specific operations and logistics of the individual entities involved
JDMC	Joint Data Monitoring Committee (responsible to monitor adjudicated and confirmed primary events related from all four sponsor's clinical studies with an independent, unbiased input to the decision process)
JOSC	Joint Oversight/Steering Committee
LABA	Long-acting β_2-agonist
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
NAEPP EPR 3	National Asthma Education and Prevention Program Expert Panel Report 3
PEF	Peak expiratory flow
PGx	Pharmacogenetic research
PI	Principal Investigator
pMDI	pressurized Metered-Dose Inhaler
PRO	Patient Reported Outcome
SABA	Short-acting β_2-adrenoceptor agonist
SAE	Serious Adverse Event (see definition in Section 6.4.2).
SPC	EU Summary of Product Characteristics
TDMC	Trial Data Monitoring Committee (responsible for monitoring SAEs and possible events that will affect safe conduction of this study)
WBDC	Web Based Data Capture

1 INTRODUCTION

1.1 Background

Symbicort® pressurized metered-dose inhaler (pMDI) combines two drugs, budesonide, an inhaled glucocorticosteroid (ICS), and formoterol fumarate dihydrate (formoterol), a long-acting β_2-agonist (LABA), as a fixed-combination product. Budesonide is a corticosteroid indicated in the treatment of underlying airway inflammation in asthma and thus provides overall control of the disease. Formoterol is a bronchodilator with rapid onset of effect and a long duration of action. In the US, Symbicort is indicated for use in the treatment of asthma in patients 12 years and older.

Following the December 2008 Food and Drug Administration (FDA) Advisory Committee and based on an internal review of data, FDA continued to have outstanding questions on whether the addition of a LABA to an ICS increases the risk of asthma related serious adverse events (SAEs). During 2010, FDA issued external communications to consumers and healthcare professionals (HCPs) regarding LABA-containing products. The FDA requested all manufacturers of LABA-containing products indicated for the treatment of asthma to undertake the following: class-labelling changes and the conduction of a post-marketing safety study.

1.2 Research hypothesis

The addition of formoterol to budesonide is non-inferior to budesonide therapy alone in terms of the risk of serious asthma related events. This hypothesis will be assessed by Cox regression analysis of time to first serious asthma related event with terms for randomised treatment and strata for incoming asthma treatment/asthma control. If the resulting upper CL estimate for the relative risk is <2.0, then non-inferiority will be concluded.

1.3 Rationale for conducting this study

Several studies in adults and adolescents, such as FACET (Pauwels et al 1997) and GOAL (Bateman et al 2004), have demonstrated that the addition of LABA to an ICS improves several aspects of asthma control, such as improving lung function and current control of asthma symptoms as well as reducing the risk of asthma deteriorations requiring treatment with systemic corticosteroids (CS). Conversely, some studies have shown that LABAs when used alone may increase the risk of asthma-related death and other serious asthma outcomes. A 28-week placebo-controlled study with salmeterol showed an increase in asthma related deaths in salmeterol versus placebo treated patients (Nelson et al 2006).

Using specific portions of data sets provided by Glaxo Smith Kline, Novartis and AstraZeneca, a recent meta-analysis conducted internally by the FDA suggested a potential risk of serious asthma outcomes (a composite endpoint defined as asthma-related hospitalizations, intubations and deaths) with the addition of a LABA to an ICS, particularly in certain populations (FDA Division Memorandum and Briefing Book, February 2010).

The interpretation of all these data is difficult due to the diversity in power, studies, populations, treatments, and endpoint selection. Although the efficacy of combination products and their ability to improve multiple asthma control measures have been substantiated, it remains unclear whether the incidence of serious asthma events may be affected by the addition of a LABA to an ICS.

This study has been designed to evaluate whether the addition of formoterol to budesonide maintenance therapy increases the incidence of serious asthma related events compared to budesonide during a 26-week treatment period in patients with persistent asthma.

Similar brand specific studies will be performed by the other manufacturers (Sponsors) of LABAs that have an indication for asthma. The AstraZeneca study and other Sponsor specific studies will be conducted concurrently.

1.4 Benefit/risk and ethical assessment

The treatment arms in this study are identical to active-treatment arms in previous Symbicort pMDI studies evaluating the recommended doses of Symbicort in the US. Patients treated in the budesonide-only arm will derive benefit from treatment with ICS medication consistent with standard medical practice. The risk/benefit profile is therefore considered to be appropriate in both treatment arms. Patients will be followed at least on a monthly basis by the research site, either by monthly clinic visits or monthly telephone contacts. Unstable asthma will be assessed between study visits on a daily basis via telephone calls to the Interactive Voice Response System (IVRS). The Investigator will receive an electronic alert to contact patients with unstable asthma. Patients in need of treatment due to an exacerbation can obtain additional medication while remaining on randomized treatment. There are no significant ethical concerns.

2 STUDY OBJECTIVES

2.1 Primary objective

To evaluate the risk of serious asthma related events during treatment with Symbicort pMDI or budesonide pMDI alone over a 26-week treatment period in adult and adolescent patients with asthma.

The primary outcome variable is a composite safety endpoint of serious asthma events:

- asthma-related deaths, see Section 6.4.5.1
- asthma-related intubations, see Section 6.4.5.2
- asthma-related hospitalizations, see Section 6.4.5.3

Other safety assessments are SAEs and discontinuation of treatment with investigational product due to adverse event (DAEs) or discontinuations due to asthma exacerbations.

2.2 Secondary objectives

To evaluate the efficacy of Symbicort pMDI compared to budesonide pMDI alone over a 26-week treatment period in adult and adolescent patients with asthma. The variables for this objective will include:

Primary efficacy endpoint:

- Asthma exacerbations, defined as a deterioration of asthma requiring systemic corticosteroids (tablets, suspension, or injection) for at least 3 days or an inpatient hospitalization or emergency room visit due to asthma that required systemic corticosteroids, see Section 6.3.1.1

Secondary efficacy endpoint:

- Healthcare utilization for asthma: Telephone contact with study doctor, Telephone contact with other physician or healthcare provider, Unscheduled or unplanned visit to study doctor (including home visits), Unscheduled or unplanned visit to other physician or healthcare provider (including home visits), Emergency department or hospital (<24 hrs), Hospital admission or Emergency Department (≥24 hrs). Hospitalizations will be collected with the SAE reports
- Days (a part of a day will be counted as a full day) of school or work missed due to asthma, see section 6.3.1.2
- Rescue medication use, see Section 6.3.1.2
- Asthma symptoms, see Section 6.3.1.2
- Asthma symptoms leading to activity limitations see Section 6.3.1.2
- Nights with awakening(s) due to asthma, see Section 6.3.1.2
- Assessment of current asthma control by the Asthma Control Questionnaire (ACQ), see Section 6.3.2

2.3 Exploratory objective

To collect and store deoxyribonucleic acid (DNA) samples for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to Symbicort and/or budesonide; and/or susceptibility to, progression of and prognosis of asthma.

3 STUDY PLAN AND PROCEDURES

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

3.1 Overall study design and flow chart

This is a 26 week, randomized, double-blind, parallel-group, active-controlled, multi-centre, multinational study evaluating the risk of serious asthma-related events during long term treatment with Symbicort pMDI and budesonide pMDI in adult and adolescent (≥12 years) patients either currently treated with ICS/LABA combination or with asthma not adequately controlled on a long-term asthma control medication or whose disease severity warrants initiation of treatment with ICS/LABA.

This study will be conducted at approximately 700 centres in approximately 25 countries. Each site will recruit an estimated 12-20 patients. Eleven thousand seven hundred (11 700) male and female patients will be randomized, whereof 10 to 12% will be adolescents (from 12 years up to and including 17 years). To reach this goal, it is projected that about 16 000 patients will need to be enrolled. This study will recruit patients worldwide. A minimum of twenty percent of the patients will be recruited in the US.

All potentially suitable patients will attend the enrolment assessment (Visit 1). Informed consent and paediatric assent (if applicable) will be signed. At Visit 2, patients who fulfil the inclusion criteria and none of the exclusion criteria will be randomized. A patient who does not fulfil the study eligibility criteria may be re-screened (checked for eligibility criteria) after at least 4 weeks, but only once per calendar year.

Eligible patients will be stratified (at Visit 2) to one of the two dose levels of Symbicort/budesonide based upon assessment of ACQ and prior therapy, see Section 5.2.1. Patients will thereafter be randomized to Symbicort or budesonide treatment arms and enter a 26 week treatment period. Both stratification and randomization will be communicated to site personnel utilizing an Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS).

Dose levels:

- Symbicort pMDI 80/4.5 µg x 2 actuations bid (morning and evening), or Budesonide pMDI 80 µg x 2 actuations bid (morning and evening)

- Symbicort pMDI 160/4.5 µg x 2 actuations bid (morning and evening), or Budesonide pMDI 160 µg x 2 actuations bid (morning and evening)

Patients will be provided with albuterol pMDI (US), administered as 90 µg, 2 actuations or salbutamol pMDI (outside US), administered as 100 µg, 2 actuations as needed, for use as rescue medication. Patients that use more than 1 canister of rescue medication per month should be retrained and counselled according to the investigator's judgement.

During the treatment period, patients will attend 3 scheduled visits to the clinic (Visits 3, 5 and End of Treatment (EoT)), see Section 6.2.2. Study personnel will contact the patients monthly by telephone between scheduled visits, see Section 6.2.3. An unscheduled visit may be conducted as a result of the telephone contact.

Patients will record missed days of work/school, rescue medication use, asthma symptoms, ability to perform daily activities and night time awakenings in a daily diary by using a telephone to access the IVRS. The patient and, if applicable, the patient's parent/legal guardian will be trained by the investigational team and also supplied with written instructions on how to enter data and where to turn if problems occur. A reminder about intake of study medication will be given in connection to the IVRS call.

The clinical assessment should include a regular review (in connection with clinic and telephone visits) of patient data available in IVRS. Investigators should assess the patient's clinical status and make a decision as to the need for treatment with systemic corticosteroids. The study personnel are responsible to follow up on asthma related events and transfer all relevant information according to the electronic Case Report Form (eCRF) instructions and any indications of SAEs to the eCRF.

In case the patient fulfils any of the criteria for unstable asthma, see Section 6.2.5, an alert in the IVRS will trigger the responsible investigator to contact the patient for further instructions.

At the conclusion of the double blind treatment period or at discontinuation, patients will undergo study procedures (EoT visit) and be placed on appropriate asthma maintenance therapy based on investigators judgement. There will be a telephone contact 7 days post EoT visit to collect any SAEs and concomitant medication information (only collected in relation to an SAE or asthma exacerbation).

For information regarding discontinuation due to asthma exacerbations, see Section 5.8.

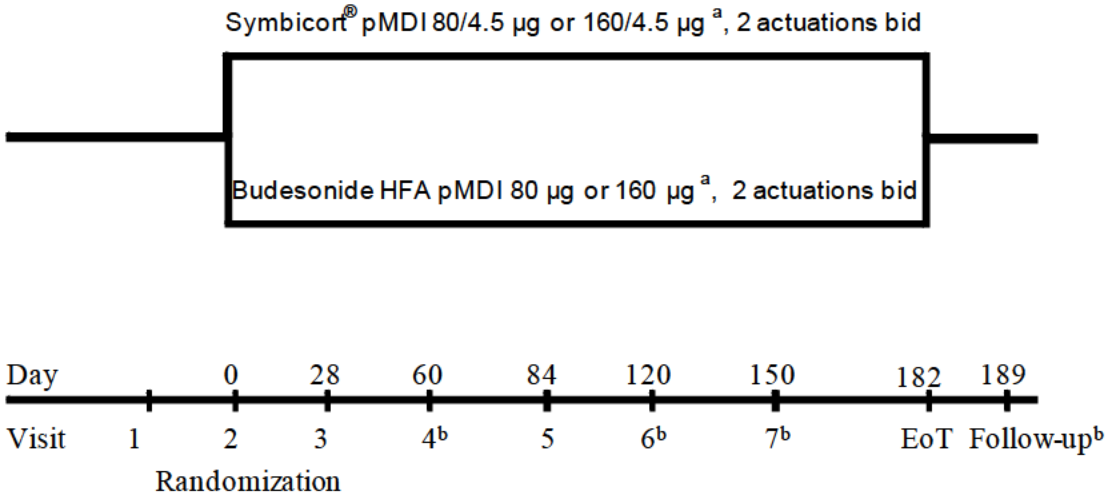
The study will include exploratory objectives include future pharmacogenetic research. All patients will be asked to participate in the genetic research. Participation is optional. If a patient declines to participate there will be no penalty or loss of benefit. The patient will not be excluded from any aspect of the main study.

This study will be conducted under the supervision of a Joint Oversight/Steering Committee (JOSC) and an independent Joint Data Monitoring Committee (JDMC). The composition and scope of these committees will be described in their respective charters. Both committees will be shared with other LABA Sponsor companies planning studies with the same objective.

In addition to the two committees mentioned above, each LABA Sponsor Company will have a independent Trial Data Monitoring Committee (TDMC) whose main role is to monitor possible events that will trigger a meeting of the JDMC. Representatives from each pharmaceutical company's TDMC will be members in the JDMC. The composition and detailed scope of the independent TDMC will be described in a charter.

The study is diagrammatically shown in the Study flow chart (Figure 1). Study procedures are shown in Table 1.

Figure 1 Study flow chart



[a] Dose based on previous level of treatment and asthma control (see Table 3)
[b] Telephone contact
EoT = End of Treatment

Table 1 Study Plan

	Enrol-ment	Rando-mization	Treatment						Follow Up
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**EoT**	**Follow - up**
Telephone contacts				**X**		**X**	**X**		**X**
Day (+ visit window)		**0 (<15)[a]**	**28(±3)[a]**	**60(±3)[a]**	**84(±3)[a]**	**120(±3)[a]**	**150(±3)[a]**	**182(±3)[a]**	**189(±3)[a]**
Informed consent/assent (if applicable)	X								
Informed consent and blood sample for exploratory genetics research (if applicable)		X[b]							
Inclusion/Exclusion criteria reviewed	X	X							
Demography	X								
Weight and height		X							
Physical examination		X							
Vital signs		X							
Medical history/Surgical history		X							
Asthma history		X							
Asthma exacerbation history		X							
Urine pregnancy test (as required)		X			X			X	
Peak expiratory flow (PEF)		X							
ACQ	X		X		X			X	
Randomization		X							
Concomitant medication assessment	X	X	X	X	X	X	X	X	X[c]

	Enrol-ment	Rando-mization	Treatment						Follow Up
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**EoT**	**Follow - up**
Telephone contacts				**X**		**X**	**X**		**X**
Day (+ visit window)		**0 (<15)[a]**	**28(±3)[a]**	**60(±3)[a]**	**84(±3)[a]**	**120(±3)[a]**	**150(±3)[a]**	**182(±3)[a]**	**189(±3)[a]**
Instruct/Remind patient of allowed/disallowed medications	X	X	X		X			X	
Check Potential Study Endpoints			X	X	X	X	X	X	X
Check asthma exacerbations			X	X	X	X	X	X	
Assessment of unstable asthma[d]			X	X	X	X	X	X	
Healthcare utilization			X	X	X	X	X	X	
Collect/dispense rescue medication (as needed)		X	X		X			X	
pMDI and ePRO training		X							
Collect/dispense study medication		X	X		X			X	
Dose actuation count			X	X	X	X	X	X	
Review patients asthma status via IVRS			X	X	X	X	X	X	
SAE/DAE assessment	X	X	X	X	X	X	X	X	X

a Suggested visit windows. Visits occurring outside of the visit window will not necessarily be considered a protocol deviation unless specifically stated within the protocol.
b Blood samples for DNA will be collected for exploratory genetics. Sampling is optional and subject to separate approval/consent. Sample will be taken at Visit 2 or if this day is not suitable, on any of the remaining planned visits the patient will attend.
c Only required for patients reporting an AE(s) or asthma exacerbation (s).
d For definition of unstable asthma see Section 6.2.5.2

3.2 Rationale for study design, doses and control groups

The design of this 26 week, randomized, double-blind, active-controlled study comparing the safety of Symbicort pMDI 80/4.5 and 160/4.5 µg x 2 actuations bid to budesonide pMDI 80 and 160 µg x 2 actuations bid in adult and adolescent (≥12 years) patients currently treated with ICS/LABA combination or not adequately controlled on a long-term asthma control medication or whose disease severity warrants initiation of treatment with ICS/LABA, was chosen to specifically examine the effect of administration of formoterol with budesonide, as Symbicort pMDI, compared to budesonide alone.

Ethical conduct of the study will be ensured through site surveillance of patient asthma status using alerts in IVRS, a once daily reminder about intake of study medication, monthly contacts with patients and patient withdrawal criteria.

4 PATIENT SELECTION CRITERIA

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

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.

4.1 Inclusion criteria

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

1. Provision of signed informed consent/ paediatric assent (if applicable) prior to any study specific procedures including medication withdrawal. NB: Patients agreeing to participate in the optional exploratory genetic research must provide a separate informed consent.

2. Male or Female, ≥12 years of age

3. Documented clinical diagnosis of asthma as defined by national and international asthma guidelines (ie, NAEPP EPR-3 2007, GINA, ATS/ERS etc) for at least 1 year prior to Visit 2

4. Patient must have history of at least 1 asthma exacerbation including one of the following:

   – requiring treatment with systemic corticosteroids (tablets, suspension, or injectable) between 4 weeks and 12 months prior to randomization

   – an asthma-related hospitalization (defined as an inpatient stay or >24 hour stay in observation area in ER or other equivalent facility depending on the country and healthcare system) between 4 weeks and 12 months prior to randomization

NB: Investigators must use appropriate means to ensure the accuracy of the subject's exacerbation history (eg, patient history, pharmacy records, hospital records, or chart records, etc).

5. Current Asthma Therapy: Patients must be appropriately using one of the following for the treatment of asthma and meet the criteria outlined below:

   – ICS, ICS/LABA combination, or ICS/LTRA combination, or ICS plus other maintenance therapy(ies) for at least 4 weeks prior to randomization. The dose of ICS must have been stable for at least 4 weeks prior to randomization. Any subject maintained on a stable high dose ICS with or without a LABA or LTRA or other maintenance therapy(ies) must have an ACQ6 <1.5 at Visit 1 (see Table 2)

Table 2 Estimated Daily Dosage for ICS

Asthma Therapy	**Total Daily Dose (µg/day)**		
Inhaled Corticosteroid	**Low**	**Medium**	**High**
Beclomethasone dipropionate	200 to 500	>500 to 1000	>1000-2000
Beclomethasone HFA	80 to 240	>240 to 480	>480
Ciclesonide	80 to 160	>160 to 320	>320 - 1280
Triamcinolone acetonide	400 to 1000	>1000 to 2000	>2000
Flunisolide	500 to 1000	>1000 to 2000	>2000
Fluticasone propionate	100 to 250	>250 to 500	>500 - 1000
Fluticasone propionate HFA	88 to 264	>364 to 440	>440
Budesonide	200 to 400	>400 to 800	>800-1600
Mometasone furoate	200 to <400	≥400 to 800	≥800

   – Leukotriene receptor antagonist (ie LTRAs such as montelukast, zafirlukast, or pranlukast) OR xanthines (eg theophylline) as monotherapy at a stable dose for at least 4 weeks prior to randomization. Patients on LTRAs, or xanthines, are eligible only if they record an ACQ score of ≥1.5 and in the investigator's clinical judgement, the patient's asthma severity could justify treatment with ICS or ICS/LABA combination

- Daily SABA in the 4 weeks prior to randomization but not more than 8 puffs a day on 2 consecutive days, or ≥25 puffs in one day, in the 7 days prior to Visit 1. Patients on daily SABA are eligible only if they record an ACQ score of ≥1.5 and in the investigator's clinical judgement, the patient's asthma severity could justify treatment with ICS or ICS/LABA combination

1. Availability and ability to perform the necessary manoeuvres and procedures required by the study (eg, use a pMDI, perform daily telephone calls)

4.2 Exclusion criteria

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

1. Has a history of life-threatening asthma. Defined for this protocol as an asthma episode that required intubation and/or was associated with hypercapnea requiring non-invasive ventilatory support

2. Has required treatment with systemic corticosteroids (tablets, suspension, or injectable) for any reason within 4 weeks prior to Visit 2

3. Has an ongoing exacerbation, defined as a worsening of asthma that requires treatment with systemic corticosteroids (tablets, suspension, or injectable)

4. Asthma exacerbation:

   - Any asthma exacerbation requiring systemic corticosteroids (tablets, suspension or injection) within 4 weeks of randomization or more than 4 separate exacerbations in the 12 months preceding randomization. For exacerbations to be considered separate events there must be at least 7 days from the resolution of one exacerbation to the start of the second exacerbation

   NB: Investigators should use clinical judgement and consider the subject's history of exacerbation, including the severity and interval since the last exacerbation per current clinical guidelines, in determining whether a subject with multiple exacerbations in the prior year should be enrolled in the study.

   Asthma hospitalizations:

   - More than 2 hospitalizations (defined as an inpatient stay or >24 hour stay in observation area in ER or other equivalent facility depending on the country and healthcare system) for treatment of asthma in the 12 months preceding randomization. Each hospitalization must be separated by >7 days to be considered an individual event

5. Has a respiratory infection or other viral/bacterial illness, or is recovering from such an illness at the time of Visit 2 that, in the investigator's opinion, will interfere with the patient's lung function

6. Unstable asthma status: Patients must not meet the following unstable asthma severity criteria within 7 days prior to randomization:

   - Asthma symptoms that persisted throughout the day on 2 consecutive days
   - Nighttime awakening due to asthma during 3 or more nights
   - Rescue medication use for the acute worsening of asthma symptoms >8 inhalations a day over 2 consecutive days or 25 inhalations or more in one day
   - Asthma symptoms so severe that the patient was limited in their ability to perform normal daily activity

7. Peak expiratory flow (PEF) (can be either pre- or post-bronchodilatory) that is <50% of predicted normal, according to regional guidelines, at Visit 2. Percent predicted PEF values must be calculated using NHANES III with relevant equations that adjust for race and national origin (Hankinson et al 1999, Hankinson et al 2010)

8. Has any clinically relevant abnormal findings in physical examination or vital signs at Visit 2, which, in the opinion of the investigator, may put the patient at risk because of his/her participation in the study

9. Pregnancy, breast-feeding or planned pregnancy during the study; fertile females not using acceptable contraceptive measures, as judged by the investigator.

