AstraZeneca

Clinical Study Protocol

Drug Substance	Formoterol pMDI
Study Code	D589GC00002
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Date	

A Phase 2, randomized, blinded, 5-period cross-over, placebo and active-controlled, multicenter, dose-finding study of single doses of formoterol 2.25 µg, 4.5 µg, and 9 µg delivered via Symbicort pMDI and Foradil® Aerolizer® 12 µg evaluating the bronchodilating effects and safety in children, ages 6 to <12 years, with asthma who are receiving background treatment with budesonide pMDI 160 µg bid

Sponsor: AstraZeneca AB, SE-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

AstraZeneca

PROTOCOL SYNOPSIS

A Phase 2, randomized, blinded, 5-period cross-over, placebo and active-controlled, multicenter, dose-finding study of single doses of formoterol 2.25 µg, 4.5 µg, and 9 µg delivered via Symbicort pMDI and Foradil® Aerolizer 12 µg evaluating the bronchodilating effects and safety in children, ages 6 to <12 years, with asthma who are receiving background treatment with budesonide pMDI 160 µg bid

International Coordinating Investigator or Principal Investigator or National Coordinating Investigator

Study centers and number of patients planned

This study will be conducted in approximately 30 centers globally. An adequate number of patients will be randomized to obtain 50 completed patients.

Study period	Phase of development

Objectives

The primary objective of this study is to evaluate the bronchodilating effects of 3 doses of formoterol given in combination with budesonide as Symbicort pMDI in a population of asthmatic children demonstrated to be stable on a medium dose range of ICS therapy.

The secondary objectives of this study are to:

- evaluate the bronchodilating effect of Foradil Aerolizer (formoterol fumarate inhalation powder; Schering) 12 µg
- determine the systemic exposure to formoterol following administration of formoterol 2.25 µg, 4.5 µg, and 9 µg, given in combination with budesonide as Symbicort pMDI or Foradil Aerolizer 12 µg.

The safety objective of this study is to evaluate the safety of formoterol, given in combination with budesonide, in a population of asthmatic children demonstrated to be stable on a medium dose range of ICS therapy.

Study design

This is a Phase 2 single-dose, randomized, double-blind, 5-way crossover, active- and placebo-controlled, multicenter study comparing single doses of 2.25 µg, 4.5 µg and 9 µg of inhaled formoterol given as Symbicort pMDI and Foradil Aerolizer 12 µg dry powder inhaler (DPI) with placebo, given in combination with budesonide pMDI 160 µg, in pediatric patients with asthma. The primary outcome is AUC_{0-12} for FEV_1.

The study consists of a screening visit (Visit 1), an enrollment visit (Visit 2), a 1 to 2 week run-in (standardization) period, randomization at Visit 3, and 4 further visits separated by approximately 7-day washout (stabilization) periods. A telephone follow-up will be done after the last visit.

Target patient population

The study will enroll male and female patients (ages 6 to <12 years inclusive) who have a documented clinical diagnosis of asthma as defined by the American Thoracic Society for at least 6 months prior to Visit 1 and have required daily inhaled glucocorticosteroid therapy in the medium dose range (as defined by 2007 NAEPP guidelines) for at least 4 weeks prior to Visit 1. Patients must demonstrate sufficient reversibility to bronchodilators and meet lung-function criteria.

Investigational product, dosage and mode of administration

Single formoterol delivered doses of 2.25 µg, 4.5 µg, and 9 µg will be investigated by the administration of 1 and 2 inhalations of Symbicort 80/2.25 and 2 inhalations of Symbicort pMDI 80/4.5.

Additional study maintenance medication

Open-label budesonide 160 µg (as 80 µg hydrofluoroalkane pMDI, 2 actuations) will be administered in the morning and evening.

Albuterol 90 µg (hydrofluoroalkane pMDI, 1 to 2 actuations, as needed) or salbutamol 100 µg (hydrofluoroalkane pMDI, 1 to 2 actuations, as needed) will be administered for relief of asthma symptoms.

Comparator, dosage and mode of administration

Comparator treatments include a matching placebo pMDI and a single inhalation of open-label Foradil (formoterol) Aerolizer, 12 µg metered dose.

Duration of treatment

The study consists of 5 single-day treatment periods, preceded by a 1 to 2 week run-in standardization period and separated by 3-14 day washout periods. The total study duration is expected to be from 4 to 8 weeks dependent upon variability of the washout periods.

Outcome variable(s):

- Efficacy
  - The primary efficacy variable will be AUC_{0-12} for FEV_1.
  - The secondary efficacy variables are FEV_1 at 12 hours after study medication inhalation and the maximal FEV_1 for the 12-hour study period.
- Pharmacokinetics
  - 12-hour urine collection to measure unchanged formoterol
- Safety
  - Incidence of adverse events, discontinuations due to adverse events, serious adverse events

Statistical methods

The primary analysis of efficacy will be based on the full analysis set, which includes all patients who were randomized, took at least 1 dose of study medication and contributed sufficient data for at least 1 efficacy endpoint to be calculated. The per-protocol analysis set will be based on the full analysis set excluding patients for protocol deviations, as described in the statistical analysis plan. The safety analysis set will include all randomized patients who took at least 1 dose of study medication.

The primary analysis of efficacy/pharmacodynamic data will be based on the full analysis set. Average 12-hour FEV_1 will be used as the primary variable for comparing the bronchodilating effect of 3 doses of formoterol, Foradil Aerolizer and placebo. The primary efficacy endpoint will be analyzed with an additive analysis of covariance (ANCOVA) model appropriate for a crossover design, adjusting for the fixed factors of patient, period, and treatment, and for the covariate of pre-dose FEV_1 from each visit.

The secondary efficacy endpoint maximum FEV_1 will be analyzed in the same way that the average 12-hour FEV_1 was analyzed. Using the FEV_1 values at each time point, descriptive statistics will be presented to show the pattern of FEV_1 responses over time from the 12-hour serial FEV_1 assessments.

Multiplicity for the 3 doses of formoterol will be addressed by using a hierarchical testing procedure starting with the highest dose. If statistical significance is not achieved at the 0.05

level for a given dose, formal statistical testing will stop but nominal p-values will be reported.

Urinary excretion of formoterol will be summarized descriptively for each treatment, including a summary of the number of values below the limit of detection for each treatment. A multiplicative analysis of variance (ANOVA) model with patient, period, and treatment as fixed factors will be fit to the data.

No formal hypothesis testing of safety data is planned.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
AE	adverse event (see definition in Section 6.4.1)
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ATS	American Thoracic Society
AUC	area under the curve
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CRO	contract research organization
CSA	Clinical Study Agreement
DAE	discontinuation of investigational product due to adverse event
DPI	dry powder inhaler
ECG	electrocardiogram
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
eCRF	electronic case report form
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HFA	hydrofluoroalkane
IB	investigator brochure
ICH	International Conference on Harmonisation
ICS	inhaled corticosteroid
IPS	investigational product supply
ITT	intent-to-treat
IVRS	Interactive Voice Response System
LABA	long-acting beta-2 agonist
LLOQ	lower limit of quantification
LOCF	last observation carried forward

Abbreviation or special term	Explanation
5-LOI	5-lipoxygenase inhibitor
LSMeans	least squares means
LTRA	leukotriene receptor antagonist
MDI	metered dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities
OAE	other significant adverse event (see definition in Section 11.2.2)
PI	Principal Investigator
PFT	pulmonary function tests
pMDI	pressurized metered dose inhaler
SABA	short-acting beta-agonist
SAE	serious adverse event (see definition in Section 6.4.2)
TEAE	treatment-emergent adverse event
WBDC	web based data capture

1. INTRODUCTION

Inhaled corticosteroids (ICS) are considered first-line treatment for patients with persistent asthma, with the addition of an inhaled fast-acting β_2-agonist for symptomatic relief, as needed. The addition of a long-acting inhaled β_2-agonist (LABA) to ICS has been shown to provide better control of symptoms and to improve lung function further in asthmatic patients not adequately controlled with ICS monotherapy. Combination treatment with an inhaled corticosteroid and a LABA is now well-established and is considered an effective and safe treatment (NAEPP 2007).

Symbicort® (budesonide/formoterol) Inhalation Aerosol (Symbicort® pMDI) is a fixed combination product containing budesonide, a potent ICS, and formoterol fumarate dihydrate, a LABA. In the US Symbicort pMDI is indicated for the long-term maintenance treatment of asthma in patients 12 years of age and older and for the maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema. Symbicort pMDI is administered by oral inhalation using hydrofluoroalkane (HFA) as the propellant.

The NAEPP guidelines (NAEPP 2007) for pediatric patients with asthma, ages 5 to 11 years, indicate that for patients not adequately controlled on low-dose ICS the addition of a LABA to low-dose ICS is a preferred therapy (Step 3). This study is designed to identify the appropriate dose(s) of formoterol in pediatric patients (age 6 to <12 years of age).

1.1 Background

AstraZeneca markets formoterol outside the US as a dry-powder formulation under the name of OXIS® TURBUHALER and associated trade names, which is approved in approximately 90 countries as of 31 May 2009 at doses of 9 to 18 µg once or twice daily for regular use in children 6 years and older and as Symbicort TBH which is approved for use in children in approximately 90 countries as of 31 May 2008. In addition, formoterol is available as Foradil Aerolizer® (Schering) for the maintenance treatment of asthma (12 µg) in patients 5 years of age and older. As for all LABAs, it is recommended that formoterol be used in the treatment of asthma only in combination with ICS. This led to the development of Symbicort, a fixed combination treatment containing both the glucocorticosteroid budesonide and the LABA, formoterol. AstraZeneca has previously studied Symbicort pMDI in pediatric patients with a total daily dose of formoterol of 18 µg; however, there is limited data in children on the appropriate dose range of formoterol delivered by pMDI intended for use as maintenance therapy.

The appropriate pMDI dose(s) of formoterol for pediatric patients (ages 6 to <12 years) will be determined in a single-dose, placebo-controlled and active-controlled efficacy and safety study using a crossover design. Available data suggest that the most appropriate doses of formoterol pMDI to be evaluated are formoterol 2.25 µg, 4.5 µg, and 9 µg. AstraZeneca does not have formoterol as a monoproduct in a pMDI device; therefore; Symbicort pMDI device will be utilized to deliver formoterol and budesonide during the study. Foradil Aerolizer

(12 µg), the US-approved formoterol product for pediatric patients >5 years of age, will also be included as an active control arm. During the run-in/qualification and wash-out periods, all patients will receive budesonide pMDI 160 µg bid (80 µg × 2 inhalations bid) in order to maintain patient stability during the study period. As there is no pMDI formulation of formoterol as a monocomponent available, Symbicort pMDI will be used to deliver the formoterol doses of interest, with additional inhalations of budesonide pMDI 80 µg provided to ensure a background budesonide dose of 160 µg.