10. Had a malignancy (except basal cell carcinoma) within the past 5 years

11. Any significant disease or disorder that, in the opinion of the investigator, may either put the patient at risk because of participation in the study, or influence the results of the study, or the patient's ability to participate in the study

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

13. Has participated, and received treatment, in one of the other LABA Sponsor studies investigating the safety of the addition of LABA to ICS (ie, a safety study comparing the use of ICS to ICS/LABA combination sponsored by other LABA Sponsor companies). Has participated, and received treatment, in another interventional or investigational drug study within 4 weeks prior to Visit 2 and/or previous randomisation to treatment in the present study. Patients are not allowed to participate in other studies during the conduct of this study

14. A smoking history of >10 pack years (1 pack year = 20 cigarettes smoked per day for 1 year) at Visit 1

15. Has a diagnosis of chronic obstructive pulmonary disease, chronic bronchitis, emphysema, idiopathic pulmonary fibrosis, bronchiectasis, and/or any pulmonary disease which may diversely affect the outcome of the study

16. Requires treatment with any β-blocker (including eye drops) during the course of the study

17. Planned hospitalisation during the study

18. Has conditions associated with poor compliance, or alcohol or drug abuse

19. Has taken omalizumab or any other monoclonal or polyclonal antibody therapy, for any reason within the 6 months prior to Visit 2

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

21. Planned donation of blood during the study

Additional exclusion criteria for exploratory genetic research are detailed in Appendix D. Procedures for withdrawal of incorrectly enrolled patients see Section 5.3.

5 STUDY CONDUCT

5.1 Restrictions during the study

The investigator should be familiar with and comply with all applicable information regarding concomitant medications in the prescribing information and/or Investigators' brochure (IB) for the study medications.

5.2 Patient enrolment and randomisation

The Principal Investigator will:

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

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

3. Determine patient eligibility, see Sections 4.1 and 4.2

4. Assign eligible patient unique randomisation code (patient number) at Visit 2

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

A patient who does not fulfil the study eligibility criteria may be re-screened (checked for eligibility criteria) after at least 4 weeks, but only once per calendar year.

5.2.1 Procedures for randomisation

An IVRS/IWRS will be utilised to enrol patients into the study, and to communicate the patient's randomisation code and which investigational product should be dispensed at Visit 2 and subsequent visits. The site will receive a facsimile confirming each communication from the IVRS/IWRS. Detailed instruction on use of the IVRS/IWRS will be provided to the Investigational sites.

The randomization codes will be computer generated by AstraZeneca R&D or representative using GRand (AZ Global Randomization system) using balanced blocks and allowing an approximately equal number of patients per treatment group within each centre. The randomization codes will be loaded into the IVRS/IWRS database. As they become eligible, patients will be assigned to a treatment group in balanced blocks supplied to that centre in accordance with the randomisation scheme. Randomisation codes will be assigned strictly sequentially as patients become eligible for randomisation.

Symbicort/budesonide dose stratification will be determined by the investigator, based on the patient's current asthma treatment and level of asthma control as defined in Table 3. If patient's entering the study on more than one asthma controller medication, current clinical guidelines and physician judgment should also be considered for appropriate Symbicort/budesonide dose stratification.

Table 3 Treatment allocation 2 doses

Category	Incoming Asthma Control[a]	Incoming Asthma Treatment[b]	Randomized Treatment Assignment (µg BID)
A	ACQ-6 Total Score <1.5 (controlled)	Low dose ICS or Low-dose ICS + LABA or other adjunctive therapies	Symbicort pMDI 80µg/4.5 µg or budesonide pMDI 80µg
B		Med-dose ICS or Med-dose ICS + LABA or other adjunctive therapies	Symbicort pMDI 160µg/4.5 µg or budesonide pMDI 160µg
C		High-dose ICS or High-dose ICS + LABA or other adjunctive therapies	
D	ACQ-6 Total Score ≥1.5 (not well controlled)	SABA[c] LTRA[c] Theophylline[c]	Symbicort pMDI 80µg/4.5 µg or budesonide pMDI 80µg
E		Low-dose ICS or Low-dose ICS + LABA or other adjunctive therapies	Symbicort pMDI 160µg/4.5 µg or budesonide pMDI 160µg
F		Med-dose ICS or Med-dose ICS + LABA or other adjunctive therapies	

a In general, a subject's ICS dose stratification is to be based on the ACQ-6 total score determined at the Screening Visit (Visit 1).

b A subject on SABA, LTRA or theophylline monotherapy are only eligible for study inclusion, if the ACQ¬6 Total Score ≥1.5 (not well controlled) and if in the judgment of the investigator, the subject's disease severity could warrant initiation of ICS ± LABA treatment. However, a subject maintained on a stable high dose ICS with or without adjunctive therapy (ie, LABA, LTRA or theophylline) must be controlled as measured by an ACQ-6 Total Score <1.5 in order to be randomized.

c Subjects classified as SABA or LTRA, or theophylline users consist of those subjects who have not used any other asthma controller medications for at least 4 weeks prior to the Screening Visit.

Study medication will be dispatched to the investigational sites, as needed, based on threshold values set by AstraZeneca.

5.3 Procedures for handling patients incorrectly enrolled or randomized

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

If a patient does not fulfil the study eligibility criteria they may be re-screened after at least 4 weeks, but only once per calendar year.

Patients discontinuing the study prior to Visit 2 will be classified as screening failures.

Where patients that do not meet the selection criteria are randomized in error or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post

initiation, a discussion should occur between the AstraZeneca Study Team Physician and the investigator regarding whether to continue or discontinue the patient from treatment.

The AstraZeneca Study Team Physician is to ensure all such decisions are appropriately documented.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

All study medication will be labelled using a unique medication identification number (Kit ID) that is linked to a treatment arm. IVRS/IWRS will assign the study medication to be dispensed to each patient at each drug-dispensing visit. Investigational products with equal strengths of the budesonide component, will appear identical and will also be presented in identical packaging to ensure blinding of the treatment arms.

5.4.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomisation for each randomized 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 centre. Patients and investigators are to remain blinded to the investigational products (Symbicort/Budesonide) used during the randomized treatment period. Investigators will select the appropriate dose stratum to which subjects are allocated based on control status and previous therapy. As such, they will be blinded to whether the subject is randomized to Symbicort or budesonide, but not the dose strata.

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

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities, and in exceptional cases, for other safety reasons. 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.

5.5 Treatments

5.5.1 Identity of investigational product(s)

The investigational products to be used in the study are described in Table 4.

Table 4 Identity of Investigational product

Product Name	Dosage form and strength	Manufacturer
Symbicort	pMDI (HFA) for oral inhalation with Actuation Counter Module (ACM), budesonide/formoterol 80µg/4.5 µg	AstraZeneca
Symbicort	pMDI (HFA) for oral inhalation with Actuation Counter Module (ACM), budesonide/formoterol 160µg/4.5 µg	AstraZeneca
Budesonide	pMDI (HFA) for oral inhalation with Actuation Counter Module (ACM), 80 µg	AstraZeneca
Budesonide	pMDI (HFA) for oral inhalation with Actuation Counter Module (ACM), 160 µg	AstraZeneca
Placebo for training	pMDI (HFA) for oral inhalation with Actuation Counter Module (ACM), PLACEBO	AstraZeneca

Symbicort and budesonide pMDI units will be packed together with desiccant bags in sealed pouches and placed in cartons. Training pMDI units will be delivered in cartons together with bags of extra actuators.

5.5.2 Doses and treatment regimens

Upon qualification for randomisation at Visit 2, patients will be instructed to stop using asthma medication in accordance with Table 8 and will be assigned a randomisation code and the appropriate blinded study medication through IVRS/IWRS. Patients will be stratified to one of the two dose levels of Symbicort/budesonide, see Section 5.2.1. Patients will thereafter be randomized to Symbicort or budesonide treatment arms and enter a 26 week treatment period.

Dose levels:

- Symbicort pMDI 80/4.5 µg x 2 actuations bid (morning and evening), or Budesonide pMDI 80 µg x 2 actuations bid (morning and evening)
- Symbicort pMDI 160/4.5 µg x 2 actuations bid (morning and evening), or Budesonide pMDI 160 µg x 2 actuations bid (morning and evening)

AstraZeneca or a designated representative will provide all investigational products. At each visit, the patient will receive sufficient quantity of drug to last the duration of time between visits. The first dose should be taken at Visit 2. In the event the patient loses her/his drug, the site should call into the IVRS/IWRS system in order to allow the system to determine the appropriate alternative kit ID(s) to be dispensed from the site's remaining inventory.

At Visit 2, the patients will be instructed on how to use the pMDI inhaler (see priming instructions). The patient will also receive written information on how the priming is done. Each site will be provided with sufficient training pMDI's. These devices will be used in the clinic only and will not be dispensed to the patients to take home. An assessment of inhalation technique will be made at Visit 2, followed by further instructions as needed. The training device contains excipients but no active ingredients.

Priming of the inhalers

The study drug and placebo pMDI will require priming when initially dispensed, if dropped or if not used for greater than 48 hours.

Prepare the pMDI inhaler according to the following instructions:

- Shake well to mix the contents of the canister
- Remove the mouthpiece cover
- Hold the inhaler upright and press the top of the canister firmly to release a shot of medicine into the air
- Release your finger from the top of the canister to allow it to reset
- Wait for at least 10 seconds, and then repeat this procedure one more time
- The pMDI inhaler is now ready for use

5.5.3 Additional study drug

The rescue medications to be used in the study are described in Table 5.

Table 5 Rescue Medications

Investigational product	Dosage form and strength	Manufacturer
Albuterol (US)	pMDI for oral inhalation, 90 µg	Commercially Available
Salbutamol (non US)	pMDI for oral inhalation, 100 µg	Commercially Available

Patients will receive rescue medication at Visit 2 and throughout the study to be administered as needed for relief of bronchospasm. Patients that use more than 1 canister of rescue medication per month should be retrained and counselled according to the investigator's judgement. This medication is not to be used on a regularly scheduled basis.

5.5.4 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.

These labels will be designed to meet country specific requirements and be translated into local language.

5.5.5 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label on the patient kits specifies the appropriate storage. Access must be restricted to authorized personnel. On each kit there will be an instruction illustrating its proper orientation, which must be adhered to.

The storage area must also have adequate control of temperature, in order to maintain stability and potency of study drug supplies. The clinical monitor will inventory the initial shipment of study drug supplies and will inspect study drug supplies during monitoring visits.

5.6 Concomitant and post-study treatment(s)

For allowed medications during the study, see Table 6 and Table 7. For disallowed medication during the study, see Table 8.

Table 6 Allowed asthma medication

Medications from Visit 2 and throughout study:	
–	Inhaled disodium cromoglycate, inhaled nedocromil sodium or if on treatment with these medications prior to Visit 2. The dose is to be kept stable during the treatment period.
–	Antitussives prn not containing ephedrine or other bronchodilators
–	Mucolytics not containing ephedrine
–	Nasal steroids
–	Albuterol/salbutamol as rescue medication. From Visit 2 onward, patients must use the study provided albuterol/salbutamol, which will be the only allowed rescue medication.
–	If receiving immunotherapy (desensitization), must be on a stable regimen for at least 4 weeks prior to Visit 2 and use a stable dose throughout the double blind treatment period

Table 7 Allowed medications to treat an asthma exacerbation (maximum 14 days)

Medications to treat an asthma exacerbation:	
–	ICS other than study medication only during hospitalisation/ER treatment
–	Systemic corticosteroids (tablets, suspension or injections)
–	Any short-acting β2-agonists other than study medication only during hospitalisation/ER treatment
–	Leukotriene antagonists, 5-Lipoxygenase inhibitor, ephedrine, inhaled disodium cromoglycate or inhaled nedocromil sodium

Medications to treat an asthma exacerbation:
– Inhaled anticholinergics only during hospitalisation/ER treatment
– Xanthines

Table 8 Disallowed asthma medications

DISALLOWED Medications prior to Visit 2
– Systemic corticosteroids (tablets, suspension or injections) within 4 weeks prior to Visit 2
– Omalizumab or any other monoclonal or polyclonal antibody therapy taken for any reason within 6 months prior to Visit 2

DISALLOWED Medications during the Randomized Treatment Period:
– ICS other than study medication[a]
– Systemic corticosteroids (tablets, suspension or injections)[a]
– Any β2-agonists other than study medication[a]
– Inhaled anticholinergics[a]
– Ephedrine-containing medication[a]
– β-blockers (including eye drops)
– Omalizumab or any other monoclonal or polyclonal antibody therapy for any reason
– Systemic treatment with potent Cytochrome P (CYP) 3A4 inhibitors (eg, ketoconazole)
– Leukotriene antagonists and 5-lipoxygenase inhibitors[a]
– Xanthines[a]

a Except for treatment of an asthma exacerbation, see Table 6.

The investigator should be familiar with and comply with all applicable information regarding concomitant medication in the IB/prescribing information for the study drugs.

Other non-respiratory medication, which is considered necessary for the patient's safety and well being, may be given at the discretion of the investigator. The administration of all concomitant medication (excluding investigational products and rescue medications) must be recorded in the appropriate sections of the eCRF. Written informed consent/paediatric assent must be obtained prior to discontinuation of any asthma treatments at Visit 1. At the end of the treatment period, patients will resume appropriate asthma maintenance therapy.

5.7 Treatment compliance

Each patient is required to comply with the prescribed treatment regimen throughout the study. At Visit 2, the patients will be instructed on how to use a pMDI inhaler correctly. In order to ensure correct inhalation technique, training devices (pMDI) will be available at each study centre for instructional purposes as well as for patients to practice the correct inhalation technique. Instruction and practice should occur prior to dispensing blinded study medication. These devices will be used in the clinic only and will not be dispensed to patients for use at home.

The administration of all study drugs (including investigational products) should be recorded in the appropriate sections of the eCRF. The intake of study medication will be recorded as dose actuation count in the eCRF on the scheduled study visits (Visits 3, 5 and EoT) and monthly telephone calls.

A daily reminder will be addressed via IVRS. If the patient is not compliant, he or she will receive additional training on how to use the pMDI.

5.7.1 Accountability

The investigational products are to be dispensed only by the investigator or the sub-investigator(s). The study drug provided for this study will be used only as directed in the study protocol. The study personnel will account for all study drugs dispensed to and returned from the patient. If appropriate, drug storage, drug dispensing, and drug accountability may be delegated to the pharmacy section of the investigational site.

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

The investigator or designated study personnel are responsible for maintaining accurate dispensing records of the study drug. All study drugs must be accounted for, including study drug accidentally or deliberately destroyed. All discrepancies between amounts of study drug dispensed and amounts returned must be documented.

All study drug, including partially used or unused pMDI canisters and albuterol/salbutamol, is to be returned by patients. The clinical monitor will coordinate the return of drug supplies for proper disposal.

5.8 Discontinuation of investigational product

Patient, who is discontinued from investigational product, should continue in the study through 26 weeks and will be followed via telephone contact approximately every 4 weeks.

Patients may be discontinued from investigational product (IP) in the following situations:

1. Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment

2. Adverse Event

3. Severe non-compliance to study protocol

4. Pregnancy

5. Safety reasons as judged by the investigator and/or AstraZeneca

6. Intake of certain concomitant medications may necessitate withdrawal (see Section 5.6)

7. Experience of more than 1 asthma exacerbation within 13 weeks (during the randomized treatment period) or more than 2 asthma exacerbations within 26 weeks (during the randomized treatment period) will necessitate withdrawal. For definition of asthma exacerbations, see Section 6.3.1.1

8. A patient whose exacerbation is not responding to therapy in the judgment of the investigator or is not responding to 14 days of treatment with systemic corticosteroids

9. A patient requires intubation for asthma

10. A patient has an adverse event that would, in the investigator's judgement, make continued participation an unacceptable risk

Discontinuation of investigational product does not mean discontinuation of follow-up. Telephone contacts should be continued in all cases.

5.8.1 Procedures for discontinuation of a patient from investigational product

Patients who are discontinued from IP should always be asked to continue study procedures.

The patient should complete the EoT visit and then be followed through the 26-week treatment period via telephone contact approximately every 4-weeks, see Section 6.2.4.

A patient that decides to discontinue investigational product will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator(s). SAEs/DAEs will be followed up (See Sections 6.4.3 and 6.4.4) and all study drugs should be returned by the patient. This is also applicable for a patient that discontinues due to any study specific criteria.

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

5.8.2 End of Treatment

At the EoT visit, patients will be put on appropriate asthma maintenance medication as judged by the investigator.

5.9 Withdrawal from study

Patients are at any time free to withdraw from study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Withdrawal of consent must be ascertained and documented by the investigator in the eCRF as well as in the ICF (if applicable) and medical records. If possible, the ICF should be signed again and dated by both the patient and the investigator. Such patients will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator. SAEs/DAEs will be followed up (See Sections 6.4.3 and 6.4.4) and all study drugs should be returned by the patient.

Withdrawn patients will not be replaced.

At the time of withdrawal, patients should, if possible complete the EoT visit. To ensure validity of study data, it is very important to collect at least vital status (dead or alive). AstraZeneca or its delegate will therefore attempt to collect information on withdrawn patients or lost to follow-up patients from publicly available sources to determine the patient's vital status during the 26 weeks following randomization. If needed, the attempt to collect information will continue until the end of the study.

Every effort should be made to contact any patient lost to follow-up during the course of the study in order to complete assessments and retrieve any outstanding data, drug, or clinical supplies. These efforts should be recorded in the source documentation.

Patients who withdraw from the main study should always be asked specifically whether they are withdrawing or continuing their consent for the exploratory genetic research.

6 COLLECTION OF STUDY VARIABLES

6.1 Recording of data

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 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 eCRF. A copy of the completed eCRF will be archived at the study site.

Patients will record missed days of work/school, rescue medication use, asthma symptoms, ability to perform daily activities and night time awakenings in IVRS on a daily basis.

The patients will answer questions in a patient-reported outcome test (ACQ). ACQ will be administered on paper and recorded into the eCRF by investigator or delegate.

6.2 Data collection and enrolment

6.2.1 Screening and demographic measurements

6.2.1.1 Physical examination

A complete physical examination will be performed at Visit 2 and include an assessment of the following: general appearance, head, ears, nose, mouth, teeth, throat, neck, respiratory, cardiovascular, abdomen, and extremities.

6.2.1.2 Vital signs

Blood pressure and pulse rate measurements will be performed at Visit 2. Pulse rate (beats/min) will be measured over 30 seconds in a sitting position, after 5-minute rest. Systolic and diastolic blood pressure (mmHg) will be measured using a cuff appropriate for arm circumference.

6.2.1.3 Asthma exacerbation history

The assessment will include number of exacerbations during last year, the date of last exacerbation, and the type of exacerbation (oral steroid treatment, or hospitalization due to asthma).

6.2.1.4 Peak expiratory flow (PEF)

All sites will be provided with peak flow meters to standardize the measurements. Additional information and training will be provided outside this protocol. The guidelines published by ATS/ERS, should be followed for PEF measurements, as described below. A peak flow meter, which meets ATS standards, will be used.

PEF must be achieved as rapidly as possible and at as high a lung volume as possible, in order to obtain the maximum value. The neck should be in a neutral position, not flexed or extended, and the patient must not cough. A nose clip is not necessary.

The patient must perform a minimum of three PEF manoeuvres from total lung capacity.

The PEF values and their order must be recorded (source data only) so that manoeuvre-induced bronchospasm can be detected. If the largest two out of three acceptable blows are not reproducible within 0.67 L/s (40 L/min), up to two additional blows can be performed. If satisfactory repeatability has not been achieved in five attempts, more are not likely to be helpful. The largest value from at least three acceptable blows should be used to calculate the PEF predicted value.

At enrolment, if the patient demonstrates a PEF <50% of predicted normal, he/she must not be randomized into the study. Percent predicted equations will be supplied separately.

6.2.1.5 Optional Exploratory genetic research

Blood samples will be collected at randomization from patients who volunteer to participate in the exploratory genetic research portion of this study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

Please refer to Appendix D for further details including blood volumes; instructions for sample handling, storage, destruction, and withdrawal of informed consent for exploratory genetic research; data protection and data management.

6.2.2 Data collection at the visits

The date when the patient signs and dates the ICF will be the Visit 1 date.

The following variables are to be collected in the eCRF at the different visits:

6.2.2.1 Visit 1

- Date of birth, sex and race
- Concomitant medication, see Section 5.6
- ACQ, see Section 6.3.1.3

6.2.2.2 Visit 2

- Height (measured in cm, with no shoes) and weight (in kg, with light clothes and no shoes)
- Physical examination, see Section 6.2.1.1
- Vital signs (pulse and blood pressure), see Section 6.2.1.2
- Medical and surgical history
- Asthma history
- Asthma exacerbation history, see section 6.2.1.3
- Urine pregnancy test, see Section 6.4.6
- PEF, see Section 6.2.1.4
- Concomitant medication, see Section 5.6
- SAE/DAE, see Section 6.4.2

6.2.2.3 Visit 3, 5 and EoT

- Urine pregnancy test (at visit 5 and EoT), see Section 6.4.6

- ACQ, see Section 6.3.1.3
- Concomitant medication, see Section 5.6
- Potential Study Endpoints, see Section 6.4.5
- Asthma exacerbations, see Section 6.3.1.1
- Assessment of unstable asthma, see Section 6.2.5
- Health care utilization, see Section 6.3.1.3
- Use of investigational product (recorded as dose actuation count), see Section 5.7
- SAE/DAE, see Section 6.4.2

6.2.3 Telephone contacts (Visit 4, 6 and 7)

Telephone contacts will be performed between the visits, see Study Plan, Table 1. The following variables are to be collected:

- Concomitant medication, see Section 5.6
- Potential Study Endpoints, see Section 6.4.5
- Asthma exacerbations, see Section 6.3.1.1
- Assessment of unstable asthma, see Section 6.2.5
- Health care utilization, see Section 6.3.1.3
- Use of investigational product (recorded as dose actuation count reported by the patient), see Section 5.7
- SAE/DAE, see Section 6.4.2

6.2.4 Follow-up procedures

A follow-up telephone contact will be performed for:

- Patients that **completed** the 26 week treatment period
  - 7 days after EoT visit
- Patients that **discontinued IP** before 26 weeks
  - Every 4-weeks through the 26-week treatment period

The following variables are to be collected:

- Concomitant medication (only required for patients reporting an SAE(s), see Section 5.6
- Potential Study Endpoints, see Section 6.4.5
- SAE(s), see Section 6.4.2

6.2.5 Assessment of UNSTABLE asthma

6.2.5.1 Assessment of UNSTABLE asthma between scheduled telephone contacts and visits

In case the patient fulfils any of the criteria for unstable asthma, an alert in the IVRS will trigger the responsible investigator to contact the patient for further instructions. In addition, if at any time the patient feels that their asthma is deteriorating or in need of additional treatment they should be instructed to contact the study site.

Any of the following criteria will trigger an alert that the investigator should contact the patient for further instructions:

- ≥8 puffs/day of rescue medication for 2 consecutive days
- ≥25 puffs or more of rescue medication in one day
- Asthma symptoms that limited the patient's ability to perform normal daily activity on 2 consecutive days
- Missing school or work due to asthma ≥2 times in one week
- Nighttime awakening due to asthma ≥3 nights in one week

An unscheduled healthcare contact (including telephone calls to the clinic, home visit by physician and unscheduled clinic visits) for asthma should be recorded in source documentation and the eCRF. The investigator should review unstable asthma criteria with the patient and determine if a site visit is warranted. This assessment should include a review of patient data available in the IVRS. Additionally, the investigator should assess the patient's clinical status and determine whether to prescribe a course of systemic corticosteroids.

6.2.5.2 Assessment of UNSTABLE Asthma at scheduled telephone contacts and visits

Unstable asthma will be assessed at each scheduled study telephone call and in-clinic visit to determine if the patient meets the criteria for unstable asthma, see Section 6.2.5.1 and if so determine whether to prescribe systemic corticosteroids.

The assessment should include a review of patient data available in IVRS. Investigators should assess the patient's clinical status and determine whether to prescribe systemic corticosteroids.

6.3 Efficacy

6.3.1 Efficacy variables

6.3.1.1 Asthma exacerbations

Method of assessment

An asthma exacerbation is defined as deterioration of asthma requiring one of the following:

- the use of systemic corticosteroids (tablets, suspension, or injection) for at least 3 days
- an inpatient hospitalization
- an emergency room visit due to asthma that required systemic corticosteroids

Courses of corticosteroids separated by 1 week or more should be treated as separate asthma exacerbations. Unscheduled physician visits to the site or to an alternate care provider will not be considered an asthma exacerbation unless treatment with systemic corticosteroids treatment is initiated.

Please note: a single depo-injectable dose of corticosteroids will be considered the equivalent to a 3-day course of systemic corticosteroids.

Patients will not be withdrawn from the study due to asthma exacerbation unless the patient experiences more than 1 asthma exacerbation within 13 weeks or more than 2 asthma exacerbations during the double-blind treatment.

The start and end date of each asthma exacerbation will be recorded in the eCRF at the clinic visits or monthly telephone calls. The start date is defined as the first day of hospitalization/emergency room treatment or the first day of systemic corticosteroids treatment. The end date is defined as the last day of hospitalization/emergency room treatment or the last day of systemic corticosteroids treatment (according to prescription). If the same asthma exacerbation includes both hospitalization/emergency room treatment and systemic corticosteroids treatment, the start and end dates are the first and last day that either of the criteria was fulfilled.

Additional hospitalizations/emergency room treatments and systemic corticosteroids treatments occurring during an asthma exacerbation should not be regarded as a new asthma exacerbation. For a hospitalization/emergency room visit or systemic corticosteroids treatment to be counted as a new exacerbation it must be preceeded by at least 7 days in which neither criteria are fulfilled.

6.3.1.2 Efficacy variables collected by IVRS

Patients will record, missed days of work/school, rescue medication use, asthma symptoms, ability to perform daily activities and night time awakenings in a daily diary by using a telephone to access the IVRS, starting the day after randomization. The questions will read more or less as below.

Missed school or working day:

1. Was yesterday a school or workday?

2. (If yes:) Did you miss any time in school or work due to your asthma? Response: Yes/No

Rescue medication use:

3. In the past 24 hours, how many puffs of your rescue medication did you take? Response: Numerical (options should include 0-99)

Asthma symptoms:

4. In the past 24 hours, did you have asthma symptoms? Response: Yes/No

5. (If yes:) In the past 24 hours, have your asthma symptoms limited your ability to perform your normal daily activities? Response: Yes/No

Night-time awakenings

6. Did you wake up last night due to your asthma? Response: Yes/No

7. (If yes:) When you woke up last night, did you need to use your rescue inhaler? Response: Yes/No

Methods of assessment

The patient and, if applicable, the patient's parent/legal guardian will be instructed to answer the above questions via IVRS between the Randomization visit and the Follow-up visit. The entering of data will be indicated once every 24 hours in the morning. The patient and, if applicable, the patient's parent/legal guardian will be trained by the study personnel and also supplied with written instructions on how to enter data and where to turn if problems occur.

The IVRS offers the possibility to monitor that the patient has entered data on a daily basis. The clinical assessment should include a regular review (in connection with clinic and telephone visits) of patient data available in IVRS. In case the patient fulfils any of the criteria for unstable asthma, see Section 6.2.5, an alert in the IVRS will trigger the investigator to contact the patient for further instructions.

In addition, a daily reminder will be addressed to the patient:

- Please remember that you should take your study medication as instructed by your study investigator.

6.3.1.3 Efficacy variables collected in eCRF at visits and monthly telephone contacts

Information about healthcare utilisation will be collected at clinic visits and monthly by telephone by study personnel. The information will be recorded in the eCRF.

Healthcare utilization for asthma:

- Telephone contact with study doctor
- Telephone contact with other physician or healthcare provider
- Unscheduled or unplanned visit to study doctor (including home visits)
- Unscheduled or unplanned visit to other physician or healthcare provider (including home visits)
- Emergency department or hospital (< 24 hrs)
- Hospital admission or Emergency Department (≥ 24 hrs)

Hospitalisations will be collected with the SAE reports.

6.3.2 Asthma Control Questionnaire

Assessment of current asthma control by the ACQ as described in the NAEPP EPR-3, 2007 Guideline (NAEPP EPR-3 2007). The ACQ has been developed by Juniper and colleagues and includes 7 questions covering criteria deemed appropriate 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. In this study, the FEV_1 question will be excluded and FEV_1 will not be measured at clinic visits. It has been shown that exclusion of this question will not alter the validity and the measurements properties of the questionnaire referred to as ACQ6.

The ACQ6 will be self-administered on paper at clinic Visits 1, 3, 5 and EoT. It takes approximately 2-3 minutes to answer the 6 questions.

The English version for North America is included in Appendix E. Translations of ACQ6 into local languages have been performed according to a linguistic validation process.

Method of assessment

It is important to administer the ACQ6 questionnaire according to the guidelines for standardized administration, and before any other study related procedures take place.

A brief introduction on how to complete the ACQ6 questionnaire will be given at Visit 1 prior to the assessment. The questionnaire will also be completed in the case of early discontinuation.

The ACQ6 should be completed in a quiet place without influence from study personnel or accompanied family or friend. The patients should be informed about the importance of their participation and be given adequate time to complete all items, ie, no time limits for completing the questions should be given. The study personnel are not to help the patients to choose an answer and must be neutral in their response to any questions from the patients. The study personnel must neither interpret nor rephrase questions in the questionnaire. After completion of the questionnaire, the study personnel will review the questionnaire for completeness only.

6.4 Safety

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

6.4.1 Definition of adverse events (AEs)

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

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

6.4.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (ie, 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 hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above

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

6.4.3 Recording of adverse events

AEs will not be collected unless they lead to DAE or qualify as an SAE.

SAEs/DAEs will be recorded from the time of informed consent through the treatment period and including the follow-up period.

Follow-up of unresolved adverse events

Any SAE/DAEs that are unresolved at the EoT Visit or at discontinuation in the study will be 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 SAE(s)/DAE(s) at the end of the study, if judged necessary.

Variables

The following variables will be collected for each AE;

- AE (verbatim)
- Date when the AE started and stopped
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to investigational product
- AE caused 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 hospitalization
- Date of discharge
- Probable cause of death

- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Other medication
- Causality assessment in relation to Additional Study Drug
- Description of AE.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.4.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

Causality collection

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

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

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

Concomitant medication

All changes in the patient's ordinary medication, eg dose change or addition or new medication, must be reported in the medication log. Reasons for changes in medication, which reflects an SAE/DAE, must be recorded on the AE form.

Patient reported outcome

The patient will answer questions in a patient-reported outcome test (ACQ). The patients should report any health problems directly to the investigational team as the questionnaire will not be reviewed for the purpose of identifying potential AEs.

Overdose

Should an overdose (accidental or deliberate) occur, it must be reported in accordance with the procedures described in Section 13.2, Overdose, regardless of whether the overdose was associated with any symptom or not.

Pregnancy

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

6.4.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF. For SAEs considered as potential study endpoints, see Section 6.4.5.

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

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

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

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

If the WBDC system is not available, then the investigator or other study site personnel reports an 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 (SPC) for the active comparator product (including any AstraZeneca comparator).

6.4.5 Reporting of Potential Study Endpoints (deaths, intubations and hospitalizations)

For this study, the primary and secondary objectives listed in Sections 2.1 and 2.2 and further defined in Section 6.4.5.1, 6.4.5.2 and 6.4.5.3 consist of clinically important medical events, which meet the typical criteria for SAEs. However, in order to protect the integrity of the study, SAEs referred to an independent Joint Adjudication Committee (JAC) to determine

asthma-relatedness will be treated as potential study endpoints and not routinely expedited to regulatory agencies. This will allow key data to remain blinded.

Potential study endpoints include all deaths, intubations and hospitalizations that are observed from randomised patients. Although the study endpoints are asthma-related deaths, intubations, and hospitalizations, asthma causality (asthma related or non-asthma related) is not determined until adjudication is completed. After adjudication, asthma related events will be reviewed by the TDMC; non-asthma related events will be sent and subject to regulatory reporting with reporting requirement starting from the time they are deemed non-asthma related. Given the extensive patient exposure to the study drugs in the doses being used, the likelihood of identifying a new safety signal outside of the study endpoints is unlikely, and therefore such an approach is justified in order to protect the blinding of the study.

Further details of this process can be found in separate charters for the JAC, JDMC and TDMC.

Potential study endpoints will be collected in the eCRF as SAEs. For each potential endpoint, the investigator will complete information specific to that type of endpoint on the eCRF and compile relevant additional source information into an Event Adjudication Package, as described in the JAC Charter and JAC Operations Manual. The Event Adjudication Package will be sent to the JAC for central adjudication.

6.4.5.1 Definition of Asthma-related deaths

Definition of an asthma related death is presented in the JAC Charter.

6.4.5.2 Definition of Asthma-related intubations

Definition of asthma related intubation is presented in the JAC Charter.

Intubation is defined as oro-tracheal or naso-tracheal placement of a tracheal tube.

Noninvasive ventilation, defined as the use of positive airway pressure delivered via nasal, oral, or oral-nasal interphase, will be captured as part of the hospitalization record; in the case of non-invasive ventilation preceding intubation, the event should be counted as an intubation.

6.4.5.3 Definition of Asthma-related hospitalizations

Definition of an asthma related hospitalization is presented in the JAC Charter.

6.4.5.4 Definition of discontinuation due to asthma exacerbation

Patients discontinued from investigational product according to criteria 7 or 8 in Section 5.8 will be defined as being discontinued from investigational product due to asthma exacerbation.

6.4.6 Laboratory safety assessment

All sites will perform urine pregnancy testing (on appropriate female patients) at Visits 2, 5 and EoT.

6.5 Patient reported outcomes (PRO)

6.5.1 Efficacy variables collected via IVRS

See Section 6.3.1.2.

6.5.2 Asthma Control Questionnaire (ACQ)

See Section 6.3.2.

6.6 Pharmacokinetics (Not applicable)

6.7 Pharmacodynamics (Not applicable)

6.8 Pharmacogenetics

The study will include exploratory objectives including future exploratory genetic research, please refer to Appendix D for further details.

6.9 Health economics (Not applicable)

7 BIOLOGICAL SAMPLING PROCEDURES

The study will include exploratory objectives including future exploratory genetic research, please refer to Appendix D for further details.

8 ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

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

8.2 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. Pursuant to this wording, patients will authorize the collection, use and disclosure of their study data by the investigator and by those persons who need that information for the purposes of the study.

Please refer to Appendix D for details of precautions specific to genetic data.

8.3 Ethics and regulatory review

An Ethics Committee or Institutional Review Board (IRB) 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/IRB 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/IRB 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/IRB 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/IRBs and Principal Investigators with safety updates/reports according to local requirements, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

Each Principal Investigator is responsible for providing the Ethics Committees/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.

8.4 Informed consent

The Principal Investigator(s) at each centre 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
- Ensures that separate consent is given for exploratory genetic research and that patients are aware that exploratory genetic research is optional
- Ensure the original, signed informed consent form is 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

If the patient is minor, the Principal Investigator will:

- Ensure that the minor patient is informed about the study to the best of his/her understanding
- Ensure that the patient, if appropriate, signs and dates the pediatric assent form
- Ensure that the parent or legal guardian is informed and signs and dates the informed consent form

8.5 Changes to the protocol and informed consent form

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

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

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

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

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

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

8.6 Audits and inspections

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

9 STUDY MANAGEMENT BY ASTRAZENECA

9.1 Pre-study activities

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

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

9.2 Training of study site personnel

Before the first 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 system(s) utilised.

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

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

9.3 Monitoring of the study

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

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

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

9.3.1 Source data

Refer to the clinical study agreement for location of source data.

9.4 Study agreements

The Principal Investigator at each centre should comply with all the terms, conditions, and obligations of the clinical study agreement, or equivalent, for this study. In the event of any inconsistency between this clinical study protocol and the clinical study agreement, the terms of clinical study protocol shall prevail with respect to the conduct of the study and the treatment of 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.

9.4.1 Archiving of study documents

The Investigator follows the principles outlined in the clinical study agreement.

9.5 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 and to end by .

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

10 DATA MANAGEMENT BY DMC

Data will be entered in the Web Based Data Capture (WBDC) system at the study site. Trained study personnel will be responsible for entering data on the observations, tests and assessments specified in the protocol into the WBDC system and according to the eCRF Instructions. The eCRF Instructions will also guide the study site in performing data entry. Data entered in the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail.

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

ePRO data will be collected electronically and data will be transferred to AstraZeneca via the IVRS service provider.

Dictionary coding

Medical coding is done using the most current version of MedDRA and AstraZeneca Drug Dictionary.

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 (eg, eDiary, IVRs etc) will be tested and validated as needed. External data reconciliation will be done with the clinical database as applicable.

Serious Adverse Event (SAE) Reconciliation

SAE Reconciliation Reports are produced and reconciled with Patient Safety database.

Data associated with biological samples will be transferred for storage to laboratories internal or external to AstraZeneca for later analyses. Please refer to Appendix D for details of data management for exploratory genetic research.

11 EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA OR DELEGATE

11.1 Calculation or derivation of efficacy variable(s)

The efficacy endpoint time to first asthma exacerbation is the time to the first event occurring due to a deterioration of asthma and requiring systemic corticosteroids (tablets, suspension, or injection) for at least 3 days or an inpatient hospitalization or emergency room visit due to asthma that required systemic corticosteroids. For this endpoint the time from randomization to the event, or the time to the last documented contact for patients with no event (last assessment of exacerbation status), will be calculated.

In addition the number of asthma exacerbations will be calculated for each patient.

Regarding healthcare utilization for asthma, the incidence of and number of events will be calculated separately for each patient and each of the categories in Section 6.3.1.3.

11.2 Calculation or derivation of safety variable(s)

The primary safety endpoint is the time to the first event included in the composite endpoint of asthma-related death, asthma-related intubation, or asthma-related hospitalization. Only events adjudicated and confirmed by the JAC will be included in the analysis of this endpoint.

For the primary safety variable, the time from the randomization to the event, or time to last documented contact for censored patients, ie, patients with no event, will be calculated. In addition the corresponding variable excluding events occurring 7 days after last dose of randomized treatment will be calculated.

A patient may have 1 or more events. However, only a patient's first occurring event will contribute to the analysis of the specified variable.

A secondary safety endpoint is discontinuation from the study due to asthma exacerbation. For this secondary safety variable, the time from the randomization to the discontinuation due to asthma exacerbation, or time to last documented contact for censored patients, ie patients that did not discontinue due to asthma exacerbation, will be calculated.

11.3 Calculation or derivation of patient reported outcome variables

11.3.1 ACQ

For ACQ all 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 five responses. At least 5 out of the 6 questions must have been answered to provide a value. The outcome variable for ACQ will be the change in overall score from Visit 1 to the mean of the values at Visits 3, 5 and EoT.

11.3.2 Missed school or working day

The number of days (a part of a day will be counted as a full day) of school or work missed due to asthma will be calculated for each patient.

11.3.3 Rescue medication use

The mean number of puffs of rescue medication, based on available values, will be calculated for each patient. In addition the % rescue free days, days with no reported use of rescue medication, will be calculated for each patient.

11.3.4 Asthma symptoms

The percent days with no asthma symptoms for most of the day, based on available values, will be calculated for each patient.

The percent days with activity limitation due to asthma, based on available values, will be calculated for each patient.

The percent nights with awakenings due to asthma, based on available values, will be calculated for each patient.

12 STATISTICAL METHODS AND SAMPLE SIZE

12.1 Description of analysis sets

The full analysis set, consisting of all patients randomized to study drug will be the primary data set used for analyses endpoints related to the safety and efficacy objectives.

12.1.1 Endpoint definitions

12.1.1.1 Primary safety endpoint

The primary safety endpoint is the time to first event included in the composite endpoint (asthma-related death, asthma-related intubation or asthma-related hospitalization), using events adjudicated and confirmed by the JAC.

12.1.1.2 Primary efficacy endpoint

Primary efficacy endpoint is the time to the first event included in the definition of an asthma exacerbation.

12.1.1.3 Secondary efficacy endpoints

Secondary efficacy endpoints include respectively percent days of respectively days with no asthma symptoms, days with no activity limitation due to asthma, and treatment means of respectively puffs of rescue medication, and ACQ. In addition number of days missed at school or work, the number of respectively telephone calls to the clinic, home visits by physician, unscheduled clinic visits and hospitalization and ER visits will also be secondary efficacy variables.

12.1.1.4 Safety endpoints

Incidence of SAEs, DAEs and time to discontinuation due to asthma exacerbation.

12.2 Methods of statistical analyses

12.2.1 Demographics and baseline characteristics

Demographic and baseline characteristics will be summarized, using frequency distributions and summary statistics based on the full analysis set.

12.2.2 Safety analysis

For the time to event variables, a Cox proportional hazards model with terms for randomized treatment and strata for incoming control/asthma treatment will be used to compare Symbicort and budesonide. Hazard ratios and 95% confidence intervals will be provided. Patients who complete the 26-week follow-up period without experiencing any event as defined by the component in the primary endpoint will be censored at 26 weeks. Any patients without an event who are lost to follow-up prior to 26 weeks will be censored at the time of the last assessment of the status of the components of the primary endpoint. For the primary endpoint the following hypothesis will be tested at the 2.5% 1-sided significance level,

- H_0: Hazard ratio ≥ 2.0 versus H_1: Hazard ratio <2.0

If the null hypothesis is rejected then a 2.0-fold increase in risk on treatment with Symbicort compared to treatment with budesonide is ruled out. Further, if the upper confidence limit estimate is <1.0, then superiority may be concluded in terms of the risk of asthma related events being lower on Symbicort vs budesonide.

A subsidiary analysis, excluding events occurring 7 days after the last dose of randomized treatment for discontinued patients, will be performed in the same manner as the primary analysis. In addition, Kaplan-Meier plots, will be provided, describing time-to-event curves by treatment groups.

A formal interim analysis will be performed once half of the required number of primary endpoint events has been achieved. Consideration will be given to early stopping, if the p-value for the HR is extreme, $p \leq 0.0001$ (1-sided), z-value ≥ 3.7, using the Haybittle-Peto rule so that the alpha level in the final analysis is largely unaltered at 0.0249 1-sided.

SAEs and DAEs will be summarized and evaluated descriptively. Time to discontinuation due to asthma exacerbation will be analyzed in the same way as the primary safety endpoint.

It is also planned that a meta-analysis of the individual sponsor studies will be conducted to explore the relative risk for patients receiving ICS/LABA combination compared to patients receiving ICS with respect to the composite endpoint of asthma-related intubation or asthma-related death and for the endpoint of asthma-related death. Details of this meta-analysis will be described in a separate analysis plan.

12.2.3 Efficacy analysis

The primary efficacy variable, time to first asthma exacerbation,will be analysed using a Cox proportional hazards model with terms for randomized treatment and strata by incoming control/asthma treatment to compare treatment groups. Hazard ratios and 95% confidence intervals will be provided. Additional descriptions of the number of asthma exacerbations will be evaluated by a Poisson regression model with terms for incoming control/asthma treatment strata and randomized treatment, and with the logarithm of the time in study as offset.

Frequency and percentage of days of unscheduled asthma-related healthcare utilization and measures of productivity (number of days of school or work missed due to asthma) will be summarized by treatment group.

Mean rescue medication use will be described and analyzed with an ANCOVA model using treatment and country as fixed factors. Percent rescue free days, percent days with no symptoms due to asthma, and percent days with activity limitation and percent days with night time awakening will be analysed by a similar model.

Change from baseline in ACQ will be summarized using descriptive statistics and analyzed with an analysis of covariance (ANCOVA) model using treatment and country as fixed factors and baseline as a covariate. Proportions of patients achieving asthma control based on intervals defined by ≤ 0.75 (ie, well-controlled) and ACQ ≥ 1.5 (ie, un-controlled) will be analyzed and presented.

No multiplicity adjustment will be performed for the testings of the primary safety endpoint and the primary efficacy endpoint, since two different hypotheses are addressed.

12.3 Determination of sample size

The incidence rate on ICS alone, based on studies with a similar population, SD-039-0668 and SD-039-0673, is estimated to be 15 events per 1000 per treatment years. To rule out 2 fold increase in the event rate with ICS/LABA combination versus ICS alone, equating to an increase from 1.5% to 3.0% per year, or from 0.75% to 1.5% per 6 months, 87 events are required. Assuming a 6-month study, an approximate linear incidence rate over time, and using 90% power, this requires a total of 11664 patients to be randomized. To rule out a true RR of 2.0, the observed RR therefore cannot exceed 1.315 and yet achieve an upper 1-sided 97.5% CL ≤ 2.0. This corresponds to observing event rates for ICS versus ICS/LABA combination not more disparate than 0.65% versus 0.85% respectively, for an absolute risk difference of 0.20% with an upper CL of 0.51%. This means that to conclude non-inferiority, the observed excess risk on ICS/LABA combination cannot be greater than 2.0 events in 1000 and the upper CL will rule out, at worst, an excess risk of 5.1 events per 1000 treated with ICS/LABA per 6 month's period.

12.4 Data monitoring committee

This study will be conducted under the supervision of a JOSC and an independent JDMC. The composition and scope of these committees will be described in their respective charters. Both committees will be shared with other LABA Sponsor companies planning studies with the same objective.

In addition to the two committees mentioned above, each LABA Sponsor company will have a independent TDMC whose main role is to monitor possible events that will trigger a meeting of the JDMC. Representatives from each pharmaceutical company's TDMC will be members in the JDMC. The composition and detailed scope of the independent TDMC will be described in a charter.

12.4.1 Joint Adjudication Committee

An external, independent, blinded JAC will be appointed jointly by the sponsors and the academic leadership of the study.

The JAC will adjudicate all the primary safety endpoints: deaths, intubations and hospitalizations and assess for asthma relatedness. A charter will be prepared to detail precise responsibilities and procedures applicable for the JAC.