1.2 Research hypothesis

Asthmatic children ages 6 to <12 years treated with maintenance ICS will demonstrate significant improvement in post-dose FEV_1 when given formoterol compared with placebo.

Formoterol is safe and well-tolerated in children with asthma.

1.3 Rationale for conducting this study

The rationale for the primary objective is to determine the appropriate dose(s) of formoterol pMDI in children ages 6 to <12 years.

The rationale for the safety objective is to demonstrate the safety and tolerability of formoterol in children ages 6 to <12 years.

1.4 Benefit/risk and ethical assessment

Overall, 1447 patients 6 to <12 years of age have participated in placebo- and active-controlled Symbicort 160 µg /9 µg and 320 µg /9 µg bid studies. Of these 1447 patients, 539 received Symbicort twice daily. The overall safety profile of these patients was similar to that observed in patients ≥12 years of age who also received Symbicort twice daily in studies of similar design. Budesonide pMDI has a safety profile comparable to other budesonide formulations. No new or unexpected adverse events have been observed during clinical studies with budesonide pMDI. As all patients will be maintained on a daily dose of inhaled budesonide, the risk/benefit profile is considered to be favorable. There are no significant ethical concerns.

Please refer to Section 3.2 for further analysis of the benefits/risks associated with this study.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of this study is to evaluate the bronchodilating effects of 3 doses of formoterol given in combination with budesonide as Symbicort pMDI in a population of asthmatic children demonstrated to be stable on a medium dose range of ICS therapy.

2.2 Secondary objective

The secondary objectives of this study are to:

- evaluate the bronchodilating effect of Foradil Aerolizer (formoterol fumarate inhalation powder; Schering) 12 µg
- determine the systemic exposure to formoterol following administration of formoterol 2.25 µg, 4.5 µg, and 9 µg, given in combination with budesonide as Symbicort pMDI or Foradil Aerolizer 12 µg.

2.3 Safety objective

The safety objective of this study is to evaluate the safety of formoterol, given in combination with budesonide, in a population of asthmatic children demonstrated to be stable on a medium dose range of ICS therapy.

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 Phase 2, single-dose, randomized, double-blind, 5-way crossover, active- and placebo-controlled, multicenter study comparing single doses of 2.25 µg, 4.5 µg, and 9 µg of inhaled formoterol given as Symbicort pMDI and Foradil Aerolizer 12 µg dry powder inhaler (DPI) with placebo, given in combination with budesonide pMDI 160 µg, in pediatric patients with asthma. The primary outcome is AUC_{0-12} for FEV_1.

This study will be conducted in approximately 30 centers globally. An adequate number of patients will be randomized to obtain 50 completed patients. Evaluable is defined as those who have assessments at baseline and have taken at least 1 dose of study medication after randomization.

The study consists of a screening visit (Visit 1), an enrollment visit (Visit 2), a 1 to 2 week run-in (standardization) period, randomization at Visit 3, and 4 further visits separated by approximately 7-day (minimum 3 days; maximum 14 days) washout (stabilization) periods. For each patient, the total study duration is expected to be from 4 to 8 weeks dependent upon variability of the washout periods (see **Figure 1**).

Patients will be assessed for eligibility at Visits 1 and 2. During the run-in/qualification and wash-out periods, patients will receive open-label budesonide pMDI 160 µg bid (80 µg x 2 inhalations) in order to maintain patient stability and albuterol/salbumatol HFA pMDI to be taken as needed.

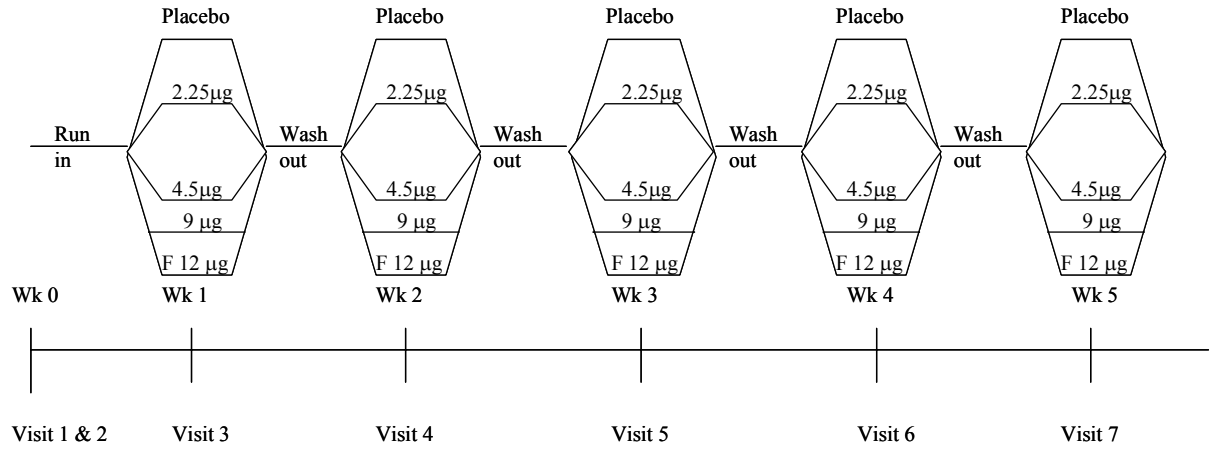
Note: Albuterol 90 µg and salbutamol 100 µg are equivalent. Salbutamol is commercially labeled to reflect the dose delivered from the canister valve, while albuterol is commercially labeled to reflect the dose delivered by the actuator mouthpiece. Therefore, only the albuterol dose will be listed throughout this protocol.

Patients will withhold the open-label budesonide pMDI on the morning of Visits 3, 4, 5, 6, and 7 and will also be required to withhold SABA medications for 6 hours prior to Visits 3, 4, 5, 6 and 7. At Visit 3, patients who fulfill the inclusion criteria and none of the exclusion criteria will be randomized to the first of 5 single-dose treatments.

The formoterol treatments will be delivered either via Symbicort pMDI (doses 2.25 µg through 9 µg) or Foradil Aerolizer (formoterol 12 µg). The Symbicort 80/2.25 µg device and the US-approved Symbicort 80/4.5 µg device will be utilized in the study. Three priming actuations of the Symbicort pMDI (and placebo pMDI) will be dispensed in the air by the study site personnel prior to administering study treatment. Foradil Aerolizer will be delivered via a DPI device, which does not require priming.

The screening period, run-in/qualification period, double-blind treatment period, and final visit or study discontinuation are described below.

Figure 1 Study Flow Chart



3.1.1 Screening period: Visit 1/2 (up to 7 days)

The purpose of the screening period is to allow time for patients to withhold/change medication prior to Visit 2 lung function assessments (see Section 5.6 for a list of restricted medications and timing for withdrawal prior to Visit 2). Visits 1 and 2 may be combined for those patients who do not need to withhold/change medication prior to Visit 2 lung function assessments.

At the screening visit (Visit 1), the following information will be collected from each patient:

- Informed consent and patient assent
- Concomitant medication

Before Visit 2, the medications listed in Table 2 must be withdrawn within the specified time limits prior to Visit 2 lung function assessments. At this visit, which must take place in the morning, the following information will be collected from each patient:

- Demography
- Medical and surgical history

And the following will be performed:

- Urine pregnancy test, in post-menarche females only. If female patients achieve menarche during the study, a urine pregnancy test should be performed before any study procedures at the next scheduled visit.
- Spirometry measurement (at least 6 hours after the last dose of SABA): FEV_1, FVC and FEF_{25-75}. FEV_1 must be ≥60% and ≤85% of predicted normal.
- Reversibility test: FEV_1 measurement before and 15 to 30 minutes after administration of a standard dose of albuterol at Visit 2 (albuterol MDI, 90 µg per inhalation, 2 to 4 actuations, with or without a spacer, or up to 2.5 mg of nebulized albuterol). At least 15 % reversibility must be shown. Patients can return to the clinic once within 7 days for a 2nd attempt at reversibility if the first attempt was ≥12 % but <15%. This 2nd attempt must also be done in the morning. Until the reversibility criterion is met, the patient must not be entered into the run-in period. This means that (s)he must not be withdrawn from his/her usual ICS and must not be dispensed run-in medication, rescue medication, or patient note book and diary. The run-in period cannot start until after the FEV_1 and reversibility criteria have been met.
- Physical examination
- Vital signs
- Review of inclusion and exclusion criteria

Each patient should be dispensed and/or instructed in the following:

- Use of allowed and disallowed medications, including withholding medications prior to each study visit (see Sections 5.1 and 5.6)
- Correct inhalation technique and dosing using the pMDI inhaler (see Section 5.5.2)
- The use of a spacer for administration of study medication (pMDI) or reliever albuterol/salbutamol medication is NOT permitted
- Dispensed open-label budesonide pMDI 160 µg bid (80 µg x 2 inhalations) in order to maintain patient stability
- Dispensed albuterol (US sites) or salbutamol (non-US sites) reliever medication.

When scheduling Visit 3 (within 7 days), remind the patient:

- Not to use dispensed or prescribed albuterol (US sites) or salbutamol (non-US sites) reliever medication within 6 hours prior to the visit unless absolutely necessary.

3.1.2 Randomization visit: Visit 3 (Week 1)

At the randomization visit, the following information will be collected from each patient:

- Concomitant medications
- Any adverse events experienced since last visit
- Review of inclusion/exclusion criteria at randomization (see Section 4.2).

Procedures to be performed at this visit include:

- Review of allowed and disallowed medications (see Table 3 and Table 4), including withholding medications prior to each study visit (see Section 5.1)
- Brief physical examination, including vital signs
- Dispense study note book and diary and review information to be recorded in the patient's note book and diary, including study maintenance medication use, concomitant medication use, and adverse events
- Pre-dose lung function measurements should be obtained using current ATS Standardization Techniques as a guideline. The following testing will be performed: FVC, FEV_1 in liters and FEF_{25-75} in liters/sec. If a patient has a pre-dose FEV_1 (L) with >12% variation from the pre-dose, baseline FEV_1(L)

measurement obtained at the visit where the patient showed reversibility of at least 15%, the patient can return to the site twice for additional spirometry testing (within the visit window) in order to meet this criterion; however, if the patient fails to meet this requirement after these attempts, the patient should be withdrawn

- Once the above criteria have been met, randomization of the patient to a treatment sequence will occur.