12.4.1.1 Study termination guidelines due to interim analysis results

When 50% of the total number of events has been accrued for the primary endpoint (ie, at 44 events), an interim analysis will be performed, see Section 12.2.2. In addition, asthma-related deaths will be monitored. Formal stopping regulations will be detailed in the independent JDMC charter.

13 IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

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

In the case of a medical emergency the investigator should contact the local study team leader/monitor, shown below. If the local study team leader/monitor is not available, the local study physician or the local team Patient Safety physician/representative at the Marketing Company should be contacted. As a secondary option, contact the clinical study team at AstraZeneca R&D, shown below.

Name	Role in the study	Address & telephone number
	Study Team Leader responsible for the protocol at central R&D site	
	ST Physician responsible for the protocol at central R&D site	
State local contact persons below: Local contact persons can be added in wet-inc above.		

13.2 Overdose

13.2.1 Background

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

13.2.2 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 ICS, systemic corticosteroids effects may appear if used chronically in excessive doses.

There is limited clinical experience regarding overdosage with inhaled formoterol. An overdose would likely lead to effects that are typical of β_2-agonists such as tremor, headache and palpitations. Symptoms and signs reported with formoterol from isolated cases are tachycardia, hyperglycaemia, hypokalaemia, prolonged QTc-interval, arrhythmia, nausea and vomiting.

Experience with other β_2-agonists has shown that overdoses may also cause restlessness, irritability, excitation, somnolence, convulsions and hyper- or hypotension. Metabolic effects may include acidosis and in serious cases, possibly rhabdomyolysis and renal failure.

13.2.3 Treatment suggestions

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

13.2.4 Procedures for reporting

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

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

If an overdose on an AstraZeneca study drug occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives **within**

one day, ie, immediately but no later than **the end of the next business day** of when he or she becomes aware of it.

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

For overdoses associated with SAE, standard reporting timelines apply, see Section 6.4.4. For other overdoses, reporting should be done within 30 days.

13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

13.3.1 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 pMDI 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 with Symbicort Turbuhaler do not indicate an increased risk when used during pregnancy.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the 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 investigators or other site personnel inform appropriate AstraZeneca representatives **within one day** ie, immediately but no later than the **end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs, see Section 6.4.4 and within 30 days for all other pregnancies. The outcome of the pregnancy should be reported as soon as it is known.

The same timelines apply when outcome information is available.

The PREGREP module in the CRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

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AstraZeneca

Revised Clinical Study Protocol

Drug Substance	Symbicort® pMDI
Study Code	D5896C00027
Edition Number	3

A 26 week, randomized, double-blind, parallel-group, active controlled, multicenter, multinational safety study evaluating the risk of serious asthma-related events during treatment with Symbicort®, a fixed combination of inhaled corticosteroid (ICS) (budesonide) and a long acting β_2-agonist (LABA) (formoterol) as compared to treatment with ICS (budesonide) alone in adult and adolescent (≥12 years of age) patients with asthma

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

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

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

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

PROTOCOL SYNOPSIS

A 26 week, randomized, double-blind, parallel-group, active controlled, multicenter, multinational safety study evaluating the risk of serious asthma-related events during treatment with Symbicort®, a fixed combination of inhaled corticosteroid (ICS) (budesonide) and a long acting β_2-agonist (LABA) (formoterol) as compared to treatment with ICS (budesonide) alone in adult and adolescent (≥12 years of age) patients with asthma

International Co-ordinating Investigator

Study centre(s) and number of patients planned

Based on initial feasibility, this study is planned to be conducted at approximately 700 centres in approximately 25 countries. Each site is planned to recruit an estimated 12-20 patients. Eleven thousand seven hundred (11 700) male and female patients will be randomized, whereof 10 to 12% will be adolescents (from 12 years up to and including 17 years). To reach this goal, it is projected that about 14 500 patients will need to be enrolled. This study will recruit patients worldwide. A minimum of twenty percent of the patients will be recruited in the US.

Study period	Phase of development
	III/IV

Objectives

Primary:

To evaluate the risk of serious asthma related events during treatment with Symbicort® pMDI or budesonide pMDI alone over a 26-week treatment period in adult and adolescent patients with asthma.

Secondary:

To evaluate the efficacy of Symbicort pMDI compared to budesonide pMDI alone over a 26-week treatment period in adult and adolescent patients with asthma.

Exploratory objective

To collect and store deoxyribonucleic acid (DNA) samples for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to Symbicort and/or budesonide; and/or susceptibility to, progression of and prognosis of asthma.

All patients will be asked to participate in the exploratory genetic research. Participation is optional. If a patient declines to participate there will be no penalty or loss of benefit. The patient will not be excluded from any aspect of the main study.

Study design

This is a 26 week, randomized, double-blind, parallel-group, active-controlled, multi-centre, multinational study evaluating the risk of serious asthma-related events during long term treatment with Symbicort pMDI and budesonide pMDI.

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 1 year prior to Visit 1 who are either currently treated with ICS/LABA combination or not adequately controlled on a long-term asthma control medication or whose disease severity warrants initiation of treatment with ICS/LABA.

Patients should have experienced at least one, but not more than 4 exacerbations within the previous year but none within 4 weeks prior to Visit 2.

Investigational product, dosage and mode of administration

- Symbicort HFA pMDI, budesonide/formoterol, 80/4.5 μg x 2 actuations bid, for oral inhalation
- Symbicort HFA pMDI, budesonide/formoterol, 160/4.5 μg x 2 actuations bid, for oral inhalation

Comparator, dosage and mode of administration

- Budesonide HFA pMDI 80 µg x 2 actuations bid, for oral inhalation
- Budesonide HFA pMDI 160 µg x 2 actuations bid, for oral inhalation

Rescue Therapy (for oral inhalation)

Albuterol pMDI (US) administered as 90 µg x 2 actuations and salbutamol pMDI (outside US) 100 µg x 2 actuations, as needed, for relief of bronchospasm.

Duration of treatment

This study starts with information visit (Visit 1) where inclusion and exclusion criteria will be reviewed, informed consent obtained and concomitant medication reviewed. A patient who does not fulfil the study eligibility criteria may be re-screened (checked for eligibility criteria) after at least 4 weeks, but only once per calendar year. Eligible patients will be randomized at the following visit (Visit 2). Patients will then enter a 26 weeks double-blind period. All patients will be followed up for the full 26 weeks intended treatment period for the primary endpoint irrespective of early cessation of randomized treatment (Intention To Treat approach).

Outcome variables:

Primary outcome variables

The primary outcome variable is a composite safety endpoint of serious asthma events:

- Asthma-related deaths
- Asthma-related intubations
- Asthma-related hospitalizations

Other safety assessments are serious adverse events (SAEs) and discontinuation of treatment with investigational product due to adverse event (DAEs) and/or discontinuations due to asthma exacerbations.

Primary efficacy variable

- Asthma exacerbations, defined as a deterioration of asthma requiring systemic corticosteroids (tablets, suspension, or injection) for at least 3 days or an inpatient hospitalization or emergency room visit due to asthma that required systemic corticosteroids

Secondary efficacy variables

- Healthcare utilization for asthma: Telephone contact with study doctor, Telephone contact with other physician or healthcare provider, Unscheduled or unplanned visit to study doctor (including home visits), Unscheduled or unplanned visit to other

physician or healthcare provider (including home visits), Emergency department or hospital (<24 hrs), Hospital admission or Emergency Department (≥24 hrs)

- Days (a part of a day will be counted as a full day) of school or work missed due to asthma
- Rescue medication use
- Asthma symptoms
- Asthma symptoms leading to activity limitations
- Nights with awakening(s) due to asthma
- Assessment of current asthma control by Asthma Control Questionnaire (ACQ) at clinic visits

This study will be conducted under the supervision of a Joint Oversight/Steering Committee (JOSC). An independent trial data monitoring committee (TDMC) will be responsible for monitoring the primary safety variable for the study but also all other aspects of safety in the study. In addition a joint data monitoring committee (JDMC) will monitor pooled data, focused on asthma related mortality, across the 4 separate LABA trials. The composition and detailed scope of these committees are described in their respective charters.

Statistical methods

For the time to event variables, a Cox proportional hazards model with terms for randomized treatment and strata for incoming control/asthma treatment will be used to compare Symbicort and budesonide. Hazard ratios and 95% confidence intervals will be provided. Patients who complete the 26-week follow-up period without experiencing any event as defined by the component in the primary endpoint will be censored at 26 weeks. Any patients without an event who are lost to follow-up prior to 26 weeks will be censored at the time of the last assessment of the status of the components of the primary endpoint. For the primary endpoint the following hypothesis will be tested at the 2.5%, 1-sided significance level,

- H_0: Hazard ratio ≥2.0 versus H_1: Hazard ratio <2.0

If the null hypothesis is rejected then a 2.0-fold increase in risk is ruled out.

A subsidiary analysis, excluding events occurring 7 days after the last dose of randomized treatment for discontinued patients, will be performed in the same manner as the primary analysis.

A formal interim analysis will be performed once half of the required number of primary endpoint events has been achieved. Consideration will be given to early stopping, if the p-value for the HR is extreme, p≤0.0001 (1-sided), z-value ≥3.7, using the Haybittle-Peto rule so that the alpha level in the final analysis is largely unaltered at 0.0249 1-sided.

SAEs and DAEs will be summarized and evaluated descriptively.

Sample size

The incidence rate on ICS alone, based on Symbicort studies with a similar population, SD-039-0668 and SD-039-0673, is estimated to be 15 events per 1000 per treatment years. To rule out 2 fold increase in the event rate with ICS/LABA combination versus ICS alone, equating to an increase from 1.5% to 3.0% per year, or from 0.75% to 1.5% per 6 months, 87 events are required. Assuming a 6-month study, an approximate linear incidence rate over time, and using 90% power, this requires a total of 11664 patients to be randomized.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this clinical study protocol.

Abbreviation or special term	Explanation
ACM	Actuation Counter Module
ACQ	Asthma Control Questionnaire (ACQ6 will be used, see Section 6.3.2)
AE	Adverse Event (see definition in Section 6.4.1)
ANCOVA	Analysis of covariance
ATS	American Thoracic Society
Bid	Twice daily
DMC	Data Management Centre
CYP	Cytochrome P
DAE	Discontinuation of investigational product due to adverse event
eCRF	electronic Case Report Form
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
EoT	End of Treatment
ER	Emergency Room
Event Adjudication Package	All available relevant data and documentation of an event; eCRF, ePRO responses, clinical summaries, diagnostic tests, death certificates, autopsy reports
FDA	(United States) Food and Drug Administration
GCP	Good Clinical Practice
HFA	Hydrofluoralkane
HFA-227	Propellant HFA-227
IB	Investigators' brochure
ICH	International Conference on Harmonisation
ICS	Inhaled glucocorticosteroids
International Co-ordinating Investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the investigator co-ordinating the investigators and/or activities internationally
IP	Investigational Product
IRB	Institutional Review Board
IVRS	Interactive Voice Response System (ePRO)

Abbreviation or special term	Explanation
IVRS/IWRS	Interactive Voice Response System/Interactive Web Response System (handle and distribute Investigational Product)
JAC	Joint Adjudication Committee (responsible for adjudication of all the primary safety endpoints: deaths, intubations and hospitalizations and assess for asthma relatedness)
JAC Charter	A brief overview of the adjudication methodology and procedures
JAC Operations Manual	Details the specific operations and logistics of the individual entities involved
JDMC	Joint Data Monitoring Committee (responsible to monitor adjudicated and confirmed primary events related from all four sponsor's clinical studies with an independent, unbiased input to the decision process)
JOSC	Joint Oversight/Steering Committee
LABA	Long-acting β_2-agonist
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
NAEPP EPR 3	National Asthma Education and Prevention Program Expert Panel Report 3
PEF	Peak expiratory flow
PGx	Pharmacogenetic research
PI	Principal Investigator
pMDI	pressurized Metered-Dose Inhaler
PRO	Patient Reported Outcome
SABA	Short-acting β_2-adrenoceptor agonist
SAE	Serious Adverse Event (see definition in Section 6.4.2).
SPC	EU Summary of Product Characteristics
TDMC	Trial Data Monitoring Committee (responsible for monitoring SAEs and possible events that will affect safe conduction of this study)
WBDC	Web Based Data Capture

1. INTRODUCTION

1.1 Background

Symbicort® pressurized metered-dose inhaler (pMDI) combines two drugs, budesonide, an inhaled glucocorticosteroid (ICS), and formoterol fumarate dihydrate (formoterol), a long-acting β_2-agonist (LABA), as a fixed-combination product. Budesonide is a corticosteroid indicated in the treatment of underlying airway inflammation in asthma and thus provides overall control of the disease. Formoterol is a bronchodilator with rapid onset of effect and a long duration of action. In the US, Symbicort is indicated for use in the treatment of asthma in patients 12 years and older.

Following the December 2008 Food and Drug Administration (FDA) Advisory Committee and based on an internal review of data, FDA continued to have outstanding questions on whether the addition of a LABA to an ICS increases the risk of asthma related serious adverse events (SAEs). During 2010, FDA issued external communications to consumers and healthcare professionals (HCPs) regarding LABA-containing products. The FDA requested all manufacturers of LABA-containing products indicated for the treatment of asthma to undertake the following: class-labelling changes and the conduction of a post-marketing safety study.

1.2 Research hypothesis

The addition of formoterol to budesonide is non-inferior to budesonide therapy alone in terms of the risk of serious asthma related events. This hypothesis will be assessed by Cox regression analysis of time to first serious asthma related event with terms for randomised treatment and strata for incoming asthma treatment/asthma control. If the resulting upper CL estimate for the relative risk is <2.0, then non-inferiority will be concluded.

1.3 Rationale for conducting this study

Several studies in adults and adolescents, such as FACET (Pauwels et al 1997) and GOAL (Bateman et al 2004), have demonstrated that the addition of LABA to an ICS improves several aspects of asthma control, such as improving lung function and current control of asthma symptoms as well as reducing the risk of asthma deteriorations requiring treatment with systemic corticosteroids (CS). Conversely, some studies have shown that LABAs when used alone may increase the risk of asthma-related death and other serious asthma outcomes. A 28-week placebo-controlled study with salmeterol showed an increase in asthma related deaths in salmeterol versus placebo treated patients (Nelson et al 2006).

Using specific portions of data sets provided by Glaxo Smith Kline, Novartis and AstraZeneca, a recent meta-analysis conducted internally by the FDA suggested a potential risk of serious asthma outcomes (a composite endpoint defined as asthma-related hospitalizations, intubations and deaths) with the addition of a LABA to an ICS, particularly in certain populations (FDA Division Memorandum and Briefing Book, February 2010).

The interpretation of all these data is difficult due to the diversity in power, studies, populations, treatments, and endpoint selection. Although the efficacy of combination products and their ability to improve multiple asthma control measures have been substantiated, it remains unclear whether the incidence of serious asthma events may be affected by the addition of a LABA to an ICS.

This study has been designed to evaluate whether the addition of formoterol to budesonide maintenance therapy increases the incidence of serious asthma related events compared to budesonide during a 26-week treatment period in patients with persistent asthma.

Similar brand specific studies will be performed by the other manufacturers (Sponsors) of LABAs that have an indication for asthma. The AstraZeneca study and other Sponsor specific studies will be conducted concurrently.

1.4 Benefit/risk and ethical assessment

The treatment arms in this study are identical to active-treatment arms in previous Symbicort pMDI studies evaluating the recommended doses of Symbicort in the US. Patients treated in the budesonide-only arm will derive benefit from treatment with ICS medication consistent with standard medical practice. The risk/benefit profile is therefore considered to be appropriate in both treatment arms. Patients will be followed at least on a monthly basis by the research site, either by monthly clinic visits or monthly telephone contacts. Unstable asthma will be assessed between study visits on a daily basis via telephone calls to the Interactive Voice Response System (IVRS). The Investigator will receive an electronic alert to contact patients with unstable asthma. Patients in need of treatment due to an exacerbation can obtain additional medication while remaining on randomized treatment. There are no significant ethical concerns.

2. STUDY OBJECTIVES

2.1 Primary objective

To evaluate the risk of serious asthma related events during treatment with Symbicort pMDI or budesonide pMDI alone over a 26-week treatment period in adult and adolescent patients with asthma.

The primary outcome variable is a composite safety endpoint of serious asthma events:

- asthma-related deaths, see Section 6.4.5.1
- asthma-related intubations, see Section 6.4.5.2
- asthma-related hospitalizations, see Section 6.4.5.3

Other safety assessments are SAEs and discontinuation of treatment with investigational product due to adverse event (DAEs) or discontinuations due to asthma exacerbations.

2.2 Secondary objectives

To evaluate the efficacy of Symbicort pMDI compared to budesonide pMDI alone over a 26-week treatment period in adult and adolescent patients with asthma. The variables for this objective will include:

Primary efficacy endpoint:

- Asthma exacerbations, defined as a deterioration of asthma requiring systemic corticosteroids (tablets, suspension, or injection) for at least 3 days or an inpatient hospitalization or emergency room visit due to asthma that required systemic corticosteroids, see Section 6.3.1.1

Secondary efficacy endpoint:

- Healthcare utilization for asthma: Telephone contact with study doctor, Telephone contact with other physician or healthcare provider, Unscheduled or unplanned visit to study doctor (including home visits), Unscheduled or unplanned visit to other physician or healthcare provider (including home visits), Emergency department or hospital (<24 hrs), Hospital admission or Emergency Department (≥24 hrs). Hospitalizations will be collected with the SAE reports
- Days (a part of a day will be counted as a full day) of school or work missed due to asthma, see section 6.3.1.2
- Rescue medication use, see Section 6.3.1.2
- Asthma symptoms, see Section 6.3.1.2
- Asthma symptoms leading to activity limitations see Section 6.3.1.2
- Nights with awakening(s) due to asthma, see Section 6.3.1.2
- Assessment of current asthma control by the Asthma Control Questionnaire (ACQ), see Section 6.3.2

2.3 Exploratory objective

To collect and store deoxyribonucleic acid (DNA) samples for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to Symbicort and/or budesonide; and/or susceptibility to, progression of and prognosis of asthma.

3. STUDY PLAN AND PROCEDURES

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

3.1 Overall study design and flow chart

This is a 26 week, randomized, double-blind, parallel-group, active-controlled, multi-centre, multinational study evaluating the risk of serious asthma-related events during long term treatment with Symbicort pMDI and budesonide pMDI in adult and adolescent (≥12 years) patients either currently treated with ICS/LABA combination or with asthma not adequately controlled on a long-term asthma control medication or whose disease severity warrants initiation of treatment with ICS/LABA.

This study will be conducted at approximately 700 centres in approximately 25 countries. Each site will recruit an estimated 12-20 patients. Eleven thousand seven hundred (11 700) male and female patients will be randomized, whereof 10 to 12% will be adolescents (from 12 years up to and including 17 years). To reach this goal, it is projected that about 14 500 patients will need to be enrolled. This study will recruit patients worldwide. A minimum of twenty percent of the patients will be recruited in the US.

All potentially suitable patients will attend the enrolment assessment (Visit 1). Informed consent and paediatric assent (if applicable) will be signed. At Visit 2, patients who fulfil the inclusion criteria and none of the exclusion criteria will be randomized. A patient who does not fulfil the study eligibility criteria may be re-screened (checked for eligibility criteria) after at least 4 weeks, but only once per calendar year. If a patient is re-screened, 3 months or later, after the last signing of the ICF, the patient needs to re-consent to the study.

Eligible patients will be stratified (at Visit 2) to one of the two dose levels of Symbicort/budesonide based upon assessment of ACQ and prior therapy, see Section 5.2.1. Patients will thereafter be randomized to Symbicort or budesonide treatment arms and enter a 26 week treatment period. Both stratification and randomization will be communicated to site personnel utilizing an Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS).

Dose levels:

- Symbicort pMDI 80/4.5 µg x 2 actuations bid (morning and evening), or Budesonide pMDI 80 µg x 2 actuations bid (morning and evening)

- Symbicort pMDI 160/4.5 µg x 2 actuations bid (morning and evening), or Budesonide pMDI 160 µg x 2 actuations bid (morning and evening)

Patients will be provided with albuterol pMDI (US), administered as 90 µg, 2 actuations or salbutamol pMDI (outside US), administered as 100 µg, 2 actuations as needed, for use as

rescue medication. Patients that use more than 1 canister of rescue medication per month should be retrained and counselled according to the investigator's judgement.

During the treatment period, patients will attend 3 scheduled visits to the clinic (Visits 3, 5 and End of Treatment (EoT)), see Section 6.2.2. Study personnel will contact the patients monthly by telephone between scheduled visits, see Section 6.2.3. An unscheduled visit may be conducted as a result of the telephone contact.

Patients will record missed days of work/school, rescue medication use, asthma symptoms, ability to perform daily activities and night time awakenings in a daily diary by using a telephone to access the IVRS. The patient and, if applicable, the patient's parent/legal guardian will be trained by the investigational team and also supplied with written instructions on how to enter data and where to turn if problems occur. A reminder about intake of study medication will be given in connection to the IVRS call.

The clinical assessment should include a regular review (in connection with clinic and telephone visits) of patient data available in IVRS. Investigators should assess the patient's clinical status and make a decision as to the need for treatment with systemic corticosteroids. The study personnel are responsible to follow up on asthma related events and transfer all relevant information according to the electronic Case Report Form (eCRF) instructions and any indications of SAEs to the eCRF.

In case the patient fulfils any of the criteria for unstable asthma, see Section 6.2.5, an alert in the IVRS will trigger the responsible investigator to contact the patient for further instructions.

At the conclusion of the double blind treatment period or at discontinuation, patients will undergo study procedures (EoT visit) and be placed on appropriate asthma maintenance therapy based on investigators judgement. There will be a telephone contact 7 days post EoT visit to collect any SAEs and concomitant medication information (only collected in relation to an SAE or asthma exacerbation).

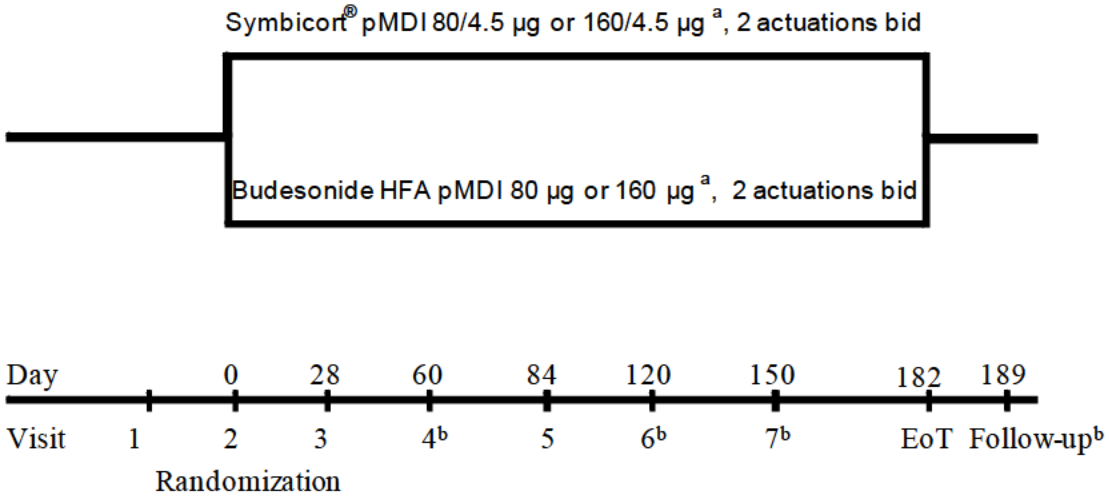
For information regarding discontinuation due to asthma exacerbations, see Section 5.8.