When scheduling Visits 4 through 7, remind the patient:

- To withhold use of the study medication the morning of the next visit (12±1 hours)
- If possible, not to use albuterol (US sites) or salbutamol (non-US sites) reliever medication within 6 hours prior to the visit unless absolutely necessary
- That the use of a spacer for administration of study medication (pMDI) or reliever albuterol/salbutamol medication is NOT permitted.

3.1.3 Visits 3 to 7

These visits should be conducted 1 week (-4/+7 days) after the previous visit.

At Visits 3 to 7, patients will be at the site for approximately 13 hours. The study visits will be separated by a minimum of 3 days and a maximum of 2 weeks. Overnight accommodations following Visits 3 to 7 may be provided for patients and their families if the long treatment visits necessitate it.

In the morning of these visits, where randomized study medication will be given, the patients will have to meet stability criteria described below in order to proceed.

Stability criteria: If a patient has a pre-dose FEV_1 (L) with >12% variation from the pre-dose, baseline FEV_1 (L) measurement obtained at the visit where the patient showed reversibility of at least 15%, the patient can return to the site twice for additional spirometry testing (within the visit window) in order to meet this criterion; however, if the patient fails to meet this requirement after these attempts, the patient should be withdrawn.

At these visits, the following information will be collected from each patient:

- Concomitant medications
- Any adverse events experienced since last visit and/or during the visit.

Procedures to be performed at these visits include:

- Review of allowed and disallowed medications (see Table 3 and Table 4), including withholding medications prior to each study visit (see Section 5.1)
- Brief physical examination, including vital signs
- Review of information recorded in the patient's note book and diary, including study maintenance medication use, concomitant medication use, and adverse events
- Pre-dose lung function measurements should be obtained using current ATS Standardization Techniques as a guideline. The following testing will be performed: FVC in liters, FEV_1 in liters, and FEF_{25-75} in liters/sec.

3.1.4 Final visit (Visit 7) or study discontinuation

At the final visit, the following information will be collected from each patient:

- Concomitant medications
- Any adverse events experienced since last visit.

Procedures to be performed at these visits include:

- A comprehensive physical examination, including:
  - Vital signs will be obtained including sitting systolic and diastolic blood pressure (from the same arm throughout study), sitting pulse, and respiratory rate for a minimum of 30 seconds
  - Height (cm)/weight (kg)
  - An assessment of general appearance, skin, respiratory, cardiovascular, abdomen, head and neck (including ENT), reflexes, lymph nodes, and musculoskeletal
- Urine pregnancy test, in post-menarche females only
- Review of information recorded in the patient's note book and diary, including study maintenance medication use, concomitant medication use, and adverse events
- Pre-dose lung function measurements should be obtained using current ATS Standardization Techniques as a guideline. The following testing will be performed: FVC in liters, FEV_1 in liters, FEF_{25-75} in liters/sec
- Review of allowed and disallowed medications (see Table 3 and Table 4), including withholding medications prior to each study visit (see Section 5.1)

- Remind the patient that they will be receiving a telephone call from study personnel in approximately 2 weeks to check for possible AEs since the final study visit.

The patient should return the following at the final visit:

- Reliever medication (if dispensed by the study site)
- Study medication
- Study note book and diary.

At the end of the treatment period, patients will resume appropriate asthma therapy and follow-up with their asthma physician.

Table 1 Study plan

Study Plan	Enrollment	Run-in	Single dose treatment				
Visit	**1**[a]	**2**[a]	**3**	**4**	**5**	**6**	**7**
Week	**0**	**0**	**1**	**2**	**3**	**4**	**5**
Visit Window (days)		**-7**	**-4/+7**	**-4/+7**	**-4/+7**	**-4/+7**	**-4/+7**
Informed consent	X						
Demography		X					
Medical history		X					
Surgical history		X					
Inclusion/exclusion criteria		X	X				
Review allowed/disallowed medication, including withholding medications prior to each study visit	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X
Physical examination		X					X
Brief physical examination			X	X	X	X	
Randomization			X				
Inhalation practice from pMDI/Aerolizer	X	X	X	X	X	X	X
Study drug inhalation			X	X	X	X	X
Study Maintenance medication (D=Dispense/R=Return)		D			D		R
Study reliever medication (D=Dispense/R=Return)		D			D		R
Vital signs		X	X[b]	X[b]	X[b]	X[b]	X[b]
Pregnancy test (post-menarche females) [c]		X					X
Pre-dose lung function (FEV_1 FVC, and FEF_{25-75}		X[d]	X[d]	X[d]	X[d]	X[d]	X[d]
Reversibility test		X[d]					
12 hour FEV_1			X[e]	X[e]	X[e]	X[e]	X[e]
12 hour urine sample[f]			X	X	X	X	X
Adverse events		X	X	X	X	X	X[g]

[a] Visits 1 and 2 may be combined for those patients who do not need to withhold/change medication prior to Visit 2 lung function assessments.
[b] Vital signs should be taken in the morning before inhalation of the study drug.
[c] If female patients achieve menarche during the study, a urine pregnancy test should be performed before any study procedures at the next scheduled visit.
[d] Spirometry to be centrally over-read to confirm valid technique as per inclusion/exclusion criteria.
[e] At 3, 9, and 15 min, and 1, 2, 3, 4, 6, 8, 10, and 12 hours after drug inhalation
[f] Collection of urine samples for determination of unchanged formoterol
[g] Two weeks after Visit 7, a follow up telephone call will be made to the patient to assess for additional adverse events[g]

3.2 Rationale for study design, doses, and control groups

The crossover study design requires fewer patients than a parallel-group study design by using patients as their own controls and therefore reducing the variability in between-treatment comparisons. In order to eliminate carryover effect, a minimum time between treatments (3 days) was chosen to ensure an adequate washout period between treatments.

Selection of dose and treatment duration

The budesonide pMDI 160 µg bid dose (80 µg × 2 inhalations bid) selected for this study approximates the monotherapy budesonide 180 µg bid dose available as Pulmicort Flexhaler, which is approved in the US for children over age 6 and exhibits a similar safety profile to comparators.

As previous studies have shown that the effects of formoterol are negligible after 48 hours, a minimum 3-day washout period between treatments was chosen.

Study design and control groups

Systemic exposure to formoterol will be assessed by measurement of urinary excretion of unchanged formoterol over the 12-hour post-dose period. The primary advantage to utilizing urinary formoterol excretion is that reliable estimates of systemic exposure over the 12-hour post-dose period can be provided. Plasma formoterol concentrations would be measurable for only 1 to 2 hours following the single actuation dose, but would be measurable for longer times at the higher doses. For AUC measurements, having a variable number of data points for the different doses could lead to the inaccurate assessments of relative exposure between treatments.

Previous data indicated that unchanged formoterol can be measured in urine following single doses as low as 4.5 µg and that urinary excretion is proportional with dose (Astra Draco clinical study report, 1993). A study has also demonstrated that pulmonary availability as measured by urinary excretion of unchanged formoterol is consistent with results based on plasma determination (AstraZeneca clinical study report, 1999). Thus, for this study design with varying doses of formoterol, urinary formoterol levels are a reliable means for measuring systemic exposure and have the added benefit of eliminating the need for phlebotomy and associated risk and discomfort in this vulnerable pediatric population. Because budesonide is administered at a constant dose, assessment of budesonide systemic exposure is not planned for this study.

Efficacy variable selection

Standard assessment tools for evaluating clinical efficacy and safety in this population are utilized. The efficacy measurements chosen for this study are those commonly used to evaluate efficacy endpoints in pediatric patients with asthma.

The primary efficacy variable of AUC_{0-12} for FEV_1 is a standard lung function assessment that has been accepted for regulatory purposes to demonstrate efficacy. FEV_1 is well-established as an efficacy measure in pediatric studies that is measured on clinic visits when spirometry is obtained.

Uniformity of patient dosing and data collection

To ensure accurate dosing of study and reliever medications, patients will be instructed on proper inhalation technique (including mouth rinsing) using placebo HFA pMDI provided in a training kit at Visit 1. An assessment of technique will be made at Visit 1, followed by further instructions as needed.

Use of centralized spirometry will ensure consistency of collected data and all spirometry will be centrally over-read to confirm valid technique.

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 fulfill the following criteria:

Inclusion criteria (Visits 1/2)

1. Provision of signed and dated informed consent prior to conducting any study-specific procedures.

2. Is between the ages of 6 and <12 years (not having reached his/her 12th birthday at the time of Visit 1).

3. Has a documented clinical diagnosis of asthma as defined by the American Thoracic Society (ATS, ie, "a disease characterized by increased responsiveness of the trachea and bronchi to various stimuli and manifested by widespread narrowing of the airway that changes in severity either spontaneously or as a result of therapy") for at least 6 months prior to Visit 1.

4. Has a FEV_1 measured at least 6 hours after the last dose of inhaled, short-acting β_2-agonist (SABA) and at least 48 hours after the last dose of inhaled LABA of ≥60% and ≤85% of predicted normal. Polgar predicted normal standards will be used for all patients. If the patient is taking a fixed combination of ICS and LABA, the

patient is to be placed on a comparable dose of ICS without the addition of a LABA at least 48 hours prior to spirometry testing.

5. Demonstrated reversibility of FEV_1 of ≥15% from pre-albuterol level within 15 to 30 minutes after administration of a standard dose of albuterol at Visit 2 (albuterol MDI, 90 μg per inhalation, 2 to 4 actuations, with or without a spacer, or up to 2.5 mg of nebulized albuterol). Patients can return to the clinic once within 7 days for a 2nd attempt at reversibility if the first attempt was ≥12 % but <15%. This 2nd attempt must be done in the morning. Until the reversibility criterion is met, the patient must not be withdrawn from his/her usual ICS and must not be dispensed run-in medication, study reliever medication, or patient notebook and diary. The run-in period cannot start until after the FEV_1 and reversibility criteria have been met.

6. Has required and received treatment with a consistent daily dose of ICS within the corresponding dose range listed below for at least 4 weeks prior to Visit 1. If the patient is not under the care of the investigator, documentation of ICS use by pharmacy records or copies of the prescribing Health Care Practitioner's records are required, to verify ICS use.

   - Beclomethasone dipropionate HFA pMDI: 160 - 320 μg/day
   - Budesonide: 360 - 540 μg/day
   - Budesonide (nebulized): 1000 μg/day
   - Flunisolide: 1000 - 1250 μg/day
   - Flunisolide HFA: 320 μg/day
   - Fluticasone 176 - 352 μg/day (HFA pMDI) or 200-400 μg/day (Diskus)
   - Triamcinolone acetonide: ≥600 - 900 μg/day
   - Ciclesonide: 320 - 480 μg/day
   - Mometasone: 440 μg/day

   Note: Other non-steroidal asthma medications (eg, leukotriene modifiers, mast cell stabilizers) could have been used in combination with any of the above and would not impact a patient's eligibility. After providing written informed consent for withdrawal of medication and at least 48 hours prior to spirometry testing, potential patients maintained on a fixed combination of ICS and LABA should be switched to a comparable dose of ICS without the addition of a long-term β2-agonist. This change will not be considered a change in the dose of maintenance ICS.

7. If receiving inhalant allergen immunotherapy, the patient must have been on a stable maintenance regimen for at least 6 weeks and is expected to remain on immunotherapy throughout the study.

Randomization criteria (Visit 3)

1. Has discontinued use of all asthma medications, including all formulations of β_2-agonists, following Visit 2 (or since meeting the FEV_1/reversibility criteria, if met after Visit 2) and used only the open-label run-in medication and reliever medication provided since Visit 2.

   Has a pre-dose morning clinic FEV_1 measured at least 6 hours after the last dose of inhaled SABA with <12% variation from the pre-dose, baseline FEV_1(L) measurement obtained at the visit where the patient showed reversibility of at least 15%.

4.2 Exclusion criteria

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

1. Has been hospitalized for >24 hours at least once or has required emergency treatment more than once in an emergency department (or equivalent) for acute deterioration of asthma during the 6 months prior to Visit 1.

2. Has required treatment with systemic corticosteroids (eg, oral, parenteral, or rectal) for any reason within the 12 weeks prior to Visit 1.

3. Has participated in another investigational drug study during the 4 weeks prior to Visit 1.

4. Has participated in a prior Symbicort clinical study within the previous 12 months.

5. Is receiving treatment with a β-blocker (including eye drops).

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

7. Positive pregnancy test at any time during the study.

8. Has any significant disease or disorder, which, 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.

9. Has a planned hospitalization during the study.

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

11. Has known or suspected hypersensitivity to study medications and/or their excipients.

Exclusion criteria at randomization (Visit 3)

1. Has been treated with systemic corticosteroids (eg, oral, parenteral, or rectal) for any reason during the run-in period or at time of Visit 3.

2. Has been hospitalized for >24 hours or has required emergency treatment in an emergency department (or equivalent) for acute deterioration of asthma during the run-in period.

3. Has a respiratory infection or other viral/bacterial illness or is recovering from such an illness at the time of Visit 3, which, in the investigator's opinion, will interfere with the patient's lung function and/or ability to perform serial spirometry.

Early termination of the serial spirometry visit

Should the patient require the use of a SABA during serial spirometry, a final pulmonary function test (PFT) should be performed, if possible, before administering albuterol. If, at any time during serial spirometry, the patient's FEV_1 falls to <50% of predicted, and is judged by the investigator as a true value not caused by technical difficulties (OR for safety reasons as judged by the investigator), the spirometry testing should be stopped, and the patient should be given albuterol 90 µg x 2 inhalations. The patient must however remain at the clinic to complete the 12 hour urine collection. Early termination of a serial spirometry does not mandate withdrawal from the study.

Withdrawal criteria for randomized study visits

Withdrawal criteria for each of Visits 3, 4, 5, 6, and 7: If a patient has a pre-dose FEV_1 (L) with >12% variation from the pre-dose, baseline FEV_1(L) measurement obtained at the visit where the patient showed reversibility of at least 15%, the patient can return to the site twice for additional spirometry testing (within the visit window) in order to meet this criterion; however, if the patient fails to meet this requirement after these attempts, the patient should be withdrawn.

Procedures for withdrawal of incorrectly enrolled patients are detailed in Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

- Patients will be asked to withhold the morning dose of budesonide and withhold reliever medication for 6 hours prior to each study visit.

- Use of concomitant medications is restricted as detailed in Section 5.6.

5.2 Patient enrollment and randomization

The Principal Investigator (PI) will:

1. Obtain signed informed consent from the patient's parent or guardian/legal representative and signed assent from the patient before any study-specific procedures are performed

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

3. Determine patient eligibility. See Sections 4.1 and 4.2

4. The IVRS will assign an eligible patient unique randomization code (patient number), beginning with "#".

As patients are screened for the study, they must be allocated an enrollment code (E-code). The E-code is a 7-digit number made up of the center number and the patient number within that particular center.

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

5.2.1 Procedures for randomization

An adequate number of patients will be randomized to reach approximately 50 completed patients. The IVRS will make sure there is an even distribution between countries and age groups.

Randomization codes will be assigned strictly sequentially as patients become eligible for randomization.

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 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 medical monitor and the investigator regarding whether to continue or discontinue the patient from treatment.

The medical monitor 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.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

The study treatment, except Foradil Aerolizer, given on Visits 3, 4, 5, 6, and 7 is double-blind for patients, investigators, and study personnel.

Packaging and labeling of the investigational products will be performed in a way to ensure blinding throughout the study.

No member of the study team in AstraZeneca, at study sites, or any contract research organization (CRO) handling data will have access to the randomization scheme during the conduct of the study with the exception of AstraZeneca's Investigational Product Supply (IPS) and Patient Safety.

The randomization scheme for blinding of randomized treatment will be maintained by AstraZeneca and will not be disclosed until after the database lock.

5.4.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomization for each randomized patient, will be available to the investigator or pharmacists from the IVRS. Routines for this will be described in the IVRS user manual that will be provided to each site.

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

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

5.5 Treatments

5.5.1 Identity of investigational product(s)

Investigational product	Dosage form and strength	Manufacturer
Symbicort 80/2.25 µg	pMDI for oral inhalation, 80/2.25 µg	AstraZeneca
Symbicort 80/4.5 µg	pMDI for oral inhalation, 80/4.5 µg	AstraZeneca
Budesonide HFA pMDI 40 µg	pMDI (HFA) for oral inhalation, 40 µg	AstraZeneca
Budesonide HFA pMDI 80 µg	pMDI (HFA) for oral inhalation, 80 µg	AstraZeneca
Foradil® Aerolizer® 12 µg	Aerolizer® DPI for oral inhalation, 12 µg	Commercially Available
Placebo	pMDI (HFA) for oral inhalation	AstraZeneca

5.5.2 Doses and treatment regimens

The study consists of a screening visit (Visit 1), an enrollment visit (Visit 2), a 1-week run-in (standardization) period, randomization at Visit 3, and 4 further visits during the treatment period separated by 3 days to 2 weeks washout (stabilization) periods. Treatment period is expected to be from 4 to 8 weeks, dependent upon variability of the washout periods.

Visits 1 and 2

Patients will be assessed for eligibility at Visits 1 and 2. Patients meeting eligibility criteria at Visit 2 will enter the run-in/qualification and randomized treatment periods, patients will receive open-label budesonide 160 µg bid (as budesonide HFA pMDI 80 µg x 2 inhalations) and as needed albuterol (US sites) or salbutamol (non-US sites) reliever therapy.

After assessments have been performed, the patients will practice inhalation technique (including mouth rinsing) with the placebo HFA pMDI provided in the training kit. The duration of the run-in/qualification period will be a minimum of 7 days.

Training

At Visit 1, the patients will be instructed on how to use the pMDI inhaler (see priming instructions). Each site will be provided with sufficient training pMDIs. These devices will be used in the clinic only and will not be dispensed to the patients to take home. An assessment of technique will be made at Visit 1, followed by further instructions as needed. The training device contains excipients, but no active ingredients.

Treatment Visits 3 to 7

At Visit 3, patients who fulfill the inclusion and randomization criteria and none of the exclusion criteria will be randomized. The randomized study visits (Visits 3 to 7) are 1 day (13 hours). The study visits will be separated by a washout period that will last a minimum of 3 days and a maximum of 2 weeks.

Patients will withhold budesonide in the morning of Visits 3, 4, 5, 6, and 7 and will also be required to withhold short acting bronchodilator medications for 6 hours prior to Visits 3, 4, 5, 6, and 7.

Randomized study medication

After the run-in/qualification period, eligible patients will be randomized at Visit 3 to 1 of 5 single-dose treatments (4 blinded and 1 partially blinded):

- The blinded single-dose treatments (each delivered in 3 inhalations following priming of devices by study site personnel):
  - 2.25 µg formoterol (as 80/2.25 µg Symbicort pMDI ×1 inhalation) + 40 µg budesonide HFA pMDI × 2 inhalations,
  - placebo HFA pMDI × 1 inhalation + 4.5 µg formoterol (as 80/2.25 µg Symbicort pMDI × 2 inhalations),
  - placebo HFA pMDI × 1 inhalation + 9 µg formoterol (as 80/4.5 µg Symbicort pMDI × 2 inhalations),
  - placebo HFA pMDI × 1 inhalation + 80 µg budesonide HFA pMDI × 2 inhalations,

- The partially blinded treatment arm will be delivered as:
  - Foradil Aerolizer 12 µg × 1 inhalation + 80 µg budesonide HFA pMDI × 2 inhalations.

Study maintenance medication

During the run-in/qualification and randomized treatment periods, patients will receive open-label budesonide 160 µg bid (as budesonide HFA pMDI 80 µg x 2 inhalations) in order to maintain patient stability. Daily use of study maintenance medication is to be recorded twice daily (morning and evening) in the study diary.

Study reliever medication

All patients will receive open-label albuterol HFA pMDI 90 µg per actuation (US sites) or salbutamol 100 µg per actuation (non-US sites), with 1 to 2 inhalations to be taken as needed. This medication is not to be used on a regularly scheduled basis.

Priming of the inhalers

The study medication and placebo pMDI will require priming when initially dispensed and 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 dose 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 2 more times
  - The pMDI inhaler is now ready for use.

5.5.3 Additional study medication

Reliever medication (US sites)

Investigational product	Dosage form and strength	Manufacturer
Albuterol HFA	pMDI (HFA) for oral inhalation, 90 µg	Commercially Available

Reliever medication (non-US sites)

Investigational product	Dosage form and strength	Manufacturer
Salbutamol pMDI	pMDI (HFA) for oral inhalation, 100 µg	Commercially Available

5.5.4 Labeling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfill GMP Annex 13 requirements for labeling. These labels will be designed to meet country-specific requirements and be translated into local language. They will contain at least the Study number, Med ID, directions for use, and storage conditions.

Booklet labels will be used for the Randomized Study Material, Run-In Material, Training Kits, and Reliever Medication. The first page of the booklet label will contain, at minimum, the study number and variable text (i.e. Med ID Number, expiry date, country code). The inner page(s) will contain the standard clinical trial information (ie, dosing instructions, storage conditions, directions for use, etc).