The study will include exploratory objectives include future pharmacogenetic research. All patients will be asked to participate in the genetic research. Participation is optional. If a patient declines to participate there will be no penalty or loss of benefit. The patient will not be excluded from any aspect of the main study.

This study will be conducted under the supervision of a Joint Oversight/Steering Committee (JOSC). An independent trial data monitoring committee (TDMC) will be responsible for monitoring the primary safety variable for the study but also all other aspects of safety in the study. In addition a joint data monitoring committee (JDMC) will monitor pooled data, focused on asthma related mortality, across the 4 separate LABA trials. The composition and detailed scope of these committees are described in their respective charters.

The study is diagrammatically shown in the Study flow chart (Figure 1). Study procedures are shown in Table 1.

Figure 1 Study flow chart



[a] Dose based on previous level of treatment and asthma control (see Table 3)
[b] Telephone contact
EoT = End of Treatment

Table 1 Study Plan

	Enrol-ment	Rando-mization	Treatment						Follow Up
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**EoT**	**Follow - up**
Telephone contacts				**X**		**X**	**X**		**X**
Day (+ visit window)		**0 (<15)**	**28(±3)**	**60(±3)**	**84(±3)**	**120(±3)**	**150(±3)**	**182(±3)**	**189(±3)**
Informed consent/assent (if applicable)	X [a]								
Informed consent and blood sample for exploratory genetics research (if applicable)		X[b]							
Inclusion/Exclusion criteria reviewed	X	X							
Demography	X								
Weight and height		X							
Physical examination		X							
Vital signs		X							
Medical history/Surgical history		X							
Asthma history		X							
Asthma exacerbation history		X							
Urine pregnancy test (as required)		X			X			X	
Peak expiratory flow (PEF)		X							
ACQ	X		X		X			X	
Randomization		X							
Concomitant medication assessment	X	X	X	X	X	X	X	X	X[c]

	Enrol-ment	Rando-mization	Treatment						Follow Up
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**EoT**	**Follow - up**
Telephone contacts				**X**		**X**	**X**		**X**
Day (+ visit window)		**0 (<15)**	**28(±3)**	**60(±3)**	**84(±3)**	**120(±3)**	**150(±3)**	**182(±3)**	**189(±3)**
Instruct/Remind patient of allowed/disallowed medications	X	X	X		X			X	
Check Potential Study Endpoints			X	X	X	X	X	X	X
Check asthma exacerbations			X	X	X	X	X	X	
Assessment of unstable asthma[d]			X	X	X	X	X	X	
Healthcare utilization			X	X	X	X	X	X	
Collect/dispense rescue medication (as needed)		X	X		X			X	
pMDI and ePRO training		X							
Collect/dispense study medication		X	X		X			X	
Dose actuation count [e]			X	X	X	X	X	X	
Review patients asthma status via IVRS			X	X	X	X	X	X	
SAE/DAE assessment	X	X	X	X	X	X	X	X	X

a If a patient is re-screened 3 months or later after the last signing of the ICF, the patient needs to re-consent to the study (ICF Supplement No 1), see section 8.4.
b Blood samples for DNA will be collected for exploratory genetics. Sampling is optional and subject to separate approval/consent. Sample will be taken at Visit 2 or if this day is not suitable, on any of the remaining planned visits the patient will attend.
c Only required for patients reporting an AE(s) that qualifies for an SAE.
d For definition of unstable asthma see Section 6.2.5.2
e See Section 5.7 for instructions regarding collection and recording of patient's compliance to dispensed study drug.

3.2 Rationale for study design, doses and control groups

The design of this 26 week, randomized, double-blind, active-controlled study comparing the safety of Symbicort pMDI 80/4.5 and 160/4.5 µg x 2 actuations bid to budesonide pMDI 80 and 160 µg x 2 actuations bid in adult and adolescent (≥12 years) patients currently treated with ICS/LABA combination or not adequately controlled on a long-term asthma control medication or whose disease severity warrants initiation of treatment with ICS/LABA, was chosen to specifically examine the effect of administration of formoterol with budesonide, as Symbicort pMDI, compared to budesonide alone.

Ethical conduct of the study will be ensured through site surveillance of patient asthma status using alerts in IVRS, a once daily reminder about intake of study medication, monthly contacts with patients and patient withdrawal criteria.

4. PATIENT SELECTION CRITERIA

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

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.

4.1 Inclusion criteria

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

1. Provision of signed informed consent/ paediatric assent (if applicable) prior to any study specific procedures including medication withdrawal. NB: Patients agreeing to participate in the optional exploratory genetic research must provide a separate informed consent.

2. Male or Female, ≥12 years of age

3. Documented clinical diagnosis of asthma as defined by national and international asthma guidelines (ie, NAEPP EPR-3 2007, GINA, ATS/ERS etc) for at least 1 year prior to Visit 2

4. Patient must have history of at least 1 asthma exacerbation including one of the following:

   – requiring treatment with systemic corticosteroids (tablets, suspension, or injectable) between 4 weeks and 12 months prior to randomization

   – an asthma-related hospitalization (defined as an inpatient stay or >24 hour stay in observation area in ER or other equivalent facility depending on the country and healthcare system) between 4 weeks and 12 months prior to randomization

NB: Investigators must use appropriate means to ensure the accuracy of the subject's exacerbation history (eg, patient history, pharmacy records, hospital records, or chart records, etc).

5. Current Asthma Therapy: Patients must be appropriately using one of the following for the treatment of asthma and meet the criteria outlined below:

   – ICS, ICS/LABA combination, or ICS/LTRA combination, or ICS plus other maintenance therapy(ies) for at least 4 weeks prior to randomization. The dose of ICS must have been stable for at least 4 weeks prior to randomization. Any subject maintained on a stable high dose ICS with or without a LABA or LTRA or other maintenance therapy(ies) must have an ACQ6 <1.5 at Visit 1 (see Table 2)

Table 2 Estimated Daily Dosage for ICS

Asthma Therapy	**Total Daily Dose (µg/day)**		
Inhaled Corticosteroid	**Low**	**Medium**	**High**
Beclomethasone dipropionate non-HFA inhalers	200 to 500	>500 to 1000	>1000-2000
Beclomethasone dipropionate HFA[a]	80 to 250	>250 to 500	>500
Ciclesonide	80 to 160	>160 to 320	>320 - 1280
Triamcinolone acetonide	400 to 1000	>1000 to 2000	>2000
Flunisolide	500 to 1000	>1000 to 2000	>2000
Fluticasone propionate non-HFA inhalers	100 to 300	>300 to 500	>500 - 1000
Fluticasone propionate HFA[b]	88 to 264	>264 to 460	>460
Budesonide	200 to 400	>400 to 800	>800-1600
Mometasone furoate	200 to <400	≥400 to 800	>800

a HFA formulations of beclomethasone dipropionate with extra-fine particles which increase lung deposition and thereby the potency of the compound. Note: An exception is Clenil Modulite®, which is an HFA inhaler without increased potency and therefore should be considered similar to Beclomethasone non-HFA inhalers when evaluated.

b Doses refer to the delivered dose of fluticasone propionate, but in some countries (e.g. Argentina, the Philippines and Slovakia) labels state the metered dose. In the latter cases, please use the dose estimates for fluticasone popionate non-HFA inhalers.

- Leukotriene receptor antagonist (ie LTRAs such as montelukast, zafirlukast, or pranlukast) OR xanthines (eg theophylline) as monotherapy at a stable dose for at least 4 weeks prior to randomization. Patients on LTRAs, or xanthines, are eligible only if they record an ACQ score of ≥1.5 and in the investigator's clinical judgement, the patient's asthma severity could justify treatment with ICS or ICS/LABA combination

- Daily SABA in the 4 weeks prior to randomization but not more than 8 puffs a day on 2 consecutive days, or ≥25 puffs in one day, in the 7 days prior to Visit 1. Patients on daily SABA are eligible only if they record an ACQ score of ≥1.5 and in the investigator's clinical judgement, the patient's asthma severity could justify treatment with ICS or ICS/LABA combination

6. Availability and ability to perform the necessary manoeuvres and procedures required by the study (eg, read the ACQ6 questionnaire, use a pMDI, perform daily telephone calls)

4.2 Exclusion criteria

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

1. Has a history of life-threatening asthma. Defined for this protocol as an asthma episode that required intubation and/or was associated with hypercapnea requiring non-invasive ventilatory support

2. Has required treatment with systemic corticosteroids (tablets, suspension, or injectable) for any reason within 4 weeks prior to Visit 2

3. Has an ongoing exacerbation, defined as a worsening of asthma that requires treatment with systemic corticosteroids (tablets, suspension, or injectable)

4. Asthma exacerbation:

   - Any asthma exacerbation requiring systemic corticosteroids (tablets, suspension or injection) within 4 weeks of randomization or more than 4 separate exacerbations in the 12 months preceding randomization. For exacerbations to be considered separate events there must be at least 7 days from the resolution of one exacerbation to the start of the second exacerbation

   NB: Investigators should use clinical judgement and consider the subject's history of exacerbation, including the severity and interval since the last exacerbation per current clinical guidelines, in determining whether a subject with multiple exacerbations in the prior year should be enrolled in the study.

   Asthma hospitalizations:

- More than 2 hospitalizations (defined as an inpatient stay or >24 hour stay in observation area in ER or other equivalent facility depending on the country and healthcare system) for treatment of asthma in the 12 months preceding randomization. Each hospitalization must be separated by >7 days to be considered an individual event

5. Has a respiratory infection or other viral/bacterial illness, or is recovering from such an illness at the time of Visit 2 that, in the investigator's opinion, will interfere with the patient's lung function

6. Unstable asthma status: Patients must not meet the following unstable asthma severity criteria within 7 days prior to randomization:

   - Asthma symptoms that persisted throughout the day on 2 consecutive days
   - Nighttime awakening due to asthma during 3 or more nights
   - Rescue medication use for the acute worsening of asthma symptoms >8 inhalations a day over 2 consecutive days or 25 inhalations or more in one day
   - Asthma symptoms so severe that the patient was limited in their ability to perform normal daily activity

7. Peak expiratory flow (PEF) (can be either pre- or post-bronchodilatory) that is <50% of predicted normal, according to regional guidelines, at Visit 2. Percent predicted PEF values must be calculated using NHANES III with relevant equations that adjust for race and national origin (Hankinson et al 1999, Hankinson et al 2010)

8. Has any clinically relevant abnormal findings in physical examination or vital signs at Visit 2, which, in the opinion of the investigator, may put the patient at risk because of his/her participation in the study

9. Pregnancy, breast-feeding or planned pregnancy during the study; fertile females not using acceptable contraceptive measures, as judged by the investigator.

10. Had a malignancy (except basal cell carcinoma) within the past 5 years

11. Any significant disease or disorder that, in the opinion of the investigator, may either put the patient at risk because of participation in the study, or influence the results of the study, or the patient's ability to participate in the study

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

13. Has participated, and received treatment, in one of the other LABA Sponsor studies investigating the safety of the addition of LABA to ICS (ie, a safety study

comparing the use of ICS to ICS/LABA combination sponsored by other LABA Sponsor companies). Has participated, and received treatment, in another interventional or investigational drug study within 4 weeks prior to Visit 2 and/or previous randomisation to treatment in the present study. Patients are not allowed to participate in other studies during the conduct of this study

14. A smoking history of >10 pack years (1 pack year = 20 cigarettes smoked per day for 1 year) at Visit 1

15. Has a diagnosis of chronic obstructive pulmonary disease, chronic bronchitis, emphysema, idiopathic pulmonary fibrosis, bronchiectasis, and/or any pulmonary disease which may diversely affect the outcome of the study

16. Requires treatment with any β-blocker (including eye drops) during the course of the study

17. Planned hospitalisation during the study

18. Has conditions associated with poor compliance, or alcohol or drug abuse

19. Has taken omalizumab or any other monoclonal or polyclonal antibody therapy, for any reason within the 6 months prior to Visit 2

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

21. Planned donation of blood during the study

Additional exclusion criteria for exploratory genetic research are detailed in Appendix D. Procedures for withdrawal of incorrectly enrolled patients see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

The investigator should be familiar with and comply with all applicable information regarding concomitant medications in the prescribing information and/or Investigators' brochure (IB) for the study medications.

5.2 Patient enrolment and randomisation

The Principal Investigator will:

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

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

3. Determine patient eligibility, see Sections 4.1 and 4.2

4. Assign eligible patient unique randomisation code (patient number) at Visit 2

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

A patient who does not fulfil the study eligibility criteria may be re-screened (checked for eligibility criteria) after at least 4 weeks, but only once per calendar year. If a patient is re-screened, 3 months or later, after the last signing of the ICF, the patient needs to re-consent to the study. The patient and Investigator will sign the ICF Supplement before any further study procedures are performed.

5.2.1 Procedures for randomisation

An IVRS/IWRS will be utilised to enrol patients into the study, and to communicate the patient's randomisation code and which investigational product should be dispensed at Visit 2 and subsequent visits. The site will receive a facsimile confirming each communication from the IVRS/IWRS. Detailed instruction on use of the IVRS/IWRS will be provided to the Investigational sites.

The randomization codes will be computer generated by AstraZeneca R&D or representative using GRand (AZ Global Randomization system) using balanced blocks and allowing an approximately equal number of patients per treatment group within each centre. The randomization codes will be loaded into the IVRS/IWRS database. As they become eligible, patients will be assigned to a treatment group in balanced blocks supplied to that centre in accordance with the randomisation scheme. Randomisation codes will be assigned strictly sequentially as patients become eligible for randomisation.

Symbicort/budesonide dose stratification will be determined by the investigator, based on the patient's current asthma treatment and level of asthma control as defined in Table 3. If patient's entering the study on more than one asthma controller medication, current clinical guidelines and physician judgment should also be considered for appropriate Symbicort/budesonide dose stratification.

Table 3 Treatment allocation 2 doses

Category	Incoming Asthma Control[a]	Incoming Asthma Treatment[b]	Randomized Treatment Assignment (µg BID)
A	ACQ-6 Total Score <1.5 (controlled)	Low dose ICS or Low-dose ICS + LABA or other adjunctive therapies	Symbicort pMDI 80µg/4.5 µg or budesonide pMDI 80µg
B		Med-dose ICS or Med-dose ICS + LABA or other adjunctive therapies	Symbicort pMDI 160µg/4.5 µg or budesonide pMDI 160µg
C		High-dose ICS or High-dose ICS + LABA or other adjunctive therapies	
D	ACQ-6 Total Score ≥1.5 (not well controlled)	SABA[c] LTRA[c] Theophylline[c]	Symbicort pMDI 80µg/4.5 µg or budesonide pMDI 80µg
E		Low-dose ICS or Low-dose ICS + LABA or other adjunctive therapies	Symbicort pMDI 160µg/4.5 µg or budesonide pMDI 160µg
F		Med-dose ICS or Med-dose ICS + LABA or other adjunctive therapies	

a In general, a subject's ICS dose stratification is to be based on the ACQ-6 total score determined at the Screening Visit (Visit 1).

b A subject on SABA, LTRA or theophylline monotherapy are only eligible for study inclusion, if the ACQ¬6 Total Score ≥1.5 (not well controlled) and if in the judgment of the investigator, the subject's disease severity could warrant initiation of ICS ± LABA treatment. However, a subject maintained on a stable high dose ICS with or without adjunctive therapy (ie, LABA, LTRA or theophylline) must be controlled as measured by an ACQ-6 Total Score <1.5 in order to be randomized.

c Subjects classified as SABA or LTRA, or theophylline users consist of those subjects who have not used any other asthma controller medications for at least 4 weeks prior to the Screening Visit.

Study medication will be dispatched to the investigational sites, as needed, based on threshold values set by AstraZeneca.

5.3 Procedures for handling patients incorrectly enrolled or randomized

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

If a patient does not meet the selection criteria but is randomized in error or incorrectly started on treatment, a discussion should occur between the AstraZeneca Study Team Physician and the Investigator regarding whether to continue or discontinue the patient from treatment. Consistent with Intention-To-Treat (ITT) principles, all randomized patients should continue to be followed in the study (ie, attend protocol visits) and, unless treatment would be harmful,

patients should continue to receive study medication. Every effort must be made to ascertain all safety and efficacy events throughout the conduct of the study.

The AstraZeneca Study Team Physician is to ensure all such decisions are appropriately documented.

In situations where an agreement cannot be reached, the patient should have their study therapy stopped but continue with telephone follow-up.

If a patient does not fulfil the study eligibility criteria they may be re-screened after at least 4 weeks, but only once per calendar year.

Patients discontinuing the study prior to Visit 2 will be classified as screening failures.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

All study medication will be labelled using a unique medication identification number (Kit ID) that is linked to a treatment arm. IVRS/IWRS will assign the study medication to be dispensed to each patient at each drug-dispensing visit. Investigational products with equal strengths of the budesonide component, will appear identical and will also be presented in identical packaging to ensure blinding of the treatment arms.

5.4.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomisation for each randomized 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 centre. Patients and investigators are to remain blinded to the investigational products (Symbicort/Budesonide) used during the randomized treatment period. Investigators will select the appropriate dose stratum to which subjects are allocated based on control status and previous therapy. As such, they will be blinded to whether the subject is randomized to Symbicort or budesonide, but not the dose strata.

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

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities, and in exceptional cases, for other safety reasons. 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.

5.5 Treatments

5.5.1 Identity of investigational product(s)

The investigational products to be used in the study are described in Table 4.

Table 4 Identity of Investigational product

Product Name	Dosage form and strength	Manufacturer
Symbicort	pMDI (HFA) for oral inhalation with Actuation Counter Module (ACM), budesonide/formoterol 80µg/4.5 µg	AstraZeneca
Symbicort	pMDI (HFA) for oral inhalation with Actuation Counter Module (ACM), budesonide/formoterol 160µg/4.5 µg	AstraZeneca
Budesonide	pMDI (HFA) for oral inhalation with Actuation Counter Module (ACM), 80 µg	AstraZeneca
Budesonide	pMDI (HFA) for oral inhalation with Actuation Counter Module (ACM), 160 µg	AstraZeneca

Symbicort and budesonide pMDI units will be packed together with desiccant bags in sealed pouches and placed in cartons. Training pMDI units will be delivered in cartons together with bags of extra actuators.

5.5.2 Doses and treatment regimens

Upon qualification for randomisation at Visit 2, patients will be instructed to stop using asthma medication in accordance with Table 8 and will be assigned a randomisation code and the appropriate blinded study medication through IVRS/IWRS. Patients will be stratified to one of the two dose levels of Symbicort/budesonide, see Section 5.2.1. Patients will thereafter be randomized to Symbicort or budesonide treatment arms and enter a 26 week treatment period.

Dose levels:

- Symbicort pMDI 80/4.5 µg x 2 actuations bid (morning and evening), or Budesonide pMDI 80 µg x 2 actuations bid (morning and evening)
- Symbicort pMDI 160/4.5 µg x 2 actuations bid (morning and evening), or Budesonide pMDI 160 µg x 2 actuations bid (morning and evening)

AstraZeneca or a designated representative will provide all investigational products. At each visit, the patient will receive sufficient quantity of drug to last the duration of time between visits. The first dose should be taken at Visit 2. In the event the patient loses her/his drug, the

site should call into the IVRS/IWRS system in order to allow the system to determine the appropriate alternative kit ID(s) to be dispensed from the site's remaining inventory.

At Visit 2, the patients will be instructed on how to use the pMDI inhaler (see priming instructions). The patient will also receive written information on how the priming is done. Each site will be provided with sufficient training devices, placebo pMDI (HFA) for oral inhalation with Actuation Counter Module (ACM), manufactured by AstraZeneca. These devices will be used in the clinic only and will not be dispensed to the patients to take home. An assessment of inhalation technique will be made at Visit 2, followed by further instructions as needed. The training device contains excipients but no active ingredients.

Priming of the inhalers

The study drug and placebo pMDI will require priming when initially dispensed, if dropped or if not used for greater than 7 days.

Prepare the pMDI inhaler according to the following instructions:

- Shake well to mix the contents of the canister
- Remove the mouthpiece cover
- Hold the inhaler upright and press the top of the canister firmly to release a shot of medicine into the air
- Release your finger from the top of the canister to allow it to reset
- Wait for at least 10 seconds, and then repeat this procedure one more time
- The pMDI inhaler is now ready for use

5.5.3 Additional study drug

The rescue medications to be used in the study are described in Table 5.

Table 5 Rescue Medications

Investigational product	Dosage form and strength	Manufacturer
Albuterol (US)	pMDI for oral inhalation, 90 µg	Commercially Available
Salbutamol (non US)	pMDI for oral inhalation, 100 µg	Commercially Available

Patients will receive rescue medication at Visit 2 and throughout the study to be administered as needed for relief of bronchospasm. Patients that use more than 1 canister of rescue medication per month should be retrained and counselled according to the investigator's judgement. This medication is not to be used on a regularly scheduled basis.

5.5.4 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. These labels will be designed to meet country specific requirements and be translated into local language.

5.5.5 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label on the patient kits specifies the appropriate storage. Access must be restricted to authorized personnel. On each kit there will be an instruction illustrating its proper orientation, which must be adhered to.

The storage area must also have adequate control of temperature, in order to maintain stability and potency of study drug supplies. The clinical monitor will inventory the initial shipment of study drug supplies and will inspect study drug supplies during monitoring visits.

5.6 Concomitant and post-study treatment(s)

For allowed medications during the study, see Table 6 and Table 7. For disallowed medication during the study, see Table 8.