5.5.5 Storage

All study medications 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. An orientation label (STORE THIS WAY UP) will be affixed to every patient kit and must be adhered to.

5.6 Concomitant and post-study treatment(s)

5.6.1 Pre-study medications

The list of medications that must be discontinued by the patient prior to Visit 2 is provided in Table 2.

Table 2 Timing of pre-study drug restrictions

	Drug:	Time of withdrawal prior to Visit 2
1	Long acting anticholinergics	48 hours
2	Inhaled long-acting β_2-agonists	48 hours
3	Inhaled short-acting β_2-agonists (except albuterol/salbutamol as required for relief of bronchospasm)	6 hours
4	Oral β_2-agonists	
	Short-acting	6 hours
	Slow release	24 hours
5	Ephedrine-containing medication or herbal supplements	48 hours

5.6.2 Concomitant medications

The administration of all medications (including investigational products) must be recorded in the appropriate sections of the source documentation and electronic case report form (eCRF). The patient's parent or legal guardian must be instructed to record all medication use in the note book and report all medications given to the patient, in addition to those prescribed by the investigator.

Table 3 Medications allowed from Visit 1 and throughout the study

Generic albuterol HFA pMDI will be used as reliever medication for this study.
Nasal steroids are to be continued at a comparable dose through Visit 5, if used prior to Visit 1. Nasal cromolyn sodium will be permitted to be used and discontinued at any time.
Non-asthma medications not previously excluded and deemed necessary for the patient's safety and well-being can be given at the discretion of the investigator(s). Such medications can include: decongestants (that do not contain ephedrine), antihistamines (except hydroxyzine), mucolytics, expectorants, antibiotics, topical steroids (<1%), and vitamins.

Table 4 Concomitant medication DISALLOWED during the run-in or randomized treatment period

Note: Following Visit 2, no other asthma medications may be used. The only exceptions are in the case of patient safety and asthma deterioration. Use of a disallowed asthma medication will generally necessitate the patient being discontinued from the study.
Systemic corticosteroids (eg, oral, parenteral, or rectal) for any reason
β-blockers (including eye drops)
Short and long acting β_2-agonists (other than study medication) and anticholinergics [eg, ipratropium bromide (Atrovent®) and tiotropium (Spiriva®)]
The use of nebulized albuterol routinely as reliever or maintenance therapy will not be allowed. If a patient uses nebulized albuterol in lieu of albuterol pMDI more than once within a 24-hour period or more than 2 times throughout the study, the patient will be evaluated by the investigator for potential discontinuation from the study.
Additional medications including LTRAs and 5-LOIs (for any indication), xanthines, ephedrine, or other oral or inhaled asthma medications typically taken for asthma (eg, cromolyn sodium and nedocromil sodium)
Xolair® or any other monoclonal or polyclonal antibody therapy for any reason
Other medications including hydroxyzine and topical steroids >1%
Initiation of immunotherapy while the patient is enrolled in this study
Systemic treatment with potent CYP 3A4 inhibitors (eg, ketoconazole and itraconazole)

Note: Use of a disallowed asthma medication may necessitate the patient being discontinued from the study.

Other medication, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF.

5.7 Treatment compliance

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

At Visit 1, patients will be instructed, according to written information and verbal instruction, on how to use a pMDI device correctly. Each patient will be provided with both a placebo pMDI device and a budesonide pMDI device. The training device will be kept at the center for use when practicing the correct inhalation technique at each visit.

The intake of randomized study treatment at the clinic visits will be supervised by the study personnel and the date and time of each dose will be recorded. Patients will also need to twice-daily record when they took each maintenance dose of budesonide pMDI in their study diary.

5.7.1 Accountability

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

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

AstraZeneca personnel or its representative will account for all study medications received at the site, unused study medications, and for appropriate destruction. Certificates of delivery and destruction should be signed.

5.8 Discontinuation of investigational product

5.8.1 Other criteria for withdrawal from the study

Patients may also be withdrawn from the study in the following situations:

- Voluntary discontinuation by the patient or patient's parent or legal guardian who is at any time free to discontinue the patient's participation in the study, without prejudice to further treatment
- The patient has a clinically significant or serious (AE) that would not be consistent with continuation in the study, as determined by the investigator, AstraZeneca or representative, or the patient, the patient's parents, or legal guardian
- Severe non-compliance to study protocol
- Patient is lost to follow-up.

5.8.2 Procedures for discontinuation of a patient from investigational product and withdrawal from study

Patients who discontinue investigational product will be withdrawn, and will have a withdrawal visit equivalent to the Visit 7 assessments plus a follow-up telephone call from study personnel in approximately 2 weeks later to check for possible AEs since the final study visit.

Patients who discontinue treatment during the study cannot be re-enrolled and will not be replaced.

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). Such patients will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an investigator. Adverse events will be followed up (see Sections 6.4.3 and 6.4.4); and all study medications should be returned by the patient.

Withdrawn patients will not be replaced.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

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

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed eCRFs. .

A diary will be used by the patient to record use of study maintenance medication. A notebook will be used for the patient to note concomitant medication and AEs.

6.2 Data collection and enrollment

The following data will be collected at screening/enrollment (Visits 1/2):

- Informed consent and patient assent
- Demography (date of birth, sex, and race)
- Inclusion/exclusion criteria
- Vital signs (blood pressure, pulse rate, temperature, and respiratory rate)

- Significant medical, surgical, and smoking history
- Prior and concomitant medication history
- Physical examination (including height [cm], weight [kg]) (will also be collected at the final study visit or discontinuation)
- Urine pregnancy test for post-menarche females only (will also be collected at the final study visit or discontinuation if collected initially). If female patients achieve menarche during the study, a urine pregnancy test should be performed before any study procedures at the next scheduled visit.
- AEs.

6.2.1 Follow-up procedures

The following data will be collected at each subsequent visit:

- Vital signs (blood pressure, pulse rate, and respiratory rate)
- Concomitant medications
- Brief physical examination (including pulmonary auscultation and ENT exam)
- AEs.

Patients and their parents or legal guardians will receive a telephone call from study personnel approximately 2 weeks after the final study visit to check for possible AEs since the final study visit.

6.3 Efficacy

The primary efficacy variable will be AUC_{0-12} for FEV_1.

The secondary efficacy variables are FEV_1 at 12 hours after study medication inhalation, and the maximal FEV_1 for the 12-hour study period.

6.3.1 Pulmonary function testing

A centralized spirometry vendor will provide instrumentation and the software-controlled system for obtaining automated spirometry measurements. Additional information and training will be provided outside this protocol.

Lung function tests will be performed at the site at the time points specified; they should be performed pre-dose. See Section 5.6 for concomitant medication restrictions around the spirometry tests.

The assessments should be performed prior to the administration of any bronchodilators and should be performed with the patient in a standing or upright, seated position, having rested for 15 minutes.

A record of the measurements must be made in the patient's notes. All printouts should be marked with date and enrollment or patient number. Measurements should be performed according to American Thoracic Society/European Respiratory Society guidelines, 2005 (Miller et al 2005a, Miller et al 2005b). In general:

- An electronic spirometer should be used and the same apparatus used for each patient at the site
- The site will be responsible for calibrating and recording the calibration of the spirometer according to the recommendations of the manufacturer. Unless otherwise advised, this should be on a daily basis and where there is a significant fluctuation in temperature (±3ºC) or barometric pressure.

6.3.1.1 Pre-dose spirometry at each visit

Pulmonary function will be tested at least 6 hours after the most recent use of reliever medication. Pulmonary function tests will consist of 3 forced expiratory maneuvers in which the patient expires forcefully from total lung capacity to residual volume. A spirometer, which meets ATS standards and is calibrated daily, will be used. The patient should be sitting or standing with his/her head level and tight clothing should be loosened and a noseclip should be applied. The patient should use the same sitting or standing position for all subsequent spirometry measurements throughout the study.

FVC, FEV_1, and FEF_{25-75} are to be obtained from the full expiratory flow-volume-time curve. The guidelines established by the ATS (2005), as described below, should be followed for pulmonary function testing.

Three technically satisfactory FVC maneuvers should be performed and the largest value for each parameter for the 3 technically satisfactory attempts should be selected and documented. The difference between the largest and second largest FEV_1 should not vary by more than 0.15 L. (Note: As these are pediatric patients 6 to <12 years of age, this will in most cases correspond to a difference of ≥10% between the highest and next highest FEV_1.) The largest FVC, FEF_{25-75}, and FEV_1 can come from different curves.

A maximum of 8 maneuvers can be performed until the reproducibility criteria are met. If the test maneuvers induce bronchoconstriction, so that consecutive measurements become lower, this trend should be noted and the largest FVC and FEV_1 should be reported.

Every attempt should be made to standardize the time of day that a patient undergoes lung function testing throughout the study, starting after Visits 1/2. The timing of the baseline spirometry at Visit 3 will determine the timing requirement for pre-dose spirometry at subsequent visits, which should be conducted ±1 hour from this time.

Polgar predicted normal standards will be used for all patients.

6.3.1.2 12-hour serial spirometry

FEV_1, along with other pulmonary measures, will be collected by a 12-hour serial spirometry test. Twelve-hour serial spirometry will be performed at Visits 3, 4, 5, 6, and 7.

Every attempt should be made to standardize the time of day that a patient undergoes lung function testing throughout the study, starting after Visit 1. The timing of the baseline spirometry will determine the timing requirement for pre-dose spirometry at subsequent visits, which should be conducted ±1 hour from this time. Administration of the study treatments is followed by pulmonary function tests (PFT) at the following time points (which are in minutes, with permitted time windows in parenthesis), measured from the time of last inhalation of study medication: 3 (±1), 9 (±1), 15 (±1), 60 (±5), 120 (±10), 180 (±10), 240 (±10), 360 (±10), 480 (±10), 600 (±10), and 720 (±10) minutes. Use of a SABA (or any other bronchodilator) during serial spirometry will invalidate further test results. If SABA is administered the spirometry portion of the study visit is terminated, but the patient must remain at the study site to complete the 12 hour urine collection.

A spirometer, which meets ATS standards and is calibrated daily, will be used for all PFTs. FEV_1 is to be obtained from the full expiratory flow-volume-time curve. The guidelines established at the ATS should be followed for pulmonary function testing. Should the patient experience spirometry-induced bronchospasm or express the desire to terminate testing, the site should encourage further spirometry testing if the patient is clinically stable.

Polgar predicted normal standards will be used for all patients.

6.3.1.3 Reversibility of air flow

Airway reversibility will be tested at enrollment (Visit 2) using spirometry methods described in Section 6.3.1.1. FEV_1 measurements should be obtained before and 15 to 30 minutes after administration of albuterol/salbutamol MDI 2 to 4 actuations (albuterol 90 µg per inhalation, salbutamol 100 µg per inhalation) with or without a spacer, or up to 2.5 mg of nebulized albuterol/salbutamol. An improvement of ≥15% from pre-albuterol/salbutamol level will be considered diagnostic of reversible airway obstruction, and satisfy inclusion criteria.

6.4 Safety

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

6.4.1 Definition of 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 SAEs

A SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfills 1 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 1 of the outcomes listed above.

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

6.4.3 Recording of adverse events

Time period for collection of adverse events

Adverse events will be collected from enrollment (Visit 2) throughout the treatment period and including the 2-week follow-up period (last contact by telephone).

SAEs will be recorded from the time of informed consent.

The patients will be provided with a note book to record health problems. The investigator is responsible to review the note book together with the patient and transfer any indications of AEs to the AE form.

Follow-up of unresolved adverse events

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

Variables

The following variables will be collected for each AE:

- AE (verbatim)
- the date when the AE started and stopped
- maximum intensity
- whether the AE is serious or not
- investigator causality rating against the 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 additional study medication
- Description of AE.

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

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

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.4.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a 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 a SAE.

Causality collection

The PI will assess causal relationship between investigational product and each AE, 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 additional study medication, other medication, and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

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

Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or care provider or reported in response to the open question from the study personnel: *'Has the child had any health problems since the previous visit/since we last asked?',* or revealed by observation will be collected and recorded in the eCRF. 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.

Asthma symptoms or signs, such as wheezing, cough, chest tightness, dyspnea, breathlessness, and phlegm, will be recorded as AEs when:

- the sign or symptom is serious according to definitions, and/or
- the patient discontinues the study due to the sign or symptom and/or

- the sign or symptom is new to the patient or not consistent with the patient's pre-existing asthma history (defined as within 1 year of Visit 1) as judged by the investigator

Adverse Events based on examinations and tests

The results from protocol-mandated assessments and vital signs will be summarized in the clinical study report. Deterioration as compared with baseline in protocol-mandated vital signs or assessments should therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a vital sign or assessment is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated vital sign will be considered as additional information. Wherever possible, the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless symptoms of disease under study, see above. Worsening of a sign or symptom of asthma beyond what is typically experienced clinically for that patient should be considered an AE.

Overdose

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

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.

If any SAE occurs in the course of the study, then investigators or other site personnel must inform appropriate AstraZeneca representatives within 1 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 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel must inform AstraZeneca representatives of any follow-up information on a previously reported SAE

within 1 calendar day, ie, immediately, but **no later than the end of the next business day** of when he or she becomes aware of it.

Reporting of SAEs will be described in the Safety Handling Plan for the study.

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

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

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug.

6.4.5 Laboratory safety assessment

At Visit 2 (enrollment) and Visit 7 (end of study), urine pregnancy testing will be conducted on post-menarchal females using urine testing kits provided by AstraZeneca; dipsticks will be analyzed by the study personnel at the site.

6.4.6 Physical examination

A comprehensive physical examination will be performed at Visit 2 (enrollment) and Visit 7 (end of study) and will include an assessment of the following: general appearance, skin, respiratory (including auscultation), cardiovascular, abdomen, head and neck (including ears, eyes, nose, and throat), reflexes, lymph nodes, and musculoskeletal (including spine and extremities). Height (without shoes) and weight (light clothing, no shoes) will also be measured at these 2 visits.

A brief physical examination will be performed at Visits 3 to 6 and consists of lung and heart auscultation. At these visits, a medically qualified staff member must listen to the patient's lungs to assess whether the patient may undergo spirometry. This must be performed prior to initiating spirometry. The examination of other body systems to evaluate or follow-up on (potential) AEs may be performed at the investigator's discretion.

6.4.7 Vital signs

Sitting systolic and diastolic blood pressure (from the same arm and with the same cuff size, appropriate for arm circumference, throughout study), sitting pulse, and respiratory rate for a minimum of 30 seconds will be measured at all visits except for Visit 1. Patients should be comfortably seated for at least 2 minutes prior to blood pressure, pulse, and respiratory rate readings.

6.5 Pharmacokinetics

6.5.1 Collection of samples

A 12-hour urine sampling for formoterol determination will commence after the patient empties his/her bladder immediately before the start of inhalation of formoterol or placebo.

All subsequent urine will be collected quantitatively up to 12 hours after inhalation for the determination of total amount of formoterol excreted. The patients will remain at the site during the 12 hours after inhalation while the total 0 to 12 hour urine is collected. The last emptying of the urine bladder, in the interval, will be performed at 12 hours.

The actual sampling start and stop times of the quantitative urine collections will be noted in the eCRF. The reference time for urine collection will be at the start of inhalation. The weight of the urine will also be noted in the eCRF.

Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

6.5.2 Determination of drug concentration

Samples for determination of drug concentration in urine will be analysed by PRA International – Early Development Services Westerbrink 3, 9405 BJ Assen, the Netherlands, on behalf of AstraZeneca, using liquid chromatography and mass spectrometry after dilution of the urine samples. The method is under development. The lower limit of quantification (LLOQ) of formoterol in urine is aiming at <30 pmol/L.

7. BIOLOGICAL SAMPLING PROCEDURES

At Visit 2 (enrollment) and Visit 7 (end of study), urine pregnancy testing will be conducted on appropriate females using urine testing kits provided by AstraZeneca; dipsticks will be analyzed by the study personnel at the site. No other biological sampling procedures will be conducted.

7.1 Handling, storage and destruction of biological samples

The samples will be used up or disposed of after analyses or retained for further use as described here.

7.1.1 Pharmacokinetic samples

Samples will be disposed of after the clinical study report has been finalized, unless retained for future analyses, see below.

7.2 Labeling and shipment of biohazard samples

Not applicable to this study.

7.3 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their life cycle.

The PI at each site keeps full traceability of collected biological samples from the patients until disposal.

AstraZeneca or representative keeps oversight of the entire life cycle through internal procedures, monitoring of study sites, and auditing of external laboratory providers.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

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

8.2 Patient data protection

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

For study sites within the US or in studies where non-US patients' protected health information (patient data) will come into the US through a covered entity (eg, Central lab/Reader), the Informed Consent and Child Assent Forms will incorporate, or be accompanied by, a separate document incorporating Health Insurance Portability and Accountability Act (HIPAA)-compliant wording by which patients authorize the use and disclosure of their Protected Health Information by the investigator and by those persons who need that information for the purposes of the study.

The Master Informed Consent and Child Assent Forms will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. All data computer-processed by AstraZeneca or representative will be identified by patient enrollment number, randomization number, and study code. The Master Informed Consent and Child Assent Forms will also explain that for data verification purposes, authorized representatives of AstraZeneca, a regulatory authority, an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) may require direct access to parts of the hospital or practice records relevant to the study, including the patient's medical history.

8.3 Ethics and regulatory review

An EC/IRB should approve the final study protocol, including the final version of the Informed Consent and Child Assent Forms and any other written information and/or materials to be provided to the patients in accordance with national regulations. The investigator will ensure the distribution of these documents to the applicable EC/IRB, and to the study site staff.

The opinion of the EC/IRB should be given in writing. The investigator should submit the written approval to AstraZeneca before enrollment of any patient into the study.

The EC/IRB should approve all advertising used to recruit patients for the study in accordance with national regulations.

AstraZeneca should approve any modifications to the Informed Consent and Child Assent Forms that are needed to meet local requirements.

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

Before enrollment of any patient into the study, the final study protocol, including the final version of the Informed Consent and Child Assent Forms, should be approved by the national regulatory authority, according to local regulations.

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

AstraZeneca will provide Regulatory Authorities, Ethics Committees and PIs with safety updates/reports according to local requirements, including suspected unexpected serious adverse reactions (SUSAR), where relevant.

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

8.4 Informed consent

The PI at each site will:

- Ensure that the both the patient (assent) and the parent or legal guardian (consent) are given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent and Child Assent Forms are stored in the Investigator's Study File
- Ensure copies of the signed Informed Consent and Child Assent Forms are given to the patient and parent or legal guardian

- 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 and child assent forms that are approved by an EC/IRB, if appropriate according to local regulations.

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the coordinating investigator and AstraZeneca.

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

The amendment should be approved by each EC/IRB and if applicable, also the national regulatory authority, before implementation. Local requirements should be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each PI. For distribution to EC/IRB, see Section 8.3.

If a protocol amendment requires changes to a site's Informed Consent and Child Assent Forms, AstraZeneca and the center's Ethics Committee, and if appropriate local regulatory authorities, should approve the revised Informed Consent and Child Assent Forms before the revised forms are used.

If local regulations require, any administrative change will be communicated to or approved by each EC/IRB and local regulatory authority.

8.6 Audits and inspections

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

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 study site to:

- Determine the adequacy of the facilities and equipment
- Determine availability of appropriate patients for the study
- Discuss with the investigator (and other personnel involved with the study) their responsibilities with regard to protocol adherence, their agreement to have 24 hours a day, 7 days a week coverage for study patients, 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 site staff and also train them in any study-specific procedures.

The PI 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 PI will maintain a record of all individuals involved in the study (medical, nursing and other staff), including start and stop (if applicable) dates of study involvement.

If there is staff turnover, it is the PI's responsibility to train any newly added staff on all components of the study procedures and the study protocol.

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
- Confirm that facilities remain acceptable
- Confirm that the site team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, and that investigational product 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

- Ensure that previously agreed upon enrollment expectations are being met.

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

9.3.1 Source data

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

9.4 Study agreements

The PI at each/the site should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the CSA, the terms of the 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 CSA shall prevail.

Agreements between AstraZeneca and the PI 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 CSA.

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 the 2nd quarter of 2010 and to end by the 3rd quarter of 2011.

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

10. DATA MANAGEMENT BY ASTRAZENECA OR DELEGATE

Data management will be performed by the CRO.

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

Data entered in the eDC system will be immediately saved to a central database and changes tracked to provide an audit trail. When the PI has signed the eCRF electronically as per eCRF instructions, then the patient's data will be locked.

Electronic case report forms

The eCRF and the protocol are both confidential. The eCRF will be created by the CRO and programmed into the eDC system. All sites will need internet access to access the eCRFs and will only have access to data for patients at their own sites. Data Management (DM) and other coordinator teams will have access to data at all sites.

All eCRFs are to be completed by an authorized member of the site staff and reviewed and signed by the investigator. All entries, corrections, and alterations are to be made by the responsible investigator or an authorized member of the site staff. All eCRFs are to be completed in a manner that ensures accurate interpretation of data.

It is each investigator's responsibility to ensure that all discontinued orders or changes in the study or other medications entered on the patient's eCRF correspond to the entries on the patient's medical records.

The eCRFs for any patient leaving the study should be completed at the time study medication is terminated for whatever reason.

The eCRFs must accurately reflect data contained in the patient's records (eg, source documents).

Dataflow

After the data are entered into the eCRF by site, auto-queries that are generated by the eDC system should be addressed by the site. Data queries will be raised for inconsistent, impossible, or missing data. At the monitoring visit, the Study Monitor must perform the source data verification (SDV) of the required fields on completed forms, and if there are no open queries, freeze the form. Data management will run manual consistency checks outside of the eDC system and will raise manual queries for sites to address; if the form is frozen, DM will unfreeze it to allow sites to amend data. The same process is to be followed by any other groups creating manual queries in the eDC system (eg, for SAE reconciliation). Once all data are entered, SDV complete on required fields, manual queries and electronic data reconciliation complete, and all queries closed, then the casebook can be signed. Once the casebook is signed, DM will then lock the casebook so that no amendments can be made.

Database lock

Once all patient casebooks are locked, the final data transfer can be sent to statistics. A database lock checklist will also be completed by DM and the programmer to confirm all applicable quality control checks were performed.

Coding

All AEs and Medical Histories recorded in the eCRF will be classified according to the terminology of the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary

(AZDD). The coding will occur outside of the eDC system and will be merged with the clinical datasets sent to statistics.

Investigator site file

At the beginning of the study, an investigator's study file will be established at the study site. The investigator/institution is responsible for maintaining the study documents as specified in the guideline for ICH GCP (Committee for Proprietary Medicinal Products [CPMP]/ICH/135/95) and as required by the applicable regulatory requirement(s). The investigator/institution must take measures to prevent accidental or premature destruction of these documents.

SAE reconciliation

The CRO will perform SAE reconciliation between the CRO clinical study database and the AstraZeneca clinical patient safety database.

11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA OR DELEGATE

11.1 Calculation or derivation of efficacy variable(s)

11.1.1 Primary variable – 12-hour serial FEV_1

Twelve-hour serial FEV_1 will be used to demonstrate the bronchodilatory effect of the 4 doses of formoterol and placebo. Twelve-hour serial FEV_1 will be calculated through an AUC determination and then divided by time, so that the final value is expressed in liters.

Calculation of AUC

The AUC will be defined as the area between the x-axis (FEV_1=0) and the FEV_1-over-time (where time is defined in the PDS dataset) curve from the serial spirometry maneuvers, after the administration of study medication at each visit. Area will be calculated using the trapezoidal method using the actual times of measurements (as opposed to the protocol-specified times). Average FEV_1 over 12 hours will be calculated using the following formula:

$$\frac{\left(\sum_i \frac{(FEV_{1(i)} + FEV_{1(i+1)}) * (T_{i+1} - T_i)}{2}\right)}{12}$$

where $FEV_{1(i)}$ and $FEV1_{(i+1)}$ are FEV_1 at time i and i +1, $T_{(i)}$ and $T_{(i+1)}$ are time i and time i +1 and $FEV_{1(V2)}$ is pre-dose FEV_1 at a given Visit

Handling missing data

FEV_1 values will be interpolated and/or extrapolated for use in the calculation of the AUC if data are missing within an individual set of serial spirometric measurements at a visit, according to the following algorithm:

- For patients with "bounded" missing data, interpolate the missing value(s) with a straight line connecting the 2 points bounding the missing data.
- For patients with "unbounded" missing data, the following extrapolation techniques will be used:
  - Carry forward the FEV_1 value from the last non-missing time point to all successive time points at that visit, hereafter referred to as 'LOCF' (this method of imputation will be used for primary analyses).
  - Carry forward the pre-dose FEV_1 value from that visit to all successive time points at that visit, hereafter referred to as 'Pre-CF' (this method of imputation will be used for sensitivity analyses).

Both bounded and unbounded methods will be used simultaneously within a visit in order to complete any missing 12-hour serial spirometry measurements; AUC itself will not be carried forward to subsequent visits for any reason.

11.1.2 Secondary variables

The secondary efficacy endpoints are the maximum 12-hour FEV_1 and the FEV_1 value at 12-hours. In addition, FEV_1 at each time point will be summarized descriptively. The secondary pharmacokinetic variables are discussed in Section 11.3 below.

Maximum 12-hour FEV_1

The maximum FEV_1 value will be defined as the largest observed FEV_1 value recorded during each 12-hour serial spirometry procedure. No method of interpolation or extrapolation will be used to obtain values for this variable.

FEV_1 at each time point

FEV_1 will be collected using a 12-hour serial spirometry test. Twelve-hour serial spirometry will be performed at Visits 3, 4, 5, 6, and 7. At these visits, administration of the cross-over study treatments is followed by PFTs at the following time points (which are in minutes, with permitted time windows in parenthesis), measured from the time of last inhalation of study medication: 3 (±1), 9 (±1), 15 (±1), 60 (±5), 120 (±10), 180 (±10), 240 (±10), 360 (±10), 480 (±10), 600 (±10), and 720 (±10) minutes.

- Because not all measurements are observed at the protocol specified time points, we will define a measurement 'window' for mapping each of the observed points to the

appropriate protocol specified time points (3, 9, 15, 60, 120, 180, 240, 360, 480, 600 and 720 minutes). An observed value, which did not occur exactly during the protocol specified time, will be mapped to an appropriate time value using the ranges shown in Table 5. Furthermore, we must consider the case where 2 or more time points may be present in the same interval or the case where no time point is present in an interval. In the case were no time point is present in an interval, we will consider the time point missing. In the case were 2 or more time points are present in an interval, we will take the point that is closest to the protocol specified time point. If there are 2 points equally spaced, which are 'closest' to the protocol specified time point, then we will take the 'earlier' time point.

Table 5 Time point ranges (in minutes) for PFT measurements

Time point	Range
3	0 ≤ observed value <6
9	6 ≤ observed value <12
15	12 ≤ observed value <30
60	30 ≤ observed value <90
120	90 ≤ observed value <150
180	150 ≤ observed value <210
240	210 ≤ observed value <300
360	300 ≤ observed value <420
480	420 ≤ observed value <520
600	520 ≤ observed value <660
720	660 ≤ observed value ≤780

FEV_1 value at 12 hours

The FEV_1 value at 12 hours after dosing will be estimated from the FEV_1-over-time curve used in the determination of the AUC. Determination of this value will be performed using the observed data for each of the protocol specified time points. A time point 'window', as defined in Section 11.1.2,will be used to map data that was observed at times other than those specified in the protocol. For one of the analyses, time point 'windows' will be used to map observed values to protocol specified times but no data interpolation/extrapolation will be performed in determining the AUC (e.g., if a patient does not have a value within the range 0 to 6 then time point '3' will be missing). In addition, as a measure of sensitivity, 2 more analyses will be performed using the methods discussed in Section 12.2.1.1. and interpolation/extrapolation methods (i.e., LOCF and Pre-CF) discussed in Section 12.2.1.2.

Therefore, there will be 3 analyses used to assess the effect of treatment on FEV_1 value at 12 hours.

11.2 Calculation or derivation of safety variable(s)

11.2.1 Treatment-emergent adverse events (TEAE)

A treatment-emergent (TEAE) is defined as any AE that started on or after the first dose of study medication up to 14 days after the last dose of study medication. AEs already present at the time of the first dose of study medication that worsens in intensity following exposure to study medication or AE with an unknown/not reported onset date will also be considered as treatment-emergent.

11.2.2 Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and DAEs. Based on the expert's judgment, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the Clinical Study Report. A similar review of laboratory and vital signs data will be performed for identification of OAEs.

Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

11.2.3 Number of withdrawals due to predefined criteria for worsening of asthma

Time to withdrawal is defined as the time (in days) from Visit 3 (randomization visit) to the day of withdrawal due to a predefined asthma event. For patients completing the study without a predefined asthma event, this variable will be censored at the day of study completion up to a maximum of the last randomized dose day plus 1 day. For patients who withdraw from the study for reasons other than a predefined asthma event, this variable will be censored at the last day of treatment plus 1 day.

11.2.4 Physical examination

Changes from baseline to final visit for physical examination will be reported.

11.2.5 Vital signs

Changes from baseline at each visit will be derived as the value at the visit minus the baseline value for the same assessment.

11.3 Calculation or derivation of pharmacokinetic variables

The pharmacokinetic calculations will be performed at Quintiles. Systemic exposure to formoterol will be determined using the following parameters:

Ae(0-12h)

The amount of formoterol excreted unchanged in urine over the 12-hour period after administration [Ae(0-12h)] is calculated from the concentration of formoterol in urine multiplied by the total volume of urine collected. Volume is determined from the weight of the collected urine times an assumed urine density of 1020 g/L. Urine concentrations below LLOQ will be set to zero.

fe(0-12h)

The fraction of the formoterol nominal delivered dose excreted unchanged in urine 0 to 12 hours after administration [fe(0-12h)). This is calculated from Ae(0-12h) divided by the nominal delivered dose of formoterol assuming a molecular weight for formoterol of 420.45 g/mol.

11.3.1 Population analysis of pharmacokinetic variables

The results from the investigation will not be reported in the Clinical Study Report but separately in a bioanalytical report.

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA OR DELEGATE

12.1 Description of analysis sets

Data analyses will be based on 3 patient populations, as defined below.

12.1.1 Efficacy analysis set

The primary analysis of efficacy will be based on the full analysis set, as defined by ICH guidance document E9: Statistical Principles for Clinical Trials. This analysis will adhere as closely as practically possible to the intention-to-treat (ITT) ideal, and will be based on data from all patients who were randomized, took at least 1 dose of study medication, and contributed sufficient data for at least 1 efficacy endpoint to be calculated.

12.1.2 Per-protocol analysis set

The per-protocol analysis set will be based on the full analysis set excluding patients for protocol deviations, as described in the statistical analysis plan (SAP). An analysis of the Per-Protocol analysis set will be performed only if 20% or more of the subjects are excluded from the Per Protocol population.

12.1.3 Safety analysis set

The safety analysis set will include all randomized patients who took at least 1 dose of study medication.

12.2 Methods of statistical analyses

12.2.1 Efficacy analysis

12.2.1.1 Primary variable

The primary analysis of efficacy/pharmacodynamic data will be based on the efficacy analysis set. Average twelve-hour FEV_1 will be use as the primary variable for comparing the bronchodilating effect of 3 doses of formoterol, Foradil Aerolizer and placebo. Missing data will be interpolated/extrapolated using the methods discussed in Section 3.1.2. Analyses of 12-hour FEV_1 include the following:

- Primary analysis of average 12-hour FEV_1 will use the LOCF method of extrapolation.
- Sensitivity analysis of average 12-hour FEV_1 will be performed using the Pre-CF method of extrapolation.

The primary efficacy endpoint, average FEV_1 from 12-hour serial FEV_1 measurements, will be analyzed with an additive ANCOVA model appropriate for a crossover design, adjusting for the fixed factors of patient, period, and treatment, and for the covariate of pre-dose FEV_1 from each visit.

Based on previous experience and the available literature, the pre-dose FEV1 at each visit is expected to correlate well with the average FEV_1 at that visit and therefore have considerable explanatory power. Thus, pre-dose FEV_1 at each visit will be included as a covariate in the ANCOVA model to reduce the estimated residual variance and improve the efficiency of the analysis.

Using this model, all pair-wise comparisons (lsmeans, confidence intervals and p-values) will be presented.

In addition to the primary analysis, a sensitivity analysis will be performed on the primary efficacy endpoint. This analysis will use a mixed-effects ANCOVA appropriate for a crossover design, in order to recover inter-block information which is not utilized in the fixed-effects analysis.

12.2.1.2 Secondary variables

To support the primary analysis, several analyses of secondary variables will be conducted.

FEV_1 at 12 hours

FEV_1 measured at 12 hours is an important secondary variable as it measures the effect of the treatments at the end of the dosing interval. This secondary efficacy endpoint will be analyzed using the same ANCOVA model that was used for the analysis of average 12-hour FEV_1.

Maximum FEV_1

The secondary efficacy endpoint maximum FEV_1 will be analyzed in the same way that the average 12-hour FEV_1 was analyzed. In addition, comparisons between each pair of treatments and estimates of mean treatment differences will be made by formulating contrasts within the context of this aforementioned ANCOVA model. These comparisons are intended to be descriptive in nature and are not associated with any preconceived decision rules.

FEV_1 at each time point

Using the FEV_1 values at each time point, descriptive statistics will be presented to show the pattern of FEV_1 responses over time from the 12-hour serial FEV_1 assessments. These summaries will be presented using the values in liters, the change from predose at that visit in liters, and the percent change from predose at that visit in liters. Mean values from these summaries will also be graphically displayed. In addition, the LOCF and Pre-CF extrapolation techniques, used in conjunction with straight-line interpolation for bounded missing data, will be used to fully populate the 12-hour FEV_1-over-time profiles at each visit (ie, there will be 1 value per time point per visit for each patient over 12-hours); then these summaries will be reproduced.

Finally, the FEV_1 values at each time point (using only the values liters, as opposed to changes or percent changes) will be analyzed with an ANCOVA model (by assigned time point) so that adjusted treatment means can be presented for each assigned time point. As above, these models will be run by assigned time point: (1) for fully populated profiles using LOCF extrapolation for unbounded missing data in conjunction with straight-line interpolation for bounded missing data, (2) for fully populated profiles using Pre-CF extrapolation for unbounded missing data in conjunction with straight-line interpolation for bounded missing data and (3) for all observed data after mapping.

12.2.2 Multiplicity

Multiplicity will be addressed by using a hierarchical testing procedure. If statistical significance is not achieved at the 0.05 level for a given comparison, formal statistical testing will stop.

The first comparison will be 9 µg formoterol vs. placebo for FEV_1 AUC_{0-12} at the 0.05 level of significance. If significant then,

The next comparison will be 4.5 µg formoterol vs. placebo for FEV_1 AUC_{0-12} at the 0.05 level of significance. If significant then,

The next comparison will be 2.25 µg formoterol vs. placebo for FEV_1 AUC_{0-12} at the 0.05 level of significance.

Foradil is included in this study as an active control. A nominal p-value will be computed for the comparison of Foradil and placebo.

12.2.3 Urine formoterol

Urinary excretion of formoterol will be summarized descriptively for each treatment, including a summary of the number of values below the limit of detection for each treatment.

A multiplicative (ie, natural log formoterol weight will be used as the response variable) analysis of variance (ANOVA) model with patient, period, and treatment as fixed factors will be fit to the data. Mean treatment ratios and their 95% CIs, calculated from the exponentiated LS mean differences and CI limits, will be presented for each pair-wise comparison. In addition, an additive analysis of variance (ANOVA) model will be fit with patient, period and treatment as fixed factors to these data so that treatment comparisons expressed as differences will be available. This is not intended to be a bioequivalence or dose-proportionality study; therefore, there will be no decision rule associated with these data.

12.2.4 Safety analysis

All randomized patients who receive at least 1 dose of the study treatment and for whom data have been collected after randomization will be included in the safety analysis set.

No formal hypothesis testing of safety data is planned.

12.2.4.1 Adverse events

All AEs will be summarized from the safety analysis set. In addition, serious adverse events and deaths or discontinuations due to AEs will be summarized for all patients who provide informed consent but who do not belong to the safety analysis set.

For all tabulations, AEs will be assigned to the prior treatment received. For example, if the patient received the single dose of 1 of the crossover treatments and experienced in the hours following that inhalation an AE, then the AE will be assigned to the randomized treatment received at that visit. If the patient experienced an AE during the washout period following the randomized treatment and the patient reported the AE at the next visit but prior to the next crossover treatment, the AE would be assigned to the treatment received in the previous period. AEs reported before the 1st dose of randomized treatment will be assigned "Pre-Randomization". AEs report any time after the last of randomized treatment will be assigned to the treatment received in the last period for that patient. AEs with onset “Pre-Randomization”, those with onset during the run-in period, and those with onset during the randomized treatment phase will be summarized separately.

For serious AEs, investigators will be asked to choose which drug may have been responsible for the SAE (SAE CRF module). Investigators will be given the choice between maintenance budesonide, the 5 randomized treatments, and "other"; they will be permitted to choose more than 1 option. These causality assessments will be summarized in the individual patient listings and in the patient narratives. The narratives will mention if the investigator's causality assessment was different that the treatment mapping (specified above) used for tabulations in the clinical study report.

AEs will be tabulated (number and percentage of patients) by System Organ Class, High-Level Term, and Preferred Term according to the treatment actually received. No formal hypothesis testing of these data is planned.

12.2.4.2 Vital signs data

No hypothesis testing of these data is planned. Results for pulse and blood pressure will be listed for each patient.

12.2.4.3 Physical examination data

No hypothesis testing of these data is planned. Results for physical examination will be listed for each patient.

12.2.5 Interim analyses

There are no planned interim analyses.

12.3 Determination of sample size

An adequate number of patients aged 6 to <12 years with a clinical diagnosis of asthma will be randomized to reach approximately 50 completed patients. The target is approximately 25% of completed patients will be children under the age 8. A sample size of 51 will have 90% power to detect a difference in treatment group means of 0.065 L assuming a standard deviation of differences of 0.14 L.

The sample size for this study was selected to be consistent with the research hypothesis as described in Section 1.2.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

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

In the case of a medical emergency the investigator may contact the Medical Monitor. If the Medical Monitor is not available, contact the designated Medical Monitor backup.

Name	Role in the study	Address & telephone number

13.2 Overdose

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

Symptoms
Glucocorticosteroids have a low toxicity, and are virtually without harmful effects after a single or a few doses, even if the doses are very high. Thus, acute overdosage with

budesonide – even in excessive doses – is not a clinical problem. As with all IGCSs, systemic glucocorticoid effects may appear if used chronically in excessive doses.

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

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

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

Procedures for reporting
For the purpose of this study, an accidental or deliberate intake of blinded treatment of more than 10 actuations (>800/45 µg Symbicort*)* during one day is defined as an overdose and must be reported as such as described below.

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

If an overdose on an AstraZeneca study drug occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives **within one day**, 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 reports of pregnancy and the outcomes of the 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.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives **within 1 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 same timelines apply when outcome information is available.

14. LIST OF REFERENCES

Astra Draco Clinical Study Report:
Tolerability and pharmacokinetics of inhaled D2522 after single-dose administration of increasing doses to healthy volunteers. (Study No. 37-CR-3001/2) 1993.

AstraZeneca R&D Clinical Study Report:
Tolerability and pharmacokinetics of formoterol inhaled via Turbuhaler® and Aerolizer® (Report No. SD-037-CR-0275) June 1999.

Miller et al 2005a
Miller MR, Crapo R, Hankinson J, Brusasco V, Burgos F, Casaburi R, et al. General considerations for lung function testing. Eur Respir J 2005;26:153-161.

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Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J 2005;26:319-338.

NAEPP 2007
National Asthma Education and Prevention Program (NAEPP). Expert panel III: Guidelines for the diagnosis and management of asthma. 2007. Available at http://www.nhlbi.nih.gov/guidelines/asthma/.

AstraZeneca

Clinical Study Protocol Appendix A

Drug Substance	Formoterol pMDI
Study Code	D589GC00002
Edition Number	1.0
Date	
Protocol Dated	

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A Phase 2, randomized, blinded, 5-period cross-over, placebo and active-controlled, multicenter, dose-finding study comparing single doses of formoterol 2.25 µg, 4.5 µg, and 9 µg delivered via Symbicort pMDI and Foradil® 12 µg evaluating the relative bronchodilating effects and safety in children, ages 6 to <12 years, with asthma who are receiving background treatment with budesonide pMDI 160 µg bid

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

I agree to the terms of this study protocol.

AstraZeneca Research and Developme
site representative

QUINTILES SIGNATURE

A Phase 2, randomized, blinded, 5-period cross-over, placebo and active-controlled, multicenter, dose-finding study comparing single doses of formoterol 2.25 µg, 4.5 µg, and 9 µg delivered via Symbicort pMDI and Foradil® 12 µg evaluating the relative bronchodilating effects and safety in children, ages 6 to <12 years, with asthma who are receiving background treatment with budesonide pMDI 160 µg bid

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

I agree to the terms of this study protocol.

AstraZeneca Research and Development site representati

SIGNATURE OF INTERNATIONAL CO-ORDINATING INVESTIGATOR

A Phase 2, randomized, blinded, 5-period cross-over, placebo and active-controlled, multicenter, dose-finding study comparing single doses of formoterol 2.25 µg, 4.5 µg, and 9 µg delivered via Symbicort pMDI and Foradil® 12 µg evaluating the relative bronchodilating effects and safety in children, ages 6 to <12 years, with asthma who are receiving background treatment with budesonide pMDI 160 µg bid

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

I agree to the terms of this study protocol. 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.

Centre No.:

Signature:

AstraZeneca

Clinical Study Protocol Appendix B

Drug Substance	Formoterol pMDI
Study Code	D589GC00002
Edition Number	1.0
Date	

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.