Table 6 Allowed asthma medication

Medications from Visit 2 and throughout study:	
–	Inhaled disodium cromoglycate or inhaled nedocromil sodium, if on treatment with these medications prior to Visit 2. The dose is to be kept stable during the treatment period.
–	Antitussives prn not containing ephedrine or other bronchodilators
–	Mucolytics not containing ephedrine
–	Nasal steroids
–	Albuterol/salbutamol as rescue medication. From Visit 2 onward, patients must use the study provided albuterol/salbutamol, which will be the only allowed rescue medication.
–	If receiving immunotherapy (desensitization), must be on a stable regimen for at least 4 weeks prior to Visit 2 and use a stable dose throughout the double blind treatment period

Table 7 Allowed medications to treat an asthma exacerbation (maximum 14 days)

Medications to treat an asthma exacerbation:
– ICS other than study medication only during hospitalisation/ER treatment
– Systemic corticosteroids (tablets, suspension or injections)
– Any short-acting β2-agonists other than study medication only during hospitalisation/ER treatment
– Leukotriene antagonists, 5-Lipoxygenase inhibitor, ephedrine, inhaled disodium cromoglycate or inhaled nedocromil sodium
– Inhaled anticholinergics only during hospitalisation/ER treatment
– Xanthines

Table 8 Disallowed asthma medications

DISALLOWED Medications prior to Visit 2
– Systemic corticosteroids (tablets, suspension or injections) within 4 weeks prior to Visit 2
– Omalizumab or any other monoclonal or polyclonal antibody therapy taken for any reason within 6 months prior to Visit 2

DISALLOWED Medications during the Randomized Treatment Period:
– ICS other than study medication[a]
– Systemic corticosteroids (tablets, suspension or injections)[b]
– Short-acting β2-agonists other than study medication[a]
– Long-acting β2-agonists
– Inhaled anticholinergics[a]
– Ephedrine-containing medication[b]
– β-blockers (including eye drops)
– Omalizumab or any other monoclonal or polyclonal antibody therapy for any reason
– Systemic treatment with potent Cytochrome P (CYP) 3A4 inhibitors (eg, ketoconazole)
– Leukotriene antagonists and 5-lipoxygenase inhibitors[b]
– Xantines[b]

a Except for treatment of an asthma exacerbation during hospitalisation/ER treatment, see Table 7.

b Except for treatment of an asthma exacerbation, see Table 7.

The investigator should be familiar with and comply with all applicable information regarding concomitant medication in the IB/prescribing information for the study drugs.

Other non-respiratory medication, which is considered necessary for the patient's safety and well being, may be given at the discretion of the investigator. The administration of all concomitant medication (excluding investigational products and rescue medications) must be recorded in the appropriate sections of the eCRF. Written informed consent/paediatric assent must be obtained prior to discontinuation of any asthma treatments at Visit 1. At the end of the treatment period, patients will resume appropriate asthma maintenance therapy.

5.7 Treatment compliance

Each patient is required to comply with the prescribed treatment regimen throughout the study. At Visit 2, the patients will be instructed on how to use a pMDI inhaler correctly. In order to ensure correct inhalation technique, training devices (pMDI) will be available at each study centre for instructional purposes as well as for patients to practice the correct inhalation technique. Instruction and practice should occur prior to dispensing blinded study medication. These devices will be used in the clinic only and will not be dispensed to patients for use at home.

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

The intake of study medication for each patient will be assessed through utilization of each inhaler's dose actuation counter in order to compare expected versus actual medication taken. Thus, only the start and stop number on each dose actuation counter should be recorded in the eCRF when patients return the inhalers after treatment.

Site staff will review study medication compliance with the patient at each scheduled study visit (Visits 3, 5 and EoT) and monthly telephone contacts and make a note in Medical records.

A daily reminder will also be addressed via IVRS. If the patient is not compliant, he or she will receive additional training on how to use the pMDI.

5.7.1 Accountability

The investigational products are to be dispensed only by the investigator or the sub-investigator(s). The study drug provided for this study will be used only as directed in the study protocol. The study personnel will account for all study drugs dispensed to and returned from the patient. If appropriate, drug storage, drug dispensing, and drug accountability may be delegated to the pharmacy section of the investigational site.

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

The investigator or designated study personnel are responsible for maintaining accurate dispensing records of the study drug. All study drugs must be accounted for, including study drug accidentally or deliberately destroyed. All discrepancies between amounts of study drug dispensed and amounts returned must be documented.

All study drug, including partially used or unused pMDI canisters and albuterol/salbutamol, is to be returned by patients. The clinical monitor will coordinate the return of drug supplies for proper disposal.

5.8 Discontinuation of investigational product

Patient, who is discontinued from investigational product, should continue in the study through 26 weeks and will be followed via telephone contact approximately every 4 weeks.

Patients may be discontinued from investigational product (IP) in the following situations:

1. Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment

2. Adverse Event

3. Severe non-compliance to study protocol

4. Pregnancy

5. Safety reasons as judged by the investigator and/or AstraZeneca

6. Intake of certain concomitant medications may necessitate withdrawal (see Section 5.6)

7. Experience of more than 1 asthma exacerbation within 13 weeks (during the randomized treatment period) or more than 2 asthma exacerbations within 26 weeks (during the randomized treatment period) will necessitate withdrawal. For definition of asthma exacerbations, see Section 6.3.1.1

8. A patient whose exacerbation is not responding to therapy in the judgment of the investigator or is not responding to 14 days of treatment with systemic corticosteroids

9. A patient requires intubation for asthma

10. A patient has an adverse event that would, in the investigator's judgement, make continued participation an unacceptable risk

Discontinuation of investigational product does not mean discontinuation of follow-up. Telephone contacts should be continued in all cases.

5.8.1 Procedures for discontinuation of a patient from investigational product

Patients who are discontinued from IP should always be asked to continue study procedures.

The patient should complete the EoT visit and then be followed through the 26-week treatment period via telephone contact approximately every 4-weeks, see Section 6.2.4.

A patient that decides to discontinue investigational product will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator(s). SAEs/DAEs will be followed up (See Sections 6.4.3 and 6.4.4) and all study drugs should be returned by the patient. This is also applicable for a patient that discontinues due to any study specific criteria.

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

5.8.2 End of Treatment

At the EoT visit, patients will be put on appropriate asthma maintenance medication as judged by the investigator.

5.9 Withdrawal from study

Patients are at any time free to withdraw from study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Withdrawal of consent must be ascertained and documented by the investigator in the eCRF as well as in the ICF (if applicable) and medical records. If possible, the ICF should be signed again and dated by both the patient and the investigator. Such patients will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator. SAEs/DAEs will be followed up (See Sections 6.4.3 and 6.4.4) and all study drugs should be returned by the patient.

Withdrawn patients will not be replaced.

At the time of withdrawal, patients should, if possible complete the EoT visit. To ensure validity of study data, it is very important to collect at least vital status (dead or alive). AstraZeneca or its delegate will therefore attempt to collect information on withdrawn patients or lost to follow-up patients from publicly available sources to determine the patient's vital status during the 26 weeks following randomization. If needed, the attempt to collect information will continue until the end of the study.

Every effort should be made to contact any patient lost to follow-up during the course of the study in order to complete assessments and retrieve any outstanding data, drug, or clinical supplies. These efforts should be recorded in the source documentation.

Patients who withdraw from the main study should always be asked specifically whether they are withdrawing or continuing their consent for the exploratory genetic research.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

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 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 eCRF. A copy of the completed eCRF will be archived at the study site.

Patients will record missed days of work/school, rescue medication use, asthma symptoms, ability to perform daily activities and night time awakenings in IVRS on a daily basis.

The patients will answer questions in a patient-reported outcome test (ACQ). ACQ will be administered on paper and recorded into the eCRF by investigator or delegate.

6.2 Data collection and enrolment

6.2.1 Screening and demographic measurements

6.2.1.1 Physical examination

A complete physical examination will be performed at Visit 2 and include an assessment of the following: general appearance, head, ears, nose, mouth, teeth, throat, neck, respiratory, cardiovascular, abdomen, and extremities.

6.2.1.2 Vital signs

Blood pressure and pulse rate measurements will be performed at Visit 2. Pulse rate (beats/min) will be measured over 30 seconds in a sitting position, after 5-minute rest. Systolic and diastolic blood pressure (mmHg) will be measured using a cuff appropriate for arm circumference.

6.2.1.3 Asthma exacerbation history

The assessment will include number of exacerbations during last year, the date of last exacerbation, and the type of exacerbation (oral steroid treatment, or hospitalization due to asthma).

6.2.1.4 Peak expiratory flow (PEF)

All sites will be provided with peak flow meters to standardize the measurements. Additional information and training will be provided outside this protocol. The guidelines published by ATS/ERS, should be followed for PEF measurements, as described below. A peak flow meter, which meets ATS standards, will be used.

PEF must be achieved as rapidly as possible and at as high a lung volume as possible, in order to obtain the maximum value. The neck should be in a neutral position, not flexed or extended, and the patient must not cough. A nose clip is not necessary.

The patient must perform a minimum of three PEF manoeuvres from total lung capacity.

The PEF values and their order must be recorded (source data only) so that manoeuvre-induced bronchospasm can be detected. If the largest two out of three acceptable blows are not reproducible within 0.67 L/s (40 L/min), up to two additional blows can be performed. If satisfactory repeatability has not been achieved in five attempts, more are not likely to be helpful. The largest value from at least three acceptable blows should be used to calculate the PEF predicted value.

At randomization, if the patient demonstrates a PEF < 50% predicted normal, he/she must not be randomized into the study**.** Percent predicted equations will be supplied separately.

6.2.1.5 Optional Exploratory genetic research

Blood samples will be collected at randomization from patients who volunteer to participate in the exploratory genetic research portion of this study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

Please refer to Appendix D for further details including blood volumes; instructions for sample handling, storage, destruction, and withdrawal of informed consent for exploratory genetic research; data protection and data management.

6.2.2 Data collection at the visits

The date when the patient signs and dates the ICF will be the Visit 1 date.

The following variables are to be collected in the eCRF at the different visits:

6.2.2.1 Visit 1

- Date of birth, sex and race
- Concomitant medication, see Section 5.6
- ACQ, see Section 6.3.2

6.2.2.2 Visit 2

- Height (measured in cm, with no shoes) and weight (in kg, with light clothes and no shoes)
- Physical examination, see Section 6.2.1.1
- Vital signs (pulse and blood pressure), see Section 6.2.1.2

- Medical and surgical history
- Asthma history
- Asthma exacerbation history, see section 6.2.1.3
- Urine pregnancy test, see Section 6.4.6
- PEF, see Section 6.2.1.4
- Concomitant medication, see Section 5.6
- SAE/DAE, see Section 6.4.2

6.2.2.3 Visit 3, 5 and EoT

- Urine pregnancy test (at visit 5 and EoT), see Section 6.4.6
- ACQ, see Section 6.3.2
- Concomitant medication, see Section 5.6
- Potential Study Endpoints, see Section 6.4.5
- Asthma exacerbations, see Section 6.3.1.1
- Assessment of unstable asthma, see Section 6.2.5
- Health care utilization, see Section 6.3.1.3
- Use of investigational product, recorded as dose actuation counter start and stop number for each inhaler when returned, see Section 5.7
- SAE/DAE, see Section 6.4.2

6.2.3 Telephone contacts (Visit 4, 6 and 7)

Telephone contacts will be performed between the visits, see Study Plan, Table 1. The following variables are to be collected:

- Concomitant medication, see Section 5.6
- Potential Study Endpoints, see Section 6.4.5
- Asthma exacerbations, see Section 6.3.1.1
- Assessment of unstable asthma, see Section 6.2.5

- Health care utilization, see Section 6.3.1.3
- SAE/DAE, see Section 6.4.2

6.2.4 Follow-up procedures

A follow-up telephone contact will be performed for:

- Patients that **completed** the 26 week treatment period
  - 7 days after EoT visit
- Patients that **discontinued IP** before 26 weeks
  - Every 4-weeks through the 26-week treatment period

The following variables are to be collected:

- Concomitant medication (only required for patients reporting an SAE(s), see Section 5.6
- Potential Study Endpoints, see Section 6.4.5
- SAE(s), see Section 6.4.2

6.2.5 Assessment of UNSTABLE asthma

6.2.5.1 Assessment of UNSTABLE asthma between scheduled telephone contacts and visits

In case the patient fulfils any of the criteria for unstable asthma, an alert in the IVRS will trigger the responsible investigator to contact the patient for further instructions. In addition, if at any time the patient feels that their asthma is deteriorating or in need of additional treatment they should be instructed to contact the study site.

Any of the following criteria will trigger an alert that the investigator should contact the patient for further instructions:

- ≥8 puffs/day of rescue medication for 2 consecutive days
- ≥25 puffs or more of rescue medication in one day
- Asthma symptoms that limited the patient's ability to perform normal daily activity on 2 consecutive days
- Missing school or work due to asthma ≥2 times in one week
- Nighttime awakening due to asthma ≥3 nights in one week

An unscheduled healthcare contact (including telephone calls to the clinic, home visit by physician and unscheduled clinic visits) for asthma should be recorded in source documentation and the eCRF. The investigator should review unstable asthma criteria with the patient and determine if a site visit is warranted. This assessment should include a review of patient data available in the IVRS. Additionally, the investigator should assess the patient's clinical status and determine whether to prescribe a course of systemic corticosteroids.

6.2.5.2 Assessment of UNSTABLE Asthma at scheduled telephone contacts and visits

Unstable asthma will be assessed at each scheduled study telephone call and in-clinic visit to determine if the patient meets the criteria for unstable asthma, see Section 6.2.5.1 and if so determine whether to prescribe systemic corticosteroids.

The assessment should include a review of patient data available in IVRS. Investigators should assess the patient's clinical status and determine whether to prescribe systemic corticosteroids.

6.3 Efficacy

6.3.1 Efficacy variables

6.3.1.1 Asthma exacerbations

Method of assessment

An asthma exacerbation is defined as deterioration of asthma requiring one of the following:

- the use of systemic corticosteroids (tablets, suspension, or injection) for at least 3 days
- an inpatient hospitalization
- an emergency room visit due to asthma that required systemic corticosteroids

Courses of corticosteroids separated by 1 week or more should be treated as separate asthma exacerbations. Unscheduled physician visits to the site or to an alternate care provider will not be considered an asthma exacerbation unless treatment with systemic corticosteroids treatment is initiated.

Please note: a single depo-injectable dose of corticosteroids will be considered the equivalent to a 3-day course of systemic corticosteroids.

Patients will not be withdrawn from the study due to asthma exacerbation unless the patient experiences more than 1 asthma exacerbation within 13 weeks or more than 2 asthma exacerbations during the double-blind treatment.

The start and end date of each asthma exacerbation will be recorded in the eCRF at the clinic visits or monthly telephone calls. The start date is defined as the first day of hospitalization/emergency room treatment or the first day of systemic corticosteroids

treatment. The end date is defined as the last day of hospitalization/emergency room treatment or the last day of systemic corticosteroids treatment (according to prescription). If the same asthma exacerbation includes both hospitalization/emergency room treatment and systemic corticosteroids treatment, the start and end dates are the first and last day that either of the criteria was fulfilled.

Additional hospitalizations/emergency room treatments and systemic corticosteroids treatments occurring during an asthma exacerbation should not be regarded as a new asthma exacerbation. For a hospitalization/emergency room visit or systemic corticosteroids treatment to be counted as a new exacerbation it must be preceeded by at least 7 days in which neither criteria are fulfilled.

6.3.1.2 Efficacy variables collected by IVRS

Patients will record, missed days of work/school, rescue medication use, asthma symptoms, ability to perform daily activities and night time awakenings in a daily diary by using a telephone to access the IVRS, starting the day after randomization. The questions will read more or less as below.

Missed school or working day:

1. Was yesterday a school or workday?

2. (If yes:) Did you miss any time in school or work due to your asthma? Response: Yes/No

Rescue medication use:

3. In the past 24 hours, how many puffs of your rescue medication did you take? Response: Numerical (options should include 0-99)

Asthma symptoms:

4. In the past 24 hours, did you have asthma symptoms? Response: Yes/No

5. (If yes:) In the past 24 hours, have your asthma symptoms limited your ability to perform your normal daily activities? Response: Yes/No

Night-time awakenings

6. Did you wake up last night due to your asthma? Response: Yes/No

7. (If yes:) When you woke up last night, did you need to use your rescue inhaler? Response: Yes/No

Methods of assessment

The patient will be instructed to answer the above questions via IVRS between the Randomization visit and the Follow-up visit. The entering of data will be indicated once every 24 hours in the morning. The patient and, if applicable, the patient's parent/legal

guardian will be trained by the study personnel and also supplied with written instructions on how to enter data and where to turn if problems occur.

The IVRS offers the possibility to monitor that the patient has entered data on a daily basis. The clinical assessment should include a regular review (in connection with clinic and telephone visits) of patient data available in IVRS. In case the patient fulfils any of the criteria for unstable asthma, see Section 6.2.5, an alert in the IVRS will trigger the investigator to contact the patient for further instructions.

In addition, a daily reminder will be addressed to the patient:

- Please remember that you should take your study medication as instructed by your study investigator.

6.3.1.3 Efficacy variables collected in eCRF at visits and monthly telephone contacts

Information about healthcare utilisation will be collected at clinic visits and monthly by telephone by study personnel. The information will be recorded in the eCRF.

Healthcare utilization for asthma:

- Telephone contact with study doctor
- Telephone contact with other physician or healthcare provider
- Unscheduled or unplanned visit to study doctor (including home visits)
- Unscheduled or unplanned visit to other physician or healthcare provider (including home visits)
- Emergency department or hospital (< 24 hrs)
- Hospital admission or Emergency Department (≥ 24 hrs)

Hospitalisations will be collected with the SAE reports.

6.3.2 Asthma Control Questionnaire

Assessment of current asthma control by the ACQ as described in the NAEPP EPR-3, 2007 Guideline (NAEPP EPR-3 2007). The ACQ has been developed by Juniper and colleagues and includes 7 questions covering criteria deemed appropriate 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. In this study, the FEV_1 question will be excluded and FEV_1 will not be measured at clinic visits. It has been shown that exclusion of this question will not alter the validity and the measurements properties of the questionnaire referred to as ACQ6.

The ACQ6 will be self-administered on paper at clinic Visits 1, 3, 5 and EoT. It takes approximately 2-3 minutes to answer the 6 questions.

The English version for North America is included in Appendix E. Translations of ACQ6 into local languages have been performed according to a linguistic validation process.

Method of assessment

It is important to administer the ACQ6 questionnaire according to the guidelines for standardized administration, and before any other study related procedures take place.

A brief introduction on how to complete the ACQ6 questionnaire will be given at Visit 1 prior to the assessment. The questionnaire will also be completed in the case of early discontinuation.

The ACQ6 should be completed in a quiet place without influence from study personnel or accompanied family or friend. The patients should be informed about the importance of their participation and be given adequate time to complete all items, ie, no time limits for completing the questions should be given. The study personnel are not to help the patients to choose an answer and must be neutral in their response to any questions from the patients. The study personnel must neither interpret nor rephrase questions in the questionnaire. After completion of the questionnaire, the study personnel will review the questionnaire for completeness only.

6.4 Safety

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

6.4.1 Definition of adverse events (AEs)

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, 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.

NB: In this study only SAEs and DAEs are collected and the term AE in this document refers only to these two categories.

6.4.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (ie, 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 hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above

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

6.4.3 Recording of adverse events

AEs will not be collected unless they lead to DAE or qualify as an SAE.

SAEs/DAEs will be recorded from the time of informed consent through the treatment period and including the follow-up period.

SAEs will not be collected for patients that are enrolled but not randomized within 15 days according to the visit window, see Table 1, and therefore do not proceed in the study. If patients are re-screened and eligible for randomization, the informed consent will be re-signed and SAEs will be collected from time of the re-consent.

Follow-up of unresolved adverse events

Any SAE/DAEs that are unresolved at the EoT Visit or at discontinuation in the study will be 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 SAE(s)/DAE(s) at the end of the study, if judged necessary.

Variables

The following variables will be collected for each AE;

- AE (verbatim)
- Date when the AE started and stopped
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to investigational product

- AE caused 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 hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Other medication
- Causality assessment in relation to Additional Study Drug
- Description of AE.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.4.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

Causality collection

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

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

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

Adverse Events based on signs and symptoms

AEs, that lead to a DAE or qualify as an SAE, 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 CRF. 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.

Concomitant medication

All changes in the patient's ordinary medication, eg dose change or addition or new medication, must be reported in the medication log. Reasons for changes in medication, which reflects an SAE/DAE, must be recorded on the AE form.

Patient reported outcome

The patient will answer questions in a patient-reported outcome test (ACQ). The patients should report any health problems directly to the investigational team as the questionnaire will not be reviewed for the purpose of identifying potential AEs.

Overdose

Should an overdose (accidental or deliberate) occur, it must be reported in accordance with the procedures described in Section 13.2, Overdose, regardless of whether the overdose was associated with any symptom or not.

Pregnancy

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

6.4.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF. For SAEs considered as potential study endpoints, see Section 6.4.5.

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

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

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

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

If the WBDC system is not available, then the investigator or other study site personnel reports an 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 (SPC) for the active comparator product (including any AstraZeneca comparator).

6.4.5 Reporting of Potential Study Endpoints (deaths, intubations and hospitalizations)

For this study, the primary and secondary objectives listed in Sections 2.1 and 2.2 and further defined in Section 6.4.5.1, 6.4.5.2 and 6.4.5.3 consist of clinically important medical events, which meet the typical criteria for SAEs. However, in order to protect the integrity of the study, SAEs referred to an independent Joint Adjudication Committee (JAC) to determine asthma-relatedness will be treated as potential study endpoints and not routinely expedited to regulatory agencies. This will allow key data to remain blinded.

Potential study endpoints include all deaths, intubations and hospitalizations that are observed from randomised patients. Although the study endpoints are asthma-related deaths, intubations, and hospitalizations, asthma causality (asthma related or non-asthma related) is not determined until adjudication is completed. After adjudication, asthma related events will be reviewed by the TDMC; non-asthma related events will be sent and subject to regulatory reporting with reporting requirement starting from the time they are deemed non-asthma related. Given the extensive patient exposure to the study drugs in the doses being used, the likelihood of identifying a new safety signal outside of the study endpoints is unlikely, and therefore such an approach is justified in order to protect the blinding of the study.

Further details of this process can be found in separate charters for the JAC, JDMC and TDMC.

Potential study endpoints will be collected in the eCRF as SAEs. For each potential endpoint, the investigator will complete information specific to that type of endpoint on the eCRF and compile relevant additional source information into an Event Adjudication Package, as described in the JAC Charter and JAC Operations Manual. The Event Adjudication Package will be sent to the JAC for central adjudication.

6.4.5.1 Definition of Asthma-related deaths

Definition of an asthma related death is presented in the JAC Charter.

6.4.5.2 Definition of Asthma-related intubations

Definition of asthma related intubation is presented in the JAC Charter.

Intubation is defined as oro-tracheal or naso-tracheal placement of a tracheal tube.

Noninvasive ventilation, defined as the use of positive airway pressure delivered via nasal, oral, or oral-nasal interphase, will be captured as part of the hospitalization record; in the case of non-invasive ventilation preceding intubation, the event should be counted as an intubation.

6.4.5.3 Definition of Asthma-related hospitalizations

Definition of an asthma related hospitalization is presented in the JAC Charter.

6.4.5.4 Definition of discontinuation due to asthma exacerbation

Patients discontinued from investigational product according to criteria 7 or 8 in Section 5.8 will be defined as being discontinued from investigational product due to asthma exacerbation.

6.4.6 Laboratory safety assessment

All sites will perform urine pregnancy testing (on appropriate female patients) at Visits 2, 5 and EoT.

6.5 Patient reported outcomes (PRO)

6.5.1 Efficacy variables collected via IVRS

See Section 6.3.1.2.

6.5.2 Asthma Control Questionnaire (ACQ)

See Section 6.3.2.

6.6 Pharmacokinetics (Not applicable)

6.7 Pharmacodynamics (Not applicable)

6.8 Pharmacogenetics

The study will include exploratory objectives including future exploratory genetic research, please refer to Appendix D for further details.

6.9 Health economics (Not applicable)

7. BIOLOGICAL SAMPLING PROCEDURES

The study will include exploratory objectives including future exploratory genetic research, please refer to Appendix D for further details.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

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

8.2 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. Pursuant to this wording, patients will authorize the collection, use and disclosure of their study data by the investigator and by those persons who need that information for the purposes of the study.

Please refer to Appendix D for details of precautions specific to genetic data.

8.3 Ethics and regulatory review

An Ethics Committee or Institutional Review Board (IRB) 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/IRB 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/IRB 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/IRB 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/IRBs and Principal Investigators with safety updates/reports according to local requirements, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

Each Principal Investigator is responsible for providing the Ethics Committees/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.

8.4 Informed consent

The Principal Investigator(s) at each centre 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
- Ensures that separate consent is given for exploratory genetic research and that patients are aware that exploratory genetic research is optional
- Ensure the original, signed informed consent form is 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

If a patient is re-screened, 3 months or later, after the last signing of the ICF, the Principal Investigator will:

- Ensure that the patient signs and dates the ICF Supplement before conducting any procedure specifically for the study
- Ensure the original, signed ICF Supplement is stored in the Investigator's Study File
- Ensure a copy of the signed ICF Supplement is given to the patient

If the patient is minor, the Principal Investigator will:

- Ensure that the minor patient is informed about the study to the best of his/her understanding
- Ensure that the patient, if appropriate, signs and dates the pediatric assent form
- Ensure that the parent or legal guardian is informed and signs and dates the informed consent form

8.5 Changes to the protocol and informed consent form

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

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

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

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

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

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

8.6 Audits and inspections

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

9. STUDY MANAGEMENT BY ASTRAZENECA

9.1 Pre-study activities

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

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

9.2 Training of study site personnel

Before the first 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 system(s) utilised.

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

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

9.3 Monitoring of the study

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

- Provide information and support to the investigator(s)

- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

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

9.3.1 Source data

Refer to the clinical study agreement for location of source data.

9.4 Study agreements

The Principal Investigator at each centre should comply with all the terms, conditions, and obligations of the clinical study agreement, or equivalent, for this study. In the event of any inconsistency between this clinical study protocol and the clinical study agreement, the terms of clinical study protocol shall prevail with respect to the conduct of the study and the treatment of 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.

9.4.1 Archiving of study documents

The Investigator follows the principles outlined in the clinical study agreement.

9.5 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 and to end by

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

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

10. DATA MANAGEMENT BY DMC

Data will be entered in the Web Based Data Capture (WBDC) system at the study site. Trained study personnel will be responsible for entering data on the observations, tests and assessments specified in the protocol into the WBDC system and according to the eCRF Instructions. The eCRF Instructions will also guide the study site in performing data entry. Data entered in the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail.

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

ePRO data will be collected electronically and data will be transferred to AstraZeneca via the IVRS service provider.

Dictionary coding

Medical coding is done using the most current version of MedDRA and AstraZeneca Drug Dictionary.

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 (eg, eDiary, IVRs etc) will be tested and validated as needed. External data reconciliation will be done with the clinical database as applicable.

Serious Adverse Event (SAE) Reconciliation

SAE Reconciliation Reports are produced and reconciled with Patient Safety database.

Data associated with biological samples will be transferred for storage to laboratories internal or external to AstraZeneca for later analyses. Please refer to Appendix D for details of data management for exploratory genetic research.

11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA OR DELEGATE

11.1 Calculation or derivation of efficacy variable(s)

The efficacy endpoint time to first asthma exacerbation is the time to the first event occurring due to a deterioration of asthma and requiring systemic corticosteroids (tablets, suspension, or injection) for at least 3 days or an inpatient hospitalization or emergency room visit due to asthma that required systemic corticosteroids. For this endpoint the time from randomization to the event, or the time to the last documented contact for patients with no event (last assessment of exacerbation status), will be calculated.

In addition the number of asthma exacerbations will be calculated for each patient.

Regarding healthcare utilization for asthma, the incidence of and number of events will be calculated separately for each patient and each of the categories in Section 6.3.1.3.

11.2 Calculation or derivation of safety variable(s)

The primary safety endpoint is the time to the first event included in the composite endpoint of asthma-related death, asthma-related intubation, or asthma-related hospitalization. Only events adjudicated and confirmed by the JAC will be included in the analysis of this endpoint.

For the primary safety variable, the time from the randomization to the event, or time to last documented contact for censored patients, ie, patients with no event, will be calculated. In addition the corresponding variable excluding events occurring 7 days after last dose of randomized treatment will be calculated.

A patient may have 1 or more events. However, only a patient's first occurring event will contribute to the analysis of the specified variable.

A secondary safety endpoint is discontinuation from the study due to asthma exacerbation. For this secondary safety variable, the time from the randomization to the discontinuation due to asthma exacerbation, or time to last documented contact for censored patients, ie patients that did not discontinue due to asthma exacerbation, will be calculated.

11.3 Calculation or derivation of patient reported outcome variables

11.3.1 ACQ

For ACQ all 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 five responses. At least 5 out of the 6 questions must have been answered to provide a value. The outcome variable for ACQ will be the change in overall score from Visit 1 to the mean of the values at Visits 3, 5 and EoT.

11.3.2 Missed school or working day

The number of days (a part of a day will be counted as a full day) of school or work missed due to asthma will be calculated for each patient.

11.3.3 Rescue medication use

The mean number of puffs of rescue medication, based on available values, will be calculated for each patient. In addition the % rescue free days, days with no reported use of rescue medication, will be calculated for each patient.

11.3.4 Asthma symptoms

The percent days with no asthma symptoms for most of the day, based on available values, will be calculated for each patient.

The percent days with activity limitation due to asthma, based on available values, will be calculated for each patient.

The percent nights with awakenings due to asthma, based on available values, will be calculated for each patient.

12. STATISTICAL METHODS AND SAMPLE SIZE

12.1 Description of analysis sets

The full analysis set, consisting of all patients randomized to study drug will be the primary data set used for analyses endpoints related to the safety and efficacy objectives.

12.1.1 Endpoint definitions

12.1.1.1 Primary safety endpoint

The primary safety endpoint is the time to first event included in the composite endpoint (asthma-related death, asthma-related intubation or asthma-related hospitalization), using events adjudicated and confirmed by the JAC.

12.1.1.2 Primary efficacy endpoint

Primary efficacy endpoint is the time to the first event included in the definition of an asthma exacerbation.

12.1.1.3 Secondary efficacy endpoints

Secondary efficacy endpoints include respectively percent days of respectively days with no asthma symptoms, days with no activity limitation due to asthma, and treatment means of respectively puffs of rescue medication, and ACQ. In addition number of days missed at school or work, the number of respectively telephone calls to the clinic, home visits by physician, unscheduled clinic visits and hospitalization and ER visits will also be secondary efficacy variables.

12.1.1.4 Safety endpoints

Incidence of SAEs, DAEs and time to discontinuation due to asthma exacerbation.

12.2 Methods of statistical analyses

12.2.1 Demographics and baseline characteristics

Demographic and baseline characteristics will be summarized, using frequency distributions and summary statistics based on the full analysis set.

12.2.2 Safety analysis

For the time to event variables, a Cox proportional hazards model with terms for randomized treatment and strata for incoming control/asthma treatment will be used to compare Symbicort and budesonide. Hazard ratios and 95% confidence intervals will be provided. Patients who complete the 26-week follow-up period without experiencing any event as defined by the component in the primary endpoint will be censored at 26 weeks. Any patients without an event who are lost to follow-up prior to 26 weeks will be censored at the time of the last assessment of the status of the components of the primary endpoint. For the primary endpoint the following hypothesis will be tested at the 2.5% 1-sided significance level,

- H_0: Hazard ratio ≥ 2.0 versus H_1: Hazard ratio <2.0

If the null hypothesis is rejected then a 2.0-fold increase in risk on treatment with Symbicort compared to treatment with budesonide is ruled out. Further, if the upper confidence limit estimate is <1.0, then superiority may be concluded in terms of the risk of asthma related events being lower on Symbicort vs budesonide.

A subsidiary analysis, excluding events occurring 7 days after the last dose of randomized treatment for discontinued patients, will be performed in the same manner as the primary analysis. In addition, Kaplan-Meier plots, will be provided, describing time-to-event curves by treatment groups.

A formal interim analysis will be performed once half of the required number of primary endpoint events has been achieved. Consideration will be given to early stopping, if the p-value for the HR is extreme, $p \leq 0.0001$ (1-sided), z-value ≥ 3.7, using the Haybittle-Peto rule so that the alpha level in the final analysis is largely unaltered at 0.0249 1-sided.

SAEs and DAEs will be summarized and evaluated descriptively. Time to discontinuation due to asthma exacerbation will be analyzed in the same way as the primary safety endpoint.

It is also planned that a meta-analysis of the individual sponsor studies will be conducted to explore the relative risk for patients receiving ICS/LABA combination compared to patients receiving ICS with respect to the composite endpoint of asthma-related intubation or asthma-related death and for the endpoint of asthma-related death. Details of this meta-analysis will be described in a separate analysis plan.

12.2.3 Efficacy analysis

The primary efficacy variable, time to first asthma exacerbation,will be analysed using a Cox proportional hazards model with terms for randomized treatment and strata by incoming control/asthma treatment to compare treatment groups. Hazard ratios and 95% confidence intervals will be provided. Additional descriptions of the number of asthma exacerbations will be evaluated by a Poisson regression model with terms for incoming control/asthma treatment strata and randomized treatment, and with the logarithm of the time in study as offset.

Frequency and percentage of days of unscheduled asthma-related healthcare utilization and measures of productivity (number of days of school or work missed due to asthma) will be summarized by treatment group.

Mean rescue medication use will be described and analyzed with an ANCOVA model using treatment and strata by incoming control/asthma treatment as fixed factors. Percent rescue free days, percent days with no symptoms due to asthma, and percent days with activity limitation and percent days with night time awakening will be analysed by a similar model.

Change from baseline in ACQ will be summarized using descriptive statistics and analyzed with an analysis of covariance (ANCOVA) model using treatment and strata by incoming control/asthma treatment as fixed factors and baseline as a covariate. Proportions of patients achieving asthma control based on intervals defined by ≤ 0.75 (ie, well-controlled) and ACQ ≥ 1.5 (ie, un-controlled) will be analyzed and presented.

No multiplicity adjustment will be performed for the testings of the primary safety endpoint and the primary efficacy endpoint, since two different hypotheses are addressed.

12.3 Determination of sample size

The incidence rate on ICS alone, based on studies with a similar population, SD-039-0668 and SD-039-0673, is estimated to be 15 events per 1000 per treatment years. To rule out 2 fold increase in the event rate with ICS/LABA combination versus ICS alone, equating to an increase from 1.5% to 3.0% per year, or from 0.75% to 1.5% per 6 months, 87 events are required. Assuming a 6-month study, an approximate constant event rate over time, and using 90% power, this requires a total of 11664 patients to be randomized. To rule out a true RR of 2.0, the observed RR therefore cannot exceed 1.315 and yet achieve an upper 1-sided 97.5% CL ≤ 2.0. This corresponds to observing event rates for ICS versus ICS/LABA combination not more disparate than 0.65% versus 0.85% respectively, for an absolute risk difference of 0.20% with an upper CL of 0.51%. This means that to conclude non-inferiority, the observed excess risk on ICS/LABA combination cannot be greater than 2.0 events in 1000 and the upper CL will rule out, at worst, an excess risk of 5.1 events per 1000 treated with ICS/LABA per 6 month's period.

12.4 Data monitoring committee

This study will be conducted under the supervision of a Joint Oversight/Steering Committee (JOSC). An independent trial data monitoring committee (TDMC) will be responsible for monitoring the primary safety variable for the study but also all other aspects of safety in the study. In addition a joint data monitoring committee (JDMC) will monitor pooled data, focused on asthma related mortality, across the 4 separate LABA trials. The composition and detailed scope of these committees is described in their respective charters.

12.4.1 Joint Adjudication Committee

An external, independent, blinded JAC will be appointed jointly by the sponsors and the academic leadership of the study.

The JAC will adjudicate all the primary safety endpoints: deaths, intubations and hospitalizations and assess for asthma relatedness. A charter will be prepared to detail precise responsibilities and procedures applicable for the JAC.

12.4.1.1 Study termination guidelines due to interim analysis results

When 50% of the total number of events has been accrued for the primary endpoint (ie, at 44 events), an interim analysis will be performed, see Section 12.2.2. In addition, asthma-related deaths will be monitored. Formal stopping regulations will be detailed in the independent JDMC charter.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

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

In the case of a medical emergency the investigator should contact the local study team leader/monitor, shown below. If the local study team leader/monitor is not available, the local study physician or the local team Patient Safety physician/representative at the Marketing Company should be contacted. As a secondary option, contact the clinical study team at AstraZeneca R&D, shown below.

Name	Role in the study	Address & telephone number
State local contact persons below: Local contact persons can be added in wet-inc above.		

13.2 Overdose

13.2.1 Background

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

13.2.2 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 ICS, systemic corticosteroids effects may appear if used chronically in excessive doses.

There is limited clinical experience regarding overdosage with inhaled formoterol. An overdose would likely lead to effects that are typical of β_2-agonists such as tremor, headache and palpitations. Symptoms and signs reported with formoterol from isolated cases are tachycardia, hyperglycaemia, hypokalaemia, prolonged QTc-interval, arrhythmia, nausea and vomiting.

Experience with other β_2-agonists has shown that overdoses may also cause restlessness, irritability, excitation, somnolence, convulsions and hyper- or hypotension. Metabolic effects may include acidosis and in serious cases, possibly rhabdomyolysis and renal failure.

13.2.3 Treatment suggestions

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

13.2.4 Procedures for reporting

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

- An Overdose with associated DAEs/SAEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.

- An Overdose without associated symptoms is only reported on the Overdose CRF module

If an overdose on an AstraZeneca study drug occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives **within one day**, ie, immediately but no later than **the end of the next business day** of when he or she becomes aware of it.

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

For overdoses associated with SAE, standard reporting timelines apply, see Section 6.4.4. For other overdoses, reporting should be done within 5 days.

13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

13.3.1 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 pMDI 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 with Symbicort Turbuhaler do not indicate an increased risk when used during pregnancy.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the 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 investigators or other site personnel inform appropriate AstraZeneca representatives **within one day** ie, immediately but no later than the **end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs, see Section 6.4.4 and within 30 days for all other pregnancies. The outcome of the pregnancy should be reported as soon as it is known.

The same timelines apply when outcome information is available.

The PREGREP module in the CRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

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AstraZeneca

Clinical Study Protocol Appendix B

Drug Substance	Symbicort® pMDI
Study Code	D5896C00027
Edition Number	1

Appendix B
Additional Safety Information

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

Life threatening

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

Hospitalisation

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

Important medical event or medical intervention

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

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

<<Examples of such events are:

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

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

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

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

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

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

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

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

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

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

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

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

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

- Is there a known mechanism?

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

Clinical Study Protocol Appendix C

Drug Substance	Symbicort® pMDI
Study Code	D5896C00027
Edition Number	1

Appendix C
International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm).** For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable

- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Clinical Study Protocol Appendix D

Drug Substance	Symbicort®
Study Code	D5896C00027
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Appendix D
Exploratory Genetic Research

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LIST OF TABLES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
CSR	Clinical study report
DNA	Deoxyribonucleic acid
LIMS	Laboratory information management system
PGx	Pharmacogenetics

1. BACKGROUND AND RATIONALE

AstraZeneca intends to perform genetic research in the Symbicort® clinical development programme to explore how genetic variations may affect the clinical parameters associated with Symbicort and/or its monoproducts. Collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies.

To date pharmacogenetics in the field has been centred on the debate surrounding the affect of polymorphisms in the beta-2 adrenergic receptor gene on response to beta-2 agonists (Hawkins et al 2008). The collection of genetic samples in this clinical trial may provide the opportunity to investigate whether inter-individual variation in the response to Symbicort and/or its monoproducts correlates with genetic polymorphism.

Asthma is a heterogeneous disease. There is a growing appreciation that there may be many asthma phenotypes, each of which may be caused by the interactions of multiple genes with each other and with environmental factors (Moore et al 2010). Therefore in addition to possible pharmacogenetic applications, given the unique nature of this clinical study there is potential for genetic samples to be used to further research in to the segmentation of asthma phenotypes, or for the identification and validation of new drug targets for asthma.

Future research may suggest genes or gene categories as candidates for influencing not only response to Symbicort and/or its monoproducts but also susceptibility to asthma for which Symbicort may be evaluated. Thus, this genetic research may involve study of additional un-named genes or gene categories, but only as related to asthma and Symbicort and/or its monoproducts.

2. GENETIC RESEARCH OBJECTIVES

The objective of this research is to collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to Symbicort and/or budesonide; and/or susceptibility to, progression of and prognosis of asthma.

3. GENETIC RESEARCH PLAN AND PROCEDURES

3.1 Selection of genetic research population

3.1.1 Study selection record

All subjects will be asked to participate in this genetic research. Participation is voluntary and if a subject declines to participate there will be no penalty or loss of benefit. The subject will not be excluded from any aspect of the main study.

3.1.2 Inclusion criteria

For inclusion in this genetic research, subjects must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol **and**:

- Provide informed consent for the genetic sampling and analyses.

3.1.3 Exclusion criteria

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

- Previous allogeneic bone marrow transplant
- Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection

3.1.4 Discontinuation of subjects from this genetic research

Specific reasons for discontinuing a subject from this genetic research are:

Withdrawal of consent for genetic research: Subjects may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in Section 3.3.3.

3.2 Collection of samples for genetic research

The blood sample for genetic research will be obtained from the subjects at Visit 2, at randomisation. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE), such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 2, it may be taken at any visit until the last study visit. Only one sample should be collected per subject for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

The total volume of blood that may be drawn from each subject in this study is as follows:

Table 1 Volume of blood to be drawn from each subject

Assessment	Sample volume (mL)	No. of samples	Total volume (mL)
Pharmacogenetic	10	1	10
Total	10	1	10

3.3 Handling, storage and destruction of biological samples for pharmacogenetic research

3.3.1 Coding and storage of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. Samples will be stored for a maximum 25 years, from the date of last subject last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

For all samples irrespective of the type of coding used the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory staff working with the DNA).

The samples and data for genetic analysis in this study will be coded. The link between the subject enrolment/randomisation code and the DNA number will be maintained and stored in a secure environment, with restricted access WITHIN the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent.

3.3.2 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Principal Investigator at each centre keeps full traceability of collected biological samples from the subjects while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca biobank system during the entire life cycle.

3.3.3 Withdrawal of informed consent for donated biological samples

If a subject withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

As collection of the biological samples is an optional part of the study, then the subject may continue in the study.

The Principal Investigator:

- Ensures subjects' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site
- Ensures that the subject and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

4. ETHICAL AND REGULATORY REQUIREMENTS

The principles for ethical and regulatory requirements for the study, including the exploratory research component, are outlined in Section 8 of the main Clinical Study Protocol.

4.1 Informed consent

The genetic component of this study is optional and the subject may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the subject must sign and date both the consent form for the main study and the genetic component of the study. Copies of both signed and dated consent forms must be given to the subject and the original filed at the study centre. The principal investigator(s) is responsible for ensuring that consent is given freely and that the subject understands that they may freely discontinue from the genetic aspect of the study at any time.

4.2 Subject data protection

AstraZeneca will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a subject's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

5. DATA MANAGEMENT

Any genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyze the samples.

The results from this genetic research may be reported in the CSR for the main study, or in a separate report as appropriate.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The number of subjects that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A statistical analysis plan will be prepared where appropriate.

7. LIST OF REFERENCES

Hawkins et al 2008
Hawkins GA, Weiss ST, Bleecker ER. Clinical consequences of ADRbeta2 polymorphisms. Pharmacogenomics. 2008 Mar;9(3):349-58.

Moore et al 2010
Moore WC, Meyers DA, Wenzel SE, Teague WG, Li H, Li X, D'Agostino R Jr, Castro M, Curran-Everett D, Fitzpatrick AM, Gaston B, Jarjour NN, Sorkness R, Calhoun WJ, Chung KF, Comhair SA, Dweik RA, Israel E, Peters SP, Busse WW, Erzurum SC, Bleecker ER;

National Heart, Lung, and Blood Institute's Severe Asthma Research Program. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. Am J Respir Crit Care Med. 2010 Feb 15;181(4):315-23. Epub 2009 Nov 5.

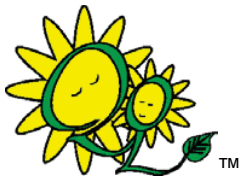
AstraZeneca

Clinical Study Protocol Appendix E	
Drug Substance	Symbicort® pMDI
Study Code	D5896C00027
Appendix Edition Number	1

Appendix E
Asthma Control Questionnaire 6

ASTHMA CONTROL QUESTIONNAIRE

ENGLISH FOR NORTH AMERICA VERSION
(QUESTIONS 1 – 6 ONLY: QUESTION 7 (FEV_1) OMITTED)



For further information:

December 2002

Please answer questions 1 - 6.

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

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

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

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

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

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

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

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

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

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

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

6. On average, during the past week, how many **puffs/inhalations of short-acting bronchodilator** (e.g. Ventolin/Bricanyl) have you used each day?
(If you are not sure how to answer this question, please ask for help)

0 None
1 1 - 2 puffs/inhalations most days
2 3 - 4 puffs/inhalations most days
3 5 - 8 puffs/inhalations most days
4 9 - 12 puffs/inhalations most days
5 13 - 16 puffs/inhalations most days
6 More than 16 puffs/inhalations most days

AstraZeneca

Clinical Study Protocol Amendment	
Amendment Number	1
Drug Substance	Symbicort ® pMDI
Study Code	D5896C00027
Date	
Protocol Dated	

A 26 week, randomized, double-blind, parallel-group, active controlled, multicenter, multinational safety study evaluating the risk of serious asthma-related events during treatment with Symbicort®, a fixed combination of inhaled corticosteroid (ICS) (budesonide) and a long acting β_2-agonist (LABA) (formoterol) as compared to treatment with ICS (budesonide) alone in adult and adolescent (≥12 years of age) patients with asthma

Sponsor:

AstraZeneca AB,

Centres affected by the Amendment:

This amendment affects all centres in the study.

The protocol for the study is to be amended as follows:

Section of protocol affected:

Synopsis

Previous text:

This study will be conducted under the supervision of a Joint Oversight/Steering Committee (JOSC) and an independent Joint Data Monitoring Committee (JDMC). The composition and scope of these committees will be described in their respective charters. Both committees will be shared with other LABA Sponsor companies planning studies with the same objective.

In addition to the two committees mentioned above, each LABA Sponsor Company will have a independent Trial Data Monitoring Committee (TDMC) whose main role is to monitor possible events that will trigger a meeting of the joint DMC. The chair from each LABA Sponsor Company's TDMC will be members in the JDMC. The composition and detailed scope of the TDMC will be described in a charter.

Revised text:

This study will be conducted under the supervision of a Joint Oversight/Steering Committee (JOSC). An independent trial data monitoring committee (TDMC) will be responsible for monitoring the primary safety variable for the study but also all other aspects of safety in the study. In addition a joint data monitoring committee (JDMC) will monitor pooled data, focused on asthma related mortality, across the 4 separate LABA trials. The composition and detailed scope of these committees is described in their respective charters.

Reason for Amendment:

Update of TDMC role according to the TDMC charter.

Section of protocol affected:

3.1 Overall study design and flow chart

Previous text:

N/A

Revised text:

If a patient is re-screened, 3 months or later, after the last signing of the ICF, the patient needs to re-consent to the study.

Reason for Amendment:

Adding text about re-consent process for re-screened patients.

Section of protocol affected:

3.1 Overall study design and flow chart

Previous text:

This study will be conducted under the supervision of a Joint Oversight/Steering Committee (JOSC) and an independent Joint Data Monitoring Committee (JDMC). The composition and scope of these committees will be described in their respective charters. Both committees will be shared with other LABA Sponsor companies planning studies with the same objective.

In addition to the two committees mentioned above, each LABA Sponsor Company will have a independent Trial Data Monitoring Committee (TDMC) whose main role is to monitor possible events that will trigger a meeting of the joint DMC. The chair from each LABA Sponsor Company's TDMC will be members in the JDMC. The composition and detailed scope of the TDMC will be described in a charter.

Revised text:

This study will be conducted under the supervision of a Joint Oversight/Steering Committee (JOSC). An independent trial data monitoring committee (TDMC) will be responsible for monitoring the primary safety variable for the study but also all other aspects of safety in the study. In addition a joint data monitoring committee (JDMC) will monitor pooled data, focused on asthma related mortality, across the 4 separate LABA trials. The composition and detailed scope of these committees is described in their respective charters.

Reason for Amendment:

Update of TDMC role according to the TDMC charter.

Section of protocol affected:

Table 1 Study Plan

Previous text:

N/A

Revised text:

Footnote a: If a patient is re-screened, 3 months or later, after the last signing of the ICF, the patient needs to re-consent to the study, see section 8.2.

Reason for Amendment:

Adding text about re-consent process for re-screened patients.

Section of protocol affected:

Table 1 Study Plan

Previous text:

Footnote a:

Suggested visit windows. Visits occurring outside of the visit window will not necessarily be considered a protocol deviation unless specifically stated within the protocol.

Revised text:

~~Footnote a:~~

~~Suggested visit windows. Visits occurring outside of the visit window will not necessarily be considered a protocol deviation unless specifically stated within the protocol. '~~

Reason for Amendment:

The text is understood as confusing according to some MCs. Sentences removed, as they don't add any value to understanding of the study design.

Section of protocol affected:

4.1 Inclusion criteria

Previous text:

Inclusion criteria 6:

Availability and ability to perform the necessary manoeuvres and procedures required by the study (eg, use a pMDI, perform daily telephone calls)

Revised text:

Inclusion criteria 6:

Availability and ability to perform the necessary manoeuvres and procedures required by the study (eg, **read the AQC6 questionnaire**, use a pMDI, perform daily telephone calls)

Reason for Amendment:

Clarification of the criteria.

Section of protocol affected:

5.2 Patient enrolment and randomisation

Previous text:

1. Obtain signed informed consent/paediatric assent from the potential patient or their parent/legal guardian….

Revised text:

1. Obtain signed informed consent/paediatric assent from the potential patient **and/**or their parent/legal guardian….

Reason for Amendment:

Clarification of the criteria.

Section of protocol affected:

5.2 Patient enrolment and randomisation

Previous text:

N/A

Revised text:

If a patient is re-screened, 3 months or later, after the last signing of the ICF, the patient needs to re-consent to the study. The patient and Investigator will sign the ICF Supplement before any further study procedures are performed.

Reason for Amendment:

Adding text about re-consent process for re-screened patients.

Section of protocol affected:

5.3 Procedures for handling patients incorrectly enrolled or randomized

Previous text:

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

Where patients that do not meet the selection criteria are randomized in error or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post initiation, a discussion should occur between the AstraZeneca Study Team Physician and the investigator regarding whether to continue or discontinue the patient from treatment.

The AstraZeneca Study Team Physician is to ensure all such decisions are appropriately documented

Revised text:

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

~~Where patients that do not meet the selection criteria are randomized in error or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post~~

~~initiation, a discussion should occur between the AstraZeneca Study Team Physician and the investigator regarding whether to continue or discontinue the patient from treatment.~~

~~The AstraZeneca Study Team Physician is to ensure all such decisions are appropriately documented.~~

Reason for Amendment:

To adhere to the new CSP template mandatory text.

Section of protocol affected:

Table 4 Identity of Investigational product

Previous text:

Placebo for training, pMDI (HFA) for oral inhalation with Actuation Counter Module (ACM), PLACEBO, AstraZeneca.

Revised text:

~~Placebo for training, pMDI (HFA) for oral inhalation with Actuation Counter Module (ACM), PLACEBO, AstraZeneca~~.

Reason for Amendment:

Correction - There is no placebo arm in this study – it is just a training device and therefore not an investigational product.

Section of protocol affected:

5.5.2 Doses and treatment regimens

Previous text:

The patient will also receive written information on how the priming is done. Each site will be provided with sufficient training pMDI's.

Revised text:

The patient will also receive written information on how the priming is done. Each site will be provided with sufficient training **devices, placebo pMDI (HFA) for oral inhalation with Actuation Counter Module (ACM), manufactured by AstraZeneca.**

Reason for Amendment:

Correction - There is no placebo arm in this study – it is just a training device and therefore not an investigational product.

Section of protocol affected:

6.3.1.2 Efficacy variables collected by IVRS

Previous text:

The patient and, if applicable, the patient's parent/legal guardian will be instructed….

Revised text:

The patient ~~and, if applicable, the patient's parent/legal guardian~~ will be instructed….

Reason for Amendment:

Criterion does not correspond to inclusion criterion 6.

Section of protocol affected:

6.4.3 Recording of adverse events

Previous text:

SAEs/DAEs will be recorded from the time of informed consent through the treatment period and including the follow-up period.

Revised text:

SAEs/DAEs will be recorded from the time of informed consent through the treatment period and including the follow-up period.

SAEs will not be collected for patients that are enrolled but not randomized within 15 days according to the visit window, see table 1, and therefore do not proceed in the study. If patients are re-screened and eligible for randomization, the informed consent will be re-signed and SAEs will be collected from time of the re-consent.

Reason for Amendment:

Clarification - Adding text about re-consent process for re-screened patients.

Section of protocol affected:

8.4 Informed consent

Previous text:

N/A

Revised text:

If a patient is re-screened, 3 months or later, after the last signing of the ICF, the Principal Investigator will:

- **Ensure that the patient signs and dates the ICF Supplement before conducting any procedure specifically for the study**
- **Ensure the original, signed ICF Supplement is stored in the Investigator's Study File**
- **Ensure a copy of the signed ICF Supplement is given to the patient**

Reason for Amendment:

Adding text about re-consent process for re-screened patients.

Section of protocol affected:

12.2.3 Efficacy analysis

Previous text:

Mean rescue medication use will be described and analyzed with an ANCOVA model using treatment and country as fixed factors. Percent rescue free days, percent days with no symptoms due to asthma, and percent days with activity limitation and percent days with night time awakening will be analysed by a similar model.

Change from baseline in ACQ will be summarized using descriptive statistics and analyzed with an analysis of covariance (ANCOVA) model using treatment and country as fixed factors and baseline as a covariate. Proportions of patients achieving asthma control based on intervals defined by ≤0.75 (ie, well-controlled) and ACQ ≥1.5 (ie, un-controlled) will be analyzed and presented.

Revised text:

Mean rescue medication use will be described and analyzed with an ANCOVA model using treatment and **strata by incoming control/asthma treatment** as fixed factors. Percent rescue free days, percent days with no symptoms due to asthma, and percent days with activity limitation and percent days with night time awakening will be analysed by a similar model.

Change from baseline in ACQ will be summarized using descriptive statistics and analyzed with an analysis of covariance (ANCOVA) model using treatment and **strata by incoming control/asthma treatment** as fixed factors and baseline as a covariate. Proportions of patients achieving asthma control based on intervals defined by ≤0.75 (ie, well-controlled) and ACQ ≥1.5 (ie, un-controlled) will be analyzed and presented.

Reason for Amendment

Adjustment according to the Final SAP.

Section of protocol affected:

12.3 Determination of sample size

Previous text:

Assuming a 6-month study, an approximate linear incidence rate over time, and using 90% power, this requires a total of 11664 patients to be randomized.

Revised text:

Assuming a 6-month study, an approximate **constant event** rate over time, and using 90% power, this requires a total of 11664 patients to be randomized.

Reason for Amendment

Adjustment according to the Final SAP.

Section of protocol affected:

12.4 Data monitoring committee

Previous text:

This study will be conducted under the supervision of a Joint Oversight/Steering Committee (JOSC) and an independent Joint Data Monitoring Committee (JDMC). The composition and scope of these committees will be described in their respective charters. Both committees will be shared with other LABA Sponsor companies planning studies with the same objective.

In addition to the two committees mentioned above, each LABA Sponsor Company will have a independent Trial Data Monitoring Committee (TDMC) whose main role is to monitor possible events that will trigger a meeting of the joint DMC. The chair from each LABA Sponsor Company's TDMC will be members in the JDMC. The composition and detailed scope of the TDMC will be described in a charter.

Revised text:

This study will be conducted under the supervision of a Joint Oversight/Steering Committee (JOSC). An independent trial data monitoring committee (TDMC) will be responsible for monitoring the primary safety variable for the study but also all other aspects of safety in the study. In addition a joint data monitoring committee (JDMC) will monitor pooled data, focused on asthma related mortality, across the 4 separate

LABA trials. The composition and detailed scope of these committees is described in their respective charters.

Reason for Amendment:

Update of TDMC role according to the final TDMC charter.

Section of protocol affected:

13.2.4 Procedures for reporting

Previous text:

For other overdoses, reporting should be done within 30 days.

Revised text:

For other overdoses, reporting should be done within **5** days.

Reason for Amendment:

Revision language does not correspond to SOP requirements.

Persons who initiated the Amendment:

Central Study Team

Clinical Study Protocol Amendment No 1
Appendix A

Drug Substance	Symbicort® pMDI
Study Code	D5896C00027
Edition Number	1
Date	
Protocol Dated	

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A 26 week, randomized, double-blind, parallel-group, active controlled, multicenter, multinational safety study evaluating the risk of serious asthma-related events after treatment with Symbicort®, a fixed combination of inhaled corticosteroid (ICS) (budesonide) and a long acting β_2-agonist (LABA) (formoterol) as compared to treatment with ICS (budesonide) alone in adult and adolescent (≥12 years of age) patients with asthma.

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

I agree to the terms of this study pr

AstraZeneca Research and Developmer
site representative

ASTRAZENECA SIGNATURE(S)

A 26 week, randomized, double-blind, parallel-group, active controlled, multicenter, multinational safety study evaluating the risk of serious asthma-related events after treatment with Symbicort®, a fixed combination of inhaled corticosteroid (ICS) (budesonide) and a long acting β_2-agonist (LABA) (formoterol) as compared to treatment with ICS (budesonide) alone in adult and adolescent (≥12 years of age) patients with asthma.

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

I agree to the terms of this study protocol amendment.

AstraZeneca Research and Developme
site representative

ASTRAZENECA SIGNATURE(S)

A 26 week, randomized, double-blind, parallel-group, active controlled, multicenter, multinational safety study evaluating the risk of serious asthma-related events after treatment with Symbicort®, a fixed combination of inhaled corticosteroid (ICS) (budesonide) and a long acting β_2-agonist (LABA) (formoterol) as compared to treatment with ICS (budesonide) alone in adult and adolescent (≥12 years of age) patients with asthma.

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

I agree to the terms of this study protocol amendment.

AstraZeneca Research and Development site representati

SIGNATURE OF INTERNATIONAL CO-ORDINATING INVESTIGATOR

A 26 week, randomized, double-blind, parallel-group, active controlled, multicenter, multinational safety study evaluating the risk of serious asthma-related events after treatment with Symbicort®, a fixed combination of inhaled corticosteroid (ICS) (budesonide) and a long acting β_2-agonist (LABA) (formoterol) as compared to treatment with ICS (budesonide) alone in adult and adolescent (≥12 years of age) patients with asthma.

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

I agree to the terms of this study protocol amendment. I will conduct the study according to the procedures specified herein, and according to the principles of Good Clinical Practice and local regulations, and I ensure that all relevant site staff follows the instructions given in the latest version of the Laboratory Manual for Investigators.

Signature:

Clinical Study Protocol Amendment	
Amendment Number	2
Drug Substance	Symbicort
Study Code	D5896C00027
Date	
Protocol Dated	

A 26 week, randomized, double-blind, parallel-group, active controlled, multicenter, multinational safety study evaluating the risk of serious asthma-related events during treatment with Symbicort®, a fixed combination of inhaled corticosteroid (ICS) (budesonide) and a long acting β_2-agonist (LABA) (formoterol) as compared to treatment with ICS (budesonide) alone in adult and adolescent (≥12 years of age) patients with asthma

Sponsor:

AstraZeneca AB,

Centres affected by the Amendment:

All centres are affected.

The protocol for the study is to be amended as follows:

Section of protocol affected:

4.1

Previous text:

Table 2 Estimated Daily Dosage for ICS

Asthma Therapy	**Total Daily Dose (µg/day)**		
Inhaled Corticosteroid	**Low**	**Medium**	**High**
Beclomethasone dipropionate non-HFA inhalers	200 to 500	>500 to 1000	>1000-2000
Beclomethasone dipropionate HFA[a]	80 to 240	>240 to 480	>480
Ciclesonide	80 to 160	>160 to 320	>320 - 1280
Triamcinolone acetonide	400 to 1000	>1000 to 2000	>2000
Flunisolide	500 to 1000	>1000 to 2000	>2000
Fluticasone propionate non-HFA inhalers[a]	100 to 300	>300 to 500	>500 - 1000
Fluticasone propionate HFA[b]	88 to 264	>264 to 460	>460
Budesonide	200 to 400	>400 to 800	>800-1600
Mometasone furoate	200 to <400	≥400 to 800	>800

Revised text:

Table 2 Estimated Daily Dosage for ICS

Asthma Therapy	**Total Daily Dose (µg/day)**		
Inhaled Corticosteroid	**Low**	**Medium**	**High**
Beclomethasone dipropionate non-HFA inhalers	200 to 500	>500 to 1000	>1000-2000
Beclomethasone dipropionate HFA[a]	80 to **250**	>**250** to **500**	>**500**
Ciclesonide	80 to 160	>160 to 320	>320 - 1280

Asthma Therapy	**Total Daily Dose (µg/day)**		
Inhaled Corticosteroid	**Low**	**Medium**	**High**
Triamcinolone acetonide	400 to 1000	>1000 to 2000	>2000
Flunisolide	500 to 1000	>1000 to 2000	>2000
Fluticasone propionate non-HFA inhalers	100 to 300	>300 to 500	>500 - 1000
Fluticasone propionate HFA[b]	88 to 264	>264 to 460	>460
Budesonide	200 to 400	>400 to 800	>800-1600
Mometasone furoate	200 to <400	≥400 to 800	>800

Reason for Administrative change:

Clarification of asthma therapy

Section of protocol affected:

5.7

Previous text:

Table 1 Study Plan

	Enrol-ment	Rando-mization			Treatment				Follow Up
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**EoT**	**Follow - up**
Telephone contacts				**X**		**X**	**X**		**X**
Day (+ visit window)		**0 (<15)[a]**	**28(±3)[a]**	**60(±3)[a]**	**84(±3)[a]**	**120(±3)[a]**	**150(±3)[a]**	**182(±3)[a]**	**189(±3)[a]**
……..									
Collect/dispense study medication		X	X		X			X	
Dose actuation count			X	X	X	X	X	X	
Review patients asthma status via IVRS			X	X	X	X	X	X	
……..									

a If a patient is re-screened, 3 months or later, after the last signing of the ICF, the patient needs to re-consent to the study, see section 8.2.
b Blood samples for DNA will be collected for exploratory genetics. Sampling is optional and subject to separate approval/consent. Sample will be taken at Visit 2 or if this day is not suitable, on any of the remaining planned visits the patient will attend.
c Only required for patients reporting an AE(s) or asthma exacerbation (s).
d For definition of unstable asthma see Section 6.2.5.2.

Revised text:

Table 2 Study Plan

	Enrol-ment	Rando-mization			Treatment				Follow Up
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**EoT**	**Follow - up**
Telephone contacts				**X**		**X**	**X**		**X**
Day (+ visit window)		**0 (<15)[a]**	**28(±3)[a]**	**60(±3)[a]**	**84(±3)[a]**	**120(±3)[a]**	**150(±3)[a]**	**182(±3)[a]**	**189(±3)[a]**
……..									
Collect/dispense study medication		X	X		X			X	
Dose actuation count[e]			X	X	X	X	X	X	
Review patients asthma status via IVRS			X	X	X	X	X	X	
…….									

a If a patient is re-screened, 3 months or later, after the last signing of the ICF, the patient needs to re-consent to the study, see section 8.2.
b Blood samples for DNA will be collected for exploratory genetics. Sampling is optional and subject to separate approval/consent. Sample will be taken at Visit 2 or if this day is not suitable, on any of the remaining planned visits the patient will attend.
c Only required for patients reporting an AE(s) or asthma exacerbation (s).
d For definition of unstable asthma see Section 6.2.5.2
e See Section 5.7 for instructions regarding collection and recording of patient's compliance to dispensed study drug.

Reason for Amendment:

Clarified instructions for collection/recording of patient's compliance to study treatment.

Section of protocol affected:

5.3 Procedures for handling patients incorrectly enrolled or randomized

Previous text:

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

Revised text:

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

If a patient does not meet the selection criteria but is randomized in error or incorrectly started on treatment, a discussion should occur between the AstraZeneca Study Team Physician and the Investigator regarding whether to continue or discontinue the patient from treatment. Consistent with Intention-To-Treat (ITT) principles, all randomized patients should continue to be followed in the study (ie, attend protocol visits) and, unless treatment would be harmful, patients should continue to receive study medication. Every effort must be made to ascertain all safety and efficacy events throughout the conduct of the study.

The AstraZeneca Study Team Physician is to ensure all such decisions are appropriately documented.

In situations where an agreement cannot be reached, the patient should have their study therapy stopped but continue with telephone follow-up.

Reason for Amendment:

Updating to clarify procedures for evaluation and handling of patients where minor violations of inclusion/exclusion criteria are detected. This is done in order to preserve study integrity and to comply with the ITT principles of an outcome trial. Patients with any safety concerns will still be excluded from further treatment

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Section of protocol affected:

5.7

Previous text:

The administration of all study drugs (including investigational products) should be recorded in the appropriate sections of the eCRF. The intake of study medication will be recorded as dose actuation count in the eCRF on the schedule study visits (Visits 3, 5 and EoT) and monthly telephone contacts.

A daily reminder will be addressed via IVRS. If the patient is not compliant, he or she will receive additional training on how to use the pMDI.

Revised text:

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

The intake of study medication **for each patient** will be **assessed through utilization of each inhaler's dose actuation counter in order to compare expected versus actual medication taken. Thus, only the start and stop number on each dose actuation counter should be recorded in the eCRF when patients return the inhalers after treatment.**

Site staff will review study medication compliance with the patient at each scheduled study visit (Visits 3, 5 and EoT) and monthly telephone contacts **and make a note in Medical records.**

A daily reminder will **also** be addressed via IVRS. If the patient is not compliant, he or she will receive additional training on how to use the pMDI.

Reason for Amendment:

Clarified instructions for collection/recording of patient's compliance with study treatment.

Section of protocol affected:

Section 6.2.2.3 Visit 3, 5 and EoT

Previous text:

- Use of investigational product (recorded as dose actuation count), see Section 5.7

Revised text:

- Use of investigational product, recorded as dose **actuation counter start and stop number for each inhaler when returned**, see Section 5.7

Reason for Amendment:

Clarified instructions for collection/recording of patient's compliance to study treatment.

Section of protocol affected:

6.2.3 Telephone contacts (Visit 4, 6 and 7)

Previous text:

- Use of investigational product (recorded as dose actuation count reported by the patient), see Section 5.7.

Revised text:

- ~~Use of investigational product (recorded as dose actuation count reported by the patient), see Section 5.7~~

Reason for Amendment:

Clarified instructions for collection/recording of patient's compliance to study treatment.

Persons who initiated the Amendment:

Central Study Team

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A 26 week, randomized, double-blind, parallel-group, active controlled, multicenter, multinational safety study evaluating the risk of serious asthma-related events during treatment with Symbicort®, a fixed combination of inhaled corticosteroid (ICS) (budesonide) and a long acting β_2-agonist (LABA) (formoterol) as compared to treatment with ICS (budesonide) alone in adult and adolescent (≥12 years of age) patients with asthma

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

I agree to the terms of this study

AstraZeneca Research and Developm
site representative

ASTRAZENECA SIGNATURE(S)

A 26 week, randomized, double-blind, parallel-group, active controlled, multicenter, multinational safety study evaluating the risk of serious asthma-related events during treatment with Symbicort®, a fixed combination of inhaled corticosteroid (ICS) (budesonide) and a long acting β_2-agonist (LABA) (formoterol) as compared to treatment with ICS (budesonide) alone in adult and adolescent (≥12 years of age) patients with asthma

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I agree to the terms of this study protocol/amendment.

AstraZeneca Research and Developmen
site representative

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I agree to the terms of this study protocol/amendment.

AstraZeneca Research and Development site representati

SIGNATURE OF INTERNATIONAL CO-ORDINATING INVESTIGATOR

A 26 week, randomized, double-blind, parallel-group, active controlled, multicenter, multinational safety study evaluating the risk of serious asthma-related events during treatment with Symbicort®, a fixed combination of inhaled corticosteroid (ICS) (budesonide) and a long acting β_2-agonist (LABA) (formoterol) as compared to treatment with ICS (budesonide) alone in adult and adolescent (≥12 years of age) patients with asthma

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

I agree to the terms of this amendment.

Signature: