Clinical Study Protocol

A RANDOMISED, OPEN-LABEL, SINGLE-DOSE, SINGLE-CENTRE, CROSSOVER STUDY IN HEALTHY SUBJECTS TO ASSESS THE RELATIVE BIOAVAILABILITY OF SYMBICORT pMDI 160/4.5 μg ADMINISTERED WITH A SPACER (WITH AND WITHOUT CHARCOAL) AND SYMBICORT pMDI 160/4.5 μg ADMINISTERED WITHOUT A SPACER (WITH AND WITHOUT CHARCOAL)

PAREXEL Study No.:	PXL229149
Sponsor Study Code:	D589WC00001
EudraCT No:	2016-001866-27
Study Type:	Relative bioavailability
Test Product:	Symbicort pMDI with a spacer device
Reference:	Symbicort pMDI without a spacer device
Therapeutic Indication:	Asthma and chronic obstructive pulmonary disease (COPD)
Pharmacological Class:	Inhaled corticosteroid and long-acting β adrenergic agonist
Development Phase:	Phase 1
Sponsor:	AstraZeneca AB
Study Centre:	PAREXEL Early Phase Clinical Unit London
Date of Protocol:	Final 2.0,

This clinical study will be conducted according to the protocol and in compliance with Good Clinical Practice, with the Declaration of Helsinki and with other applicable regulatory requirements.

PROTOCOL SYNOPSIS

Title of the study

A RANDOMISED, OPEN-LABEL, SINGLE-DOSE, SINGLE-CENTRE, CROSSOVER STUDY IN HEALTHY SUBJECTS TO ASSESS THE RELATIVE BIOAVAILABILITY OF SYMBICORT pMDI 160/4.5 μg ADMINISTERED WITH A SPACER (WITH AND WITHOUT CHARCOAL) AND SYMBICORT pMDI 160/4.5 μg ADMINISTERED WITHOUT A SPACER (WITH AND WITHOUT CHARCOAL)

Principal Investigator (PI)

Study centre

This study will be conducted at a single study centre.

PAREXEL Early Phase Clinical Unit London,

Study rationale

This study will be conducted to establish the relative bioavailability of budesonide and formoterol delivered via Symbicort pressurized metered-dose inhaler (pMDI) with a spacer device (test) and budesonide and formoterol delivered via Symbicort pMDI without a spacer device (reference). Administration under each condition will occur with the concomitant administration of activated charcoal to estimate exposure through the lung and without activated charcoal to estimate total systemic exposure.

Number of subjects planned

Additional subjects may be randomised to ensure that at least 44 evaluable subjects complete the study.

Study period

Estimated date of first subject enrolled: (signing of informed consent)

Estimated date of last subject completed:

Study objectives

Primary objective:

- To assess the relative bioavailability between Symbicort pMDI administered through a spacer device and Symbicort pMDI delivered without a spacer device both with no charcoal (total systemic exposure)
- To assess the relative bioavailability between Symbicort pMDI administered through a spacer device and Symbicort pMDI delivered without a spacer device both with charcoal (lung exposure)

Secondary objectives:

- To characterise the pharmacokinetic (PK) profiles of budesonide and formoterol delivered via Symbicort pMDI when administered with and without spacer and with and without charcoal
- To assess the safety of single doses of budesonide/formoterol delivered via Symbicort pMDI in healthy subjects

Study design

This study will be a randomised, open-label, single-dose, crossover study in healthy subjects (males and females), performed at a single study centre.

The study will comprise:

- A screening period of maximum 28 days;

- Four treatment periods during which subjects will be resident from the afternoon before dosing with Symbicort until at least 24 hours after dosing; discharged on the morning of Day 2; and
- A final visit within 5 to 7 days after the last administration of Symbicort.

There will be a minimum washout period of 3 days between each dose administration of Symbicort.

Subjects will receive single doses of Symbicort on 4 occasions under fasted conditions.

During screening, spirometry testing will be performed by a technologist or a qualified designee to ensure subjects perform adequate manoeuvres to achieve optimal lung function. Device and inhalation training will be conducted on admission to each treatment period, and prior to dosing on Day 1 of each treatment period.

Expected duration of the study

Each subject will be involved in the study for approximately 7 weeks.

Targeted study population

This study will be conducted in healthy male and female subjects, 18 years (inclusive) and older.

Investigational medicinal product

Supplier:	AstraZeneca
IMP:	Symbicort pMDI
Formulation:	Pressurized inhalation suspension
Strength/concentration:	160/4.5 µg per inhalation
Dose:	2 inhalations
Route of administration:	Inhalation
Specific device for drug administration, if applicable:	AeroChamber Plus Flow-Vu spacer device
Regimen:	Treatment A: 2 x 160/4.5 µg Symbicort pMDI administered with no spacer device; no activated charcoal - reference formulation/total systemic exposure Treatment B: 2 x 160/4.5 µg Symbicort pMDI administered through AeroChamber Plus Flow-Vu spacer device; no activated charcoal - test formulation/total systemic exposure Treatment C: 2 x 160/4.5 µg Symbicort pMDI administered with no spacer device; with activated charcoal - reference formulation/lung exposure Treatment D: 2 x 160/4.5 µg Symbicort pMDI administered through AeroChamber Plus Flow-Vu spacer device; with activated charcoal - test formulation/lung exposure

IMP = investigational medicinal product; pMDI = pressurized metered-dose inhaler

Identity of the Non-Investigational Medicinal Product (NIMP)

Manufacturer:	Beacon Pharmaceuticals Ltd
Formulation:	Carbomix (Activated charcoal) 50 g for oral suspension
Strength/concentration:	813 mg/g
Dose regimen:	10 g immediately before inhalation of IMP; 10 g immediately after mouth-rinsing (done within 5 minutes after the inhalation of IMP); 10 g 1 hour after inhalation of IMP; 10 g 2 hours after inhalation of IMP
Route of administration:	Oral
Specific device for drug administration, if applicable:	Not applicable
Regimen:	Treatment C: 2 x 160/4.5 µg Symbicort pMDI administered with no spacer device; with activated charcoal - reference formulation/lung exposure Treatment D: 2 x 160/4.5 µg Symbicort pMDI administered through AeroChamber Plus Flow-Vu spacer device; with activated charcoal - test formulation/lung exposure

Outcome endpoints

Pharmacokinetic endpoints:

Where data allow, PK parameters will be derived for budesonide and formoterol on plasma concentrations.

- Primary PK parameters: C_{max} and AUC_{0-t}
- Secondary PK parameters: AUC, t_{max}, $t_{½,\lambda z}$ λ_z, V_z/F, CL/F and t_{last}

In addition, the ratio of $C_{max(B)}$:$C_{max(A)}$ and $C_{max(D)}$:$C_{max(C)}$, $AUC_{0-t(B)}$:$AUC_{0-t(A)}$ and $AUC_{0-t(D)}$:$AUC_{0-t(C)}$, and $AUC_{(B)}$:$AUC_{(A)}$ and $AUC_{(D)}$:$AUC_{(C)}$ (using non log-transformed data) will be determined for Symbicort pMDI administered through a spacer device : Symbicort pMDI delivered without a spacer device, both with no charcoal (total systemic exposure) and both with charcoal (lung exposure).

The diagnostic parameters (λ_z upper, λ_z lower, λ_z N, λ_z Rsq_adj and $AUC_{\%extrap}$) will also be determined.

Safety endpoint:

- Adverse events (AEs)

Statistical methods

Presentation of pharmacokinetic data:

A listing of PK blood sample collection times with actual elapsed times as well as derived sampling time deviations will be provided for budesonide and formoterol. Plasma concentrations will be summarised by treatment for each analyte presenting the following summary statistics in accordance with AZ Best Practice Reference Guidelines for PK Evaluations in Clinical Studies: n, n above lower limit of quantification (LLOQ), geometric mean (G_{mean}), G_{mean}+standard deviation (SD), G_{mean}-SD, geometric coefficient of variation (percentage) (GCV[%]), median, minimum and maximum.

All primary and secondary PK parameters will be listed for each subject, analyte and treatment using descriptive statistics in accordance with AZ Best Practice Reference Guidelines for PK Evaluations in Clinical Studies as follows:

- C_{max}, AUC_{0-t} and AUC will present n, G_{mean}, G_{mean}+SD, G_{mean}-SD, GCV(%), median, minimum and maximum.
- All relative values of C_{max}, AUC_{0-t} and AUC will present n, arithmetic mean (A_{mean}), SD, G_{mean}, G_{mean}+SD, G_{mean}-SD, GCV(%), median, minimum and maximum.
- $t_{½,\lambda z}$, λ_z, CL/F and V_z/F will present n, A_{mean}, SD, median, minimum and maximum.
- t_{max} and t_{last} will present only n, median, minimum and maximum.

Statistical analysis of pharmacokinetic data:

The PK analysis set will consist of all subjects in the safety analysis set for whom at least one of the primary PK parameters for a given analyte can be calculated and who have no important protocol deviations thought to impact on the analysis of the PK data.

The treatment ratio of each of the test formulations (B and D) will be compared to the reference formulations (A and C) for budesonide and formoterol.

The statistical analysis will be conducted separately for the following:

- For total systemic exposure: Treatment B versus Treatment A
- For lung exposure: Treatment D versus Treatment C

Treatment ratio will be assessed on the ratio of log-transformed C_{max}, AUC_{0-t} and AUC of budesonide and formoterol using a 2-sided 90% confidence interval (CI) approach based on a repeated measures analysis of variance (ANOVA) model including period and treatment as fixed effects, and subject as a random effect.

All PK parameters will be log-transformed prior to analysis. The estimated treatment differences and the 90% CIs on the log scale will be back-transformed to obtain the G_{mean} ratios for each pair of treatments. The least squares means (and 95% CIs), G_{mean} ratios and 90% CIs will be tabulated for each comparison and analyte (budesonide and formoterol).

Only the data for the comparison under investigation will be included in the statistical analysis, e.g., when comparing Treatment B and Treatment A, the data for the other treatments will be removed from the dataset. Subjects must have a primary PK parameter available for both treatments for the given analyte under consideration in order to be included in a specific analysis. A subject may therefore be included in the analysis for one parameter and not for another.

Presentation of subject disposition and baseline data:

Subject disposition:

Subject disposition will be listed and summarised including the number of withdrawals and the primary reason for withdrawal. Subjects excluded from the PK analysis set will be listed including the reasons for exclusions.

Baseline data:

Demographic variables will be listed and summarised. Medical history data will be coded and listed.
Follicle-stimulating hormone (FSH) results will be listed. Spirometry results will be listed. The results of viral serology and the drugs of abuse, alcohol and cotinine screen will not be listed in the clinical study report (CSR). Prior medication will be coded and listed.

Presentation and analysis of safety variables:

The safety analysis set will include all subjects who received at least 1 dose of Symbicort pMDI and for whom any safety post-dose data are available.

All AEs will be coded using MedDRA vocabulary. AEs will be listed for each subject and summarised by treatment and overall, and presented by system organ class (SOC) and preferred term (PT), with the exception of the causality and severity (mild, moderate and severe) tables, which will be presented by PT only.

Concomitant medication will be coded and listed. Vital signs will be listed and summarised. Resting 12-lead ECG data and results of physical examinations will be listed. Laboratory assessments (haematology and clinical chemistry) will be listed and summarised.

Determination of sample size

The purpose of this study is to estimate any difference in the PK of budesonide and formoterol with adequate precision; there have been no pre-determined success limits defined as this study is considered to be descriptive in nature. To determine an adequate level of variability of the estimated relative bioavailability it was decided to use the same logic and require the same precision as would have been relevant for a bio-equivalence study. Assuming an intra-subject coefficient of variation (CV) of 33% (based on the variability of AUC_{0-12} for budesonide and AUC_{0-12} and C_{max} for formoterol observed in a similarly designed crossover study in healthy adults), 44 evaluable subjects will give at least 80% power to show that the 90% CI for the treatment effects (Treatment B vs Treatment A and Treatment D vs Treatment C) lies entirely within the range 0.8 to 1.25, i.e., would rule out a 20% change (on a log scale) in exposure to budesonide and formoterol. It is considered appropriate to base the sample size on AUC_{0-12} for budesonide rather than C_{max} (which has higher variability)

since the effects of inhaled corticosteroids are more likely related to total systemic exposure (i.e., AUC) rather than to acute exposure (i.e., C_{max}).

Additional subjects may be randomised to ensure that at least 44 evaluable subjects complete the study.

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1.1. List of Tables

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2. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 12.1.1)
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
A_{mean}	Arithmetic mean
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
ATS	American Thoracic Society
AUC	Area under plasma concentration-time curve from zero to infinity
AUC_{0-t}	Area under the plasma concentration-curve from time zero to time of last quantifiable concentration
$AUC_{\%extrap}$	Percentage of AUC obtained by extrapolation, calculated as $[(C_{last}/\lambda_z)/AUC * 100]$, where C_{last} is the drug concentration at last observed time point
AZRand	AstraZeneca randomisation system
β-hCG	Beta human chorionic gonadotropin
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
CI	Confidence interval
CL/F	Apparent total body clearance of drug from plasma after extravascular administration
ClinBase™	PAREXEL's electronic source data capturing and information management system
C_{max}	Maximum observed plasma concentration
COPD	Chronic obstructive pulmonary disease
CRF	Case report form
CRO	Contract research organization
CSR	Clinical study report
CV	Coefficient of variation
DAE	Adverse event leading to the discontinuation of IMP/NIMP
DCF	Data clarification form
DES	Data Entry Site – where serious adverse event reports from AstraZeneca Clinical studies are entered onto the AstraZeneca Patient Safety database by Tata Consultancy Services

Abbreviation or special term	Explanation
DMP	Data management plan
DVS	Data validation specification
ECG	Electrocardiogram
EClysis©	User-interactive, modular computer-based system for dECG data processing, analysis and measurement of ECG intervals and wave amplitudes, exports and reports, used by the AstraZeneca ECG Centre
ERS	European Respiratory Society
EU	European Union
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FSH	Follicle-stimulating hormone
FVC	Forced vital capacity
GCP	Good Clinical Practice
GCS	Glucocorticosteroid
GCV(%)	Geometric coefficient of variation (percentage)
GGT	Gamma glutamyl transpeptidase (transferase)
GI	Gastrointestinal
GLP	Good Laboratory Practice
G_{mean}	Geometric mean
GMP	Good Manufacturing Practice
Hb	Haemoglobin
HBsAg	Hepatitis B surface antigen
HCT	Haematocrit
HIV	Human immunodeficiency virus
HL	Hy's Law
IATA	International Airline Transportation Association
ICD	Informed Consent Document
ICH	International Conference on Harmonisation
ICS	Inhaled corticosteroid
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IRB	Institutional Review Board
λ_z	Terminal elimination rate constant
λ_z, N	Number of data points included in the log-linear regression analysis

Abbreviation or special term	Explanation
λ_z upper and λ_z lower	The time interval (h) of the log-linear regression to determine $t_{½\lambda z}$
LABA	Long-acting β2-agonist
LLOQ	Lower limit of quantification
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
ms	milliseconds
n	Number of subjects
NC	Not calculated
ND	Not determined
NIMP	Non-investigational medicinal products (refers to the activated charcoal in this document)
Non-smoker	Subject who has not smoked previously and/or has not used nicotine or nicotine-containing products for at least 3 months; subjects who have discontinued smoking or the use of nicotine / nicotine-containing products (including snuff and similar products) at least 3 months before the first administration of the IMP
NQ	Non-quantifiable
NR	No result
OAE	Other significant adverse events
OTC	Over-the-counter
PDF	Portable Document Format
PDS	Protocol deviation specification (document)
PHL	Potential Hy's Law
PI	Principal Investigator
PK	Pharmacokinetics
pMDI	Pressurized metered-dose inhaler
PT	Preferred Term
QP	Qualified Person
QRS	ECG interval measured from the onset of the QRS complex to the J point
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave

Abbreviation or special term	Explanation
R&D	Research and Development
RBC	Red blood cell
Rsq_adj	Regression coefficient adjusted for λ_z, N, Goodness of fit statistic for calculation of λ_z
SAE	Serious adverse event (see definition in Section 12.1.2).
SAP	Statistical Analysis Plan
SD	Standard deviation
SMART	Symbicort maintenance and reliever therapy
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
$t_{½\lambda z}$	Half-life associated with terminal slope (λ_z) of a semi-logarithmic concentration-time curve
TCA	Tricyclic anti-depressant
TCS	Tata Consultancy Services – an AstraZeneca partner who conduct data entry onto Sapphire
TEAE	Treatment-emergent adverse event
t_{last}	Time of last quantifiable plasma concentration
t_{max}	Time to reach maximum observed plasma concentration
UK	United Kingdom
ULN	Upper limit of normal
USA	United States of America
V_z/F	Apparent volume of distribution during the terminal phase (extravascular administration)
WAD	Windows Allowance Document
WBC	White blood cell

3. ETHICAL AND REGULATORY REQUIREMENTS

3.1. Ethical Conduct of the Study

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

3.2. Subject Data Protection

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

All clinical study findings and documents will be regarded as confidential. The investigator and members of his/her research team must not disclose such information without prior written approval from the sponsor.

The anonymity of participating subjects must be maintained. Subjects will be specified in outputs and other documents containing subject data by their subject number, not by name. Documents that identify the subject (e.g., signed ICD) will be maintained in confidence by the investigator.

Study data will be stored in accordance with local and global data protection laws.

3.3. Ethics and Regulatory Review

The study will be submitted to the national regulatory agency for review and approval, by PAREXEL in accordance with local regulatory procedures.

The study will be submitted to the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) for ethical review and approval, by PAREXEL in accordance with local procedures.

All safety update reports will be prepared by AstraZeneca.

PAREXEL will provide the IEC/IRB, and if applicable the Principal Investigator (PI), with safety updates/reports according to local requirements, and will track compliance information for the latter according to the tracker provided in the agreed Safety Reporting and Management Process.

AstraZeneca will provide the national regulatory authority with safety updates and/or reports, in accordance with local requirements, including suspected unexpected serious adverse

reactions (SUSARs), where relevant. If required by local authorities, the PI will provide the IEC/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational medicinal product (IMP). AstraZeneca will provide this information to the PI to meet these reporting requirements.

Compensation will be reasonable and related to the nature and degree of inconvenience and discomfort as a result of participation in the study. Information on how participants will be compensated is contained in the ICD.

3.4. Insurance

The sponsor has covered this clinical study by means of an insurance of the clinical study according to national requirements. The name and address of the relevant insurance company, the certificate of insurance, the policy number and the sum insured are provided in the Investigator's Site File.

3.5. Informed Consent

The subjects shall be informed of the nature, significance, implications and risks of the trial, and informed consent will be freely given and evidenced in writing, dated and signed, or otherwise marked, by the subject as evidence to indicate his/her free informed consent, prior to the start of the study.

In conformance with the law, the nature of the informed consent will comply with the appropriate version of the Declaration of Helsinki, the current requirements of GCP (CPMP/ICH/135/95) and local regulation which ever affords the greater subject protection.

3.6. Changes to the Protocol and Informed Consent Document

Study procedures will not be changed without the mutual agreement of the 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. The amendment should be approved by the IEC/IRB and the national regulatory authority, before implementation, as appropriate. Local requirements should be followed for revised protocols.

If a protocol amendment requires a change to the ICD the IEC/IRB should approve the revised ICD before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by the IEC/IRB.

4. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Sponsor: AstraZeneca AB

Sponsor's Lead Physician:

Sponsor's Global Product Statistician:

Sponsor's Biostatistician:

Principal Investigator (PI):

Contract Research Organization (CRO):	PAREXEL Early Phase Clinical Unit London
Clinical Laboratory:	The Doctors Laboratory (TDL)
Analytical Laboratory: (PK sample analysis)	Covance Laboratories, Inc.
Adverse Event Reporting:	AstraZeneca Patient Safety Data Entry Site Tata Consultancy Services

A list and contact details of investigators and other key study team members are provided in the Project Plan in the electronic Investigator's Site File. A list of all participating investigators will be provided in the clinical study report (CSR).

5. INTRODUCTION

5.1. Background Information

Symbicort is indicated in adults, aged 18 and older, for the symptomatic treatment of patients with chronic obstructive pulmonary disease (COPD) with forced expiratory volume in 1 second (FEV_1) <70% predicted normal (post-bronchodilator) and an exacerbation history despite regular bronchodilator therapy [1].

Symbicort products are inhalation products providing a fixed-dose combination of 2 active substances: budesonide, a glucocorticosteroid (GCS) with high local anti-inflammatory effect, and formoterol fumarate dihydrate, a long-acting β2-agonist (LABA) with rapid onset of action when inhaled. Budesonide given by inhalation has a glucocorticoid anti-inflammatory action within the lungs and airways, resulting in reduced symptoms and fewer exacerbations of asthma and COPD, with less adverse effects than when corticosteroids are administered systemically. The exact mechanism responsible for this anti-inflammatory effect is unknown. Formoterol is a selective β2-adrenergic agonist that produces relaxation of bronchial smooth muscle, improving lung function and reducing symptoms in patients with asthma or COPD. The bronchodilating effect is dose dependant, with an onset of effect within 1-3 minutes. The duration of effect is at least 12 hours after a single dose.

Symbicort is available in 2 multidose inhaler formulations, i.e., a dry powder formulation Symbicort Turbuhaler (which is a single inhalation formulation) and an aerosol formulation Symbicort pressurized metered-dose inhaler (pMDI) (which is a 2 actuation device).

Symbicort has never been withdrawn due to safety reasons in any country.

5.2. Clinical Pharmacokinetics

The pharmacokinetic (PK) properties of Symbicort pMDI have been evaluated in 14 different studies, including healthy subjects as well as asthmatics and patients with COPD.

Budesonide

Budesonide is rapidly absorbed with maximum plasma concentration reached within 30 minutes. It undergoes reversible esterification in airway-lung tissue and also undergoes an extensive degree of biotransformation to metabolites of low GCS activity on first passage through the liver (> 90%). The activity of the major metabolites, 6b-hydroxy-budesonide and 16a-hydroxy-prednisolone, is less than 1% of the parent compound. It has a plasma protein binding of approximately 90%, total clearance of approximately 1.2 L/min, volume of distribution of 3 L/kg, and plasma elimination half-life of approximately 4 hours.

Formoterol

Formoterol is rapidly absorbed with maximum plasma concentration reached within 10 minutes. It is inactivated via conjugation reactions. Active O-demethylated and deformylated metabolites are formed, but are seen mainly as inactivated conjugates. It has a plasma protein binding of approximately 50%, has a total clearance of approximately 1.4 L/min, volume of distribution of 4 L/kg, and late plasma elimination half-life averages 17 hours.

5.3. Study Rationale

This study intends to establish the relative bioavailability of Symbicort pMDI with and without a spacer in order to be able to include the use of a spacer in the label as required in the EU.

Budesonide and formoterol delivered via Symbicort pMDI with a spacer device (test) and without a spacer device (reference) will be administered with the concomitant administration of activated charcoal to estimate exposure through the lung [2] and without activated charcoal to estimate total systemic exposure.

The purpose of this study is to estimate any difference in the PK of budesonide and formoterol with adequate precision; there have been no pre-determined success limits defined as this study is considered to be descriptive in nature.

5.4. Dose Rationale

A single dose of Symbicort pMDI 160/4.5 µg x 2 inhalations is a standard therapeutic single dose and will generate sufficient plasma exposure to budesonide and formoterol for the assessment of relative bioavailability.

5.5. Adverse Events, Contraindications and Warnings

Hypersensitivity (allergy) to budesonide or formoterol is listed as a contraindication for administration of Symbicort pMDI [1].

Since Symbicort contains both budesonide and formoterol, the same pattern of undesirable effects as reported for these substances may occur. No increased incidence of adverse reactions has been seen following concurrent administration of the two compounds. The most common drug related adverse reactions are pharmacologically predictable side-effects of β_2 adrenoceptor agonist therapy, such as tremor and palpitations. These tend to be mild and usually disappear within a few days of treatment [1].

Adverse reactions, which have been associated with budesonide or formoterol, are presented in Table 1, listed by system organ class and frequency. Frequency is defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) and very rare (< 1/10,000) [1].

Table 1 Adverse reactions reported for Symbicort

SOC	Frequency	Adverse Drug reaction
Infections and infestations	Common	Candida infections in the oropharynx
Immune system disorders	Rare	Immediate and delayed hypersensitivity reactions, e.g., exanthema, urticaria, pruritus, dermatitis, angioedema and anaphylactic reaction
Endocrine disorders	Very rare	Cushing's syndrome, adrenal suppression, growth retardation, decrease in bone mineral density
Metabolism and nutrition disorders	Rare	Hypokalaemia
	Very rare	Hyperglycaemia
Psychiatric disorders	Uncommon	Aggression, psychomotor hyperactivity, anxiety, sleep disorders
	Very rare	Depression, behavioural changes (predominantly in children)
Nervous system disorders	Common	Headache, tremor
	Uncommon	Dizziness
	Very rare	Taste disturbances
Eye disorders	Very rare	Cataract and glaucoma
Cardiac disorders	Common	Palpitations
	Uncommon	Tachycardia
	Rare	Cardiac arrhythmias, e.g., atrial fibrillation, supraventricular tachycardia, extrasystoles
	Very rare	Angina pectoris. Prolongation of QTc-interval
Vascular disorders	Very rare	Variations in blood pressure
Respiratory, thoracic and mediastinal disorders	Common	Mild irritation in the throat, coughing, hoarseness
	Rare	Bronchospasm
Gastrointestinal disorders	Uncommon	Nausea
Skin and subcutaneous tissue disorders	Uncommon	Bruises
Musculoskeletal and connective tissue disorders	Uncommon	Muscle cramps

Candida infection in the oropharynx is a known potential adverse event (AE) due to drug deposition in the pharynx and the oral cavity. Advising the patient to rinse the mouth out with water after each dose will minimise the risk [1].

As with other inhalation therapy, paradoxical bronchospasm may occur very rarely, affecting less than 1 in 10,000 people, with an immediate increase in wheezing and shortness of breath after dosing. Paradoxical bronchospasm responds to a rapid-acting inhaled bronchodilator and should be treated straightaway. Symbicort should be discontinued immediately, the patient should be assessed and an alternative therapy instituted if necessary [1].

5.6. Benefit-risk Assessment

Based on the large body of safety data available, it is concluded that the inhaled fixed combination of budesonide and formoterol in Symbicort products continues to have a well-documented and favourable benefit-risk ratio in the treatment of asthma and COPD. It is deemed unlikely that any new, unanticipated safety signals would be found following Symbicort pMDI administration in healthy volunteers.

The participants of this study will not benefit directly when participating in this clinical trial. However, results of the study may enable the use of a named space together with Symbicort to the benefit of a COPD population with coordination difficulties between inhalation and actuation. Inclusion of a named spacer in the product information will expectedly decrease the deleterious effect of the coordination difficulties.

6. STUDY OBJECTIVES

6.1. Primary Objective

- To assess the relative bioavailability between Symbicort pMDI administered through a spacer device and Symbicort pMDI delivered without a spacer device both with no charcoal (total systemic exposure)
- To assess the relative bioavailability between Symbicort pMDI administered through a spacer device and Symbicort pMDI delivered without a spacer device both with charcoal (lung exposure)

6.2. Secondary Objectives

- To characterise the PK profiles of budesonide and formoterol delivered via Symbicort pMDI when administered with and without spacer and with and without charcoal
- To assess the safety of single doses of budesonide/formoterol delivered via Symbicort pMDI in healthy subjects

Outcome endpoints and other measurements: Refer to Section 9.2.4 for PK parameters and Section 9.3 for safety variables.

7. OVERALL DESIGN AND PLAN OF THE STUDY

7.1. Overall Study Design

This study will be a randomised, open-label, single-dose, crossover study in healthy subjects (males and females), performed at a single study centre.

The study will comprise:

- A screening period of maximum 28 days;
- Four treatment periods during which subjects will be resident from the afternoon before dosing with Symbicort until at least 24 hours after dosing; discharged on the morning of Day 2; and
- A final visit within 5 to 7 days after the last administration of Symbicort.

There will be a minimum washout period of 3 days between each dose administration of Symbicort.

Subjects will receive single doses of Symbicort on 4 occasions under fasted conditions.

During screening, spirometry testing will be performed by a technologist or a qualified designee to ensure subjects perform adequate manoeuvres to achieve optimal lung function. Device and inhalation training will be conducted on admission to each treatment period, and prior to dosing on Day 1 of each treatment period. Details of the training content will be described in a separate instruction sheet (refer to Appendix 15.4).

7.1.1. End of study

The end of study is defined as the last subject's last visit to the clinical unit.

7.1.2. Interim analyses

No interim analyses will be performed in this study.

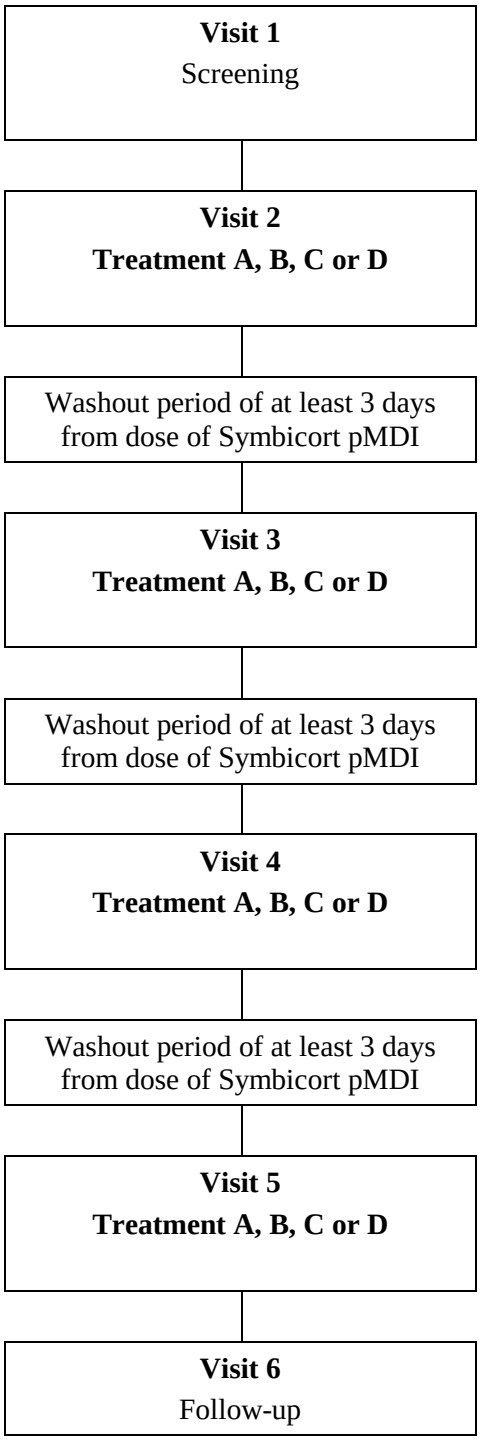
7.1.3. Expected duration of the study

Each subject will be involved in the study for approximately 7 weeks.

7.2. Study Flow Chart and Schedule of Assessments

The flow of events is illustrated in Figure 1 for all treatments, depending on the subject's assigned randomisation (refer to Section 8.10).

Figure 1 Study Flow Chart



The Schedule of Assessments displaying assessments/tasks and time points is presented in Table 2.

Table 2 Schedule of Assessments

	Screening	Treatment Periods 1, 2, 3 and 4		Post-study visit 5 to 7 days post-final dose
		Day -1	Days 1 to 2	
Informed consent	X			
Assignment of enrolment number	X			
Inclusion/ exclusion criteria	X	X (Treatment Period 1 only)		
Demographic data	X			
Medical history	X			
Urinary drug/alcohol screen and cotinine testing	X	X		
Viral serology	X			
FSH (post-menopausal women only)	X			
Pregnancy testing (females only)	X (serum)	X (urine)		
Spirometry[a]	X			
Randomisation			Day1 (Treatment Period 1 only)	
Study residency				
Check-in		X		
Check-out			Day 2 (24 hours post-dose) of each treatment period	
Non-residential visit	X			X
Training: Device and inhalation training (pMDI and spacer)[b]		X	Prior to dosing on Day 1 of each treatment period	
Administration of activated charcoal			*10 g immediately before inhalation of IMP; 10 g immediately after mouth-rinsing (done within 5 minutes after the inhalation of IMP); 10 g 1 hour after inhalation of IMP; 10 g 2 hours after inhalation of IMP	
Symbicort pMDI administration			Day 1 (0 h) of each treatment period	
Safety and tolerability				
Adverse events	X	X	X	X

	Screening	Treatment Periods 1, 2, 3 and 4		Post-study visit 5 to 7 days post-final dose
		Day -1	Days 1 to 2	
Concomitant medication reporting		X	X	X
Blood pressure and pulse (supine)	X	X		X
12-lead ECG	X			X
Clinical laboratory evaluations	X			X
Physical examination	X (full)	X (brief)		X (full)
Body weight	X			
Pharmacokinetics				
Plasma for budesonide and formoterol PK analyses			Pre-dose and at 5, 20, and 40 minutes and at 1, 2, 4, 8, 10, 12, 18 and 24 hours after Symbicort dosing; post-dose; 12 samples per treatment period (also refer to Section 9.2.1)	

ECG = electrocardiogram; FSH = follicle-stimulating hormone; PK = pharmacokinetic; pMDI = pressurized metered-dose inhaler

a. During screening, spirometry testing will be performed by a technologist or a qualified designee to ensure subjects perform adequate manoeuvres to achieve optimal lung function. Refer to Section 7.4.1.

b. Device and inhalation training will be conducted on admission to each treatment period, and prior to dosing on Day 1 of each treatment period.

* Activated charcoal dosing will be administered according to randomisation. Treatments A and B do not receive activated charcoal whereas Treatments C and D do receive activated charcoal.

It is important that PK sampling occurs as close as possible to scheduled time. In order to achieve this, other assessments scheduled at the same time may be initiated prior to the time point.

7.3. Restrictions during the Study

The following restrictions apply for the specified times during the study period:

1. On Day 1 of each treatment period, subjects will be fasted for at least 10 hours prior to dosing (IMP) and until 4 hours after dosing (IMP). No fluids will be allowed apart from water which can be given until 1 hour prior to dosing (IMP) and then from 2 hours after dosing (IMP). Also see Section 8.7.
2. Subjects should not lie fully supine (unless specified for certain assessments) for 4 hours after dosing from IMP inhalation.
3. Subjects should not engage in any strenuous activity from 72 hours prior to dosing on Day 1 of the first treatment period until after their final follow-up visit.

4. Prior to each treatment period subjects should abstain from alcohol for 72 hours prior to admission to the study unit until after their last PK sample was collected. Between treatment periods subjects should consume no more than 2 units of alcohol per day and completely abstain from 72 hours prior to their next admission. Subjects should also abstain from alcohol for 72 hours before their final follow-up visit.
5. Prior to each treatment period subjects should abstain from caffeine-containing foods and beverages for 24 hours prior to dosing until discharge from the clinical unit. At other times, subjects should limit their caffeine intake to equivalent of 3 cups of coffee per day (1 cup = 360 mL soda, 180 mL coffee, or 240 mL tea) for the duration of the study.
6. Subjects should abstain from grapefruit or grapefruit juice, Seville oranges (also called bitter orange [a hybrid between a mandarin and pomelo], including marmalade) and quinine (e.g., tonic water) from 7 days prior to admission to the study unit on Day -1 of the first treatment period until after their final follow-up visit.
7. During in-house stay subjects will receive a standard diet, which excludes all alcohol and grapefruit-containing products. No additional food or beverages must be consumed whilst in the clinical unit.
8. During the subjects' outpatient periods, subjects should abstain from consuming high energy drinks (e.g., Red Bull), and food containing poppy seeds (e.g., specialty breads and muffins) and any over-the-counter (OTC) medication or herbal preparations until after their final follow-up visit has been completed.
9. Subjects will be required to abstain from blood or plasma donation until 3 months after their final follow-up visit.
10. Medication restrictions

Refer to Section 8.8.

11. Reproductive restrictions

- Female subjects

  Women of child-bearing potential who are sexually active must use, with their partner, 2 approved methods of highly effective contraception from the time of IMP administration until 3 months after the last dose of IMP.

  Effective and acceptable means of contraception (2 are required and only 1 can be a barrier method):

  - Surgical sterilization (i.e., bilateral tubal ligation for females; vasectomy for male partners)

- Placement of an intrauterine device or intrauterine system
- Hormonal contraception (implantable, patch, oral)
- Barrier methods: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.

Alternatively, true abstinence is acceptable when it is in line with the subject's preferred and usual lifestyle. If a subject is usually not sexually active but becomes active, they, with their partner, should use 2 of the contraceptive methods listed above.

Women of non-childbearing potential are allowed in the study and are defined as female subjects who are permanently sterilized or post-menopausal.

Permanent sterilization includes hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy but excludes bilateral tubal ligation.

Females are considered post-menopausal if they have had amenorrhea for at least 12 months or more following cessation of all exogenous hormonal treatments and FSH levels are in the post-menopausal range.

- Male subjects

  As a precaution, all male subjects should avoid fathering a child by either true abstinence or the use of 2 effective means of contraception with their partner from the time of IMP administration until 3 months after the last dose of IMP.

  Effective and acceptable means of contraception (2 are required and only 1 can be a barrier method):

  – Surgical sterilization (i.e., bilateral tubal ligation for females; vasectomy for male partners)
  – Placement of an intrauterine device or intrauterine system
  – Hormonal contraception (implantable, patch, oral)
  – Barrier methods: Condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository

  Male subjects who have been sterilized are required to use 1 barrier method of contraception (condom).

- Sperm donation

Male subjects should not donate sperm for the duration of the study, starting at screening and for at least 3 months after the last day of IMP administration.

- Pregnancy

  Subjects will be instructed that if their partner becomes pregnant during the study this should be reported to the investigator. The investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a subject's partner is subsequently found to be pregnant after the subject is included in the study, then consent will be sought from the partner and if granted any pregnancy will be followed and the status of mother and/or child will be reported to the sponsor after delivery.

  A pregnancy notification form and follow-up will be completed.

7.4. Selection of Study Population

The investigator should keep a subject screening log of all potential subjects who consented and were subjected to screening procedures.

Subjects who fail to meet the inclusion criteria or meet any exclusion criterion should not, under any circumstances, be randomised into the study. There can be no exceptions to this rule.

This study will be conducted in male and female subjects. The study may not necessarily be balanced regarding gender. The study was not formally powered to detect differences between genders for the primary endpoint. It is not planned to perform sub-analyses on gender.

7.4.1. Inclusion criteria

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

1. Provision of signed and dated, written informed consent prior to any study specific procedures.
2. Healthy male and/or female subjects aged 18 years (inclusive) and older, with suitable veins for cannulation or repeated venipuncture.
3. Females must have a negative pregnancy test at screening and on first admission to the unit, must not be lactating.
4. Have a body mass index (BMI) between 18 and 30 kg/m^2 inclusive and weigh at least 50 kg and no more than 100 kg inclusive.

5. $FEV_1 \geq 80\%$ of predicted value and FEV_1/FVC ratio $\geq 70\%$ (refer to Section 9.3.6).
6. Non-smokers.

7.4.2. Exclusion criteria

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

1. History of any clinically significant disease or disorder which, in the opinion of the investigator, may either put the volunteer at risk because of participation in the study, or influence the results or the volunteer's ability to participate in the study.
2. History of diagnosed COPD or asthma.

   Note: Subjects with a history of childhood asthma only will not be excluded from the study.
3. History or presence of gastrointestinal, hepatic or renal disease, or any other condition known to interfere with absorption, distribution, metabolism, or excretion of drugs.
4. Any clinically significant illness, medical/surgical procedure, or trauma within 4 weeks of the first administration of IMP, as judged by the investigator.
5. Any clinically significant abnormalities in clinical chemistry, haematology, or urinalysis results at screening, as judged by the investigator.
6. Any clinically significant abnormal findings in vital signs at screening and first admission to the study unit, as judged by the investigator.
7. Any clinically significant abnormalities on 12-lead ECG at screening, as judged by the investigator.
8. Any positive result on screening for serum hepatitis B surface antigen (HBsAg), hepatitis C antibody and human immunodeficiency virus (HIV) antibody.
9. Known or suspected history of drug abuse, as judged by the investigator.
10. Participation in another clinical study with a non-biologic investigational product or new formulation of a marketed non-biologic drug within 3 months prior to the screening visit.
11. Participation in another clinical trial with any marketed or investigational biologic within 4 months or 5 half-lives whichever is longer, prior to the screening visit.
12. Plasma donation within 1 month of screening or any blood donation/loss more than 500 mL during the 3 months prior to screening.

13. History of severe or ongoing allergy/hypersensitivity (e.g., food allergy), as judged by the investigator, or history of hypersensitivity to drugs with a similar chemical structure or class to Symbicort.
14. Positive screen for drugs of abuse, alcohol or cotinine at screening and on first admission to the study unit.
15. Use of drugs with enzyme-inducing properties such as St John's Wort within 3 weeks prior to the first administration of IMP.
16. Use of any prescribed or non-prescribed medication including antacids, analgesics (other than paracetamol/acetaminophen), herbal remedies, megadose vitamins (intake of 20 to 600 times the recommended daily dose) and minerals during the 2 weeks prior to the first administration of IMP or longer if the medication has a long half-life.

    Note: Hormonal contraception and hormonal replacement therapy are allowed for females, as applicable.
17. Known or suspected history of alcohol or drug abuse or excessive intake of alcohol as judged by the investigator.
18. Involvement of any AstraZeneca, PAREXEL or study site employee or their close relatives.
19. Judgment by the investigator that the subject should not participate in the study if they have any ongoing or recent (i.e., during the screening period) minor medical complaints that may interfere with the interpretation of study data or are considered unlikely to comply with study procedures, restrictions and requirements.
20. Vulnerable subjects, e.g., kept in detention, protected adults under guardianship, trusteeship, or committed to an institution by governmental or juridical order.

7.4.3. Discontinuation of investigational medicinal product, individual stopping criteria and withdrawal from the study

Subjects may be discontinued from the IMP/NIMP in the following situations:

- Healthy subject decision. The healthy subject is at any time free to discontinue treatment, without prejudice to further treatment.
- Adverse event.
- Severe noncompliance to study protocol.
- Positive pregnancy testing.
- Positive screen for drugs of abuse, alcohol or cotinine.

Study specific withdrawal criteria: If a subject reports symptoms, which are considered unacceptable by the subject or the investigator, he/she will be withdrawn from the study. In particular:

- Any severe or serious adverse event (SAE) that is judged as possibly related to the IMP/NIMP by the investigator
- Any case of Potential Hy's Law (PHL) according to Appendix 15.3

The appropriate AE form in the case report form (CRF) is to be completed.

7.4.4. Premature termination of the study and stopping criteria

The study may be terminated prematurely if:

- The PI and the sponsor assess that the number and/or severity of AEs justify discontinuation of the study. For instance when there is at least 1 case of fatal SAE or 2 cases of other SAEs, in both situations considered related to the IMP/NIMP by the investigator and the sponsor.
- The sponsor considers the applied doses of the study drug to be no longer relevant.
- The sponsor decides to discontinue the study.
- Data not known before become available and raise concern about the safety of IMP so that continuation would pose potential risks to the subjects.

Premature termination of the study must be mutually agreed upon by the PI and the sponsor and must be documented. However, study results will be reported according to the requirements outlined in this clinical study protocol as far as applicable.

7.4.5. Replacement of subjects

Subjects who are withdrawn from the study will not be replaced.

7.4.6. Total blood volume

The approximate total amount of blood to be collected from each subject in this study, excluding repeat samples, is summarised in Table 3.

Table 3 Total Blood Volume

	Volume per sampling	Collection container	Number	Total
Laboratory assessments				
• Haematology	2 mL	K3 EDTA Vacutainer	2	4 mL
• Clinical chemistry*	5 mL	SST Vacutainer	2	10 mL
• FSH	2.5 mL	SST Vacutainer	1	2.5 mL
PK samples for budesonide and formoterol analyses	6 mL		12 x 4 = 48	288 mL
Total				**304.5 mL**

FSH = follicle-stimulating hormone; K3 EDTA = tripotassium ethylenediaminetetraacetate; PK = pharmacokinetic; SST = serum separator tube

* Viral serology and pregnancy testing will be analysed from the sample provided for clinical chemistry at the screening visit.

Repeat blood samples may be collected for safety reasons. The maximum volume to be drawn from each subject must not exceed 500 mL.

8. TREATMENTS

8.1. Identity of the Investigational Medicinal Product

Details on the identity of the IMP are presented in Table 4.

Table 4 Identity of the Investigational Medicinal Product (IMP)

Supplier:	AstraZeneca
IMP:	Symbicort pMDI
Formulation:	Pressurized inhalation suspension
Strength/concentration:	160/4.5 µg per inhalation
Dose:	2 inhalations
Route of administration:	Inhalation
Specific device for drug administration, if applicable:	AeroChamber Plus Flow-Vu spacer device
Regimen:	Treatment A: 2 x 160/4.5 µg Symbicort pMDI administered with no spacer device; no activated charcoal - reference formulation/total systemic exposure Treatment B: 2 x 160/4.5 µg Symbicort pMDI administered through AeroChamber Plus Flow-Vu spacer device; no activated charcoal - test formulation/total systemic exposure Treatment C: 2 x 160/4.5 µg Symbicort pMDI administered with no spacer device; with activated charcoal - reference formulation/lung exposure Treatment D: 2 x 160/4.5 µg Symbicort pMDI administered through AeroChamber Plus Flow-Vu spacer device; with activated charcoal - test formulation/lung exposure

AstraZeneca will provide detailed preparation, storage and handling instructions for each treatment. Details of the batch numbers will be included in the Trial Master File and the final CSR, as applicable. Device and inhalation training will be conducted using a placebo containing pMDI. The training material will be provided by AstraZeneca (see Section 8.12).

8.2. Identity of Additional Study Drug

Details on the identity of the NIMP are presented in Table 5.

Table 5 Identity of the Non-Investigational Medicinal Product (NIMP)

Manufacturer:	Beacon Pharmaceuticals Ltd
Formulation:	Carbomix (Activated charcoal) 50 g for oral suspension
Strength/concentration:	813 mg/g
Dose regimen:	10 g immediately before inhalation of IMP; 10 g immediately after mouth-rinsing (done within 5 minutes after the inhalation of IMP); 10 g 1 hour after inhalation of IMP; 10 g 2 hours after inhalation of IMP
Route of administration:	Oral
Specific device for drug administration, if applicable:	Not applicable
Regimen:	Treatment C: 2 x 160/4.5 µg Symbicort pMDI administered with no spacer device; with activated charcoal - reference formulation/lung exposure Treatment D: 2 x 160/4.5 µg Symbicort pMDI administered through AeroChamber Plus Flow-Vu spacer device; with activated charcoal - test formulation/lung exposure

PAREXEL will source the activated charcoal. Charcoal will be given using the procedure described by Thorsson *et al.*, [2]. Preparation, storage and handling will follow the instructions described in the Summary of Product Characteristics (SmPC) of Carbomix. Details of the batch numbers will be included in the Trial Master File and the final CSR, as applicable.

8.3. Supply of Investigational Medicinal Product/Non-Investigational Product

The IMP will be manufactured in accordance with Good Manufacturing Practice (GMP) and will be supplied by AstraZeneca. The IMP will be provided in kits with a study specific label.

The NIMP (activated charcoal) will be purchased locally by PAREXEL.

If applicable, a technical agreement between PAREXEL and AstraZeneca will be in place to cover all pharmacy related activities, detailing roles and responsibilities prior to receipt of the IMP/NIMP at the clinical unit.

If applicable, a release document signed by a legally authorized Qualified Person (QP) at PAREXEL will be placed in the appropriate section of the Trial Master File to document labelling.

8.4. Storage and Handling Procedures

The IMP/NIMP will be stored in a secure facility under appropriate storage conditions. Details of storage conditions will be provided on the label of the IMP. Storage and handling of the activated charcoal will follow instructions described in the SmPC of Carbomix.

AstraZeneca will be permitted upon request to audit the supplies, storage, dispensing procedures and records.

8.5. Labelling

Labels will be prepared in accordance with GMP and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements and medical device directive for labelling.

8.6. Drug Accountability, Dispensing and Destruction

The IMP/NIMP provided for this clinical study will be used only as directed in the clinical study protocol.

In accordance with GCP, the clinical unit will account for all supplies of the IMP. Details of receipt, storage, assembly/dispensing and return will be recorded.

All used and unused supplies of the IMP/NIMP, including used devices, will be destroyed by PAREXEL at the end of the study. The certificate of delivery and destruction must be signed, in accordance with instruction by AstraZeneca. Destruction must not take place unless the responsible person at AstraZeneca has approved it.

8.7. Dose and Treatment Regimens

Subjects will receive single doses of Symbicort on 4 different occasions under fasted conditions. Device and inhalation training is described in Section 8.12.

Administration of IMP/NIMP will take place in a room separate from the room where blood samples will be drawn. During administration patients and clinic personnel will wear protective clothing and vinyl gloves which will be discarded immediately after administration in the room used for inhalation, to avoid subsequent contamination of blood samples, according to the routines at the clinic. The subjects will wash their hands and faces with water and rinse their mouths twice with 25 mL of water after the administration of the IMP and, when applicable, before the administration of NIMP.

Following an overnight fast of at least 10 hours, each subject will receive a single dose of Symbicort pMDI.

> Treatment A: 2 x 160/4.5 µg Symbicort pMDI administered with no spacer device; no activated charcoal - reference formulation/total systemic exposure
>
> Treatment B: 2 x 160/4.5 µg Symbicort pMDI administered through AeroChamber Plus Flow-Vu spacer device; no activated charcoal - test formulation/total systemic exposure

Treatment C: 2 x 160/4.5 µg Symbicort pMDI administered with no spacer device; with activated charcoal - reference formulation/lung exposure

Treatment D: 2 x 160/4.5 µg Symbicort pMDI administered through AeroChamber Plus Flow-Vu spacer device; with activated charcoal - test formulation/lung exposure

The IMP, following priming, will be self-administered in the standing position, in accordance with the Instruction Sheet in Appendix 15.4.

Activated charcoal will be administered concomitantly with the IMP in Treatment C and Treatment D. Charcoal will be given using the procedure described by Thorsson *et al*., [2]. Activated charcoal will be prepared as a charcoal-water suspension (approximately 10 g charcoal in 80 mL of water). The charcoal slurry must be drunk, in its entirety, once the effervescence has subsided. The charcoal block regimen will be as follows: 10 g immediately before inhalation of IMP; 10 g immediately after mouth-rinsing (done within 5 minutes after the inhalation of IMP); 10 g 1 hour after inhalation of IMP; and, 10 g 2 hours after inhalation of IMP. The subjects should rinse their mouths with water after each charcoal administration. The water for the mouth rinse should not be swallowed.

No fluids will be allowed apart from water which can be given until 1 hour prior to administration of the IMP and then from 2 hours after administration of the IMP.

Other restrictions, including posture control are described in Section 7.3. Data of subjects may be excluded from the PK analysis set as described in Section 11.3.2.

8.8. Concomitant Medication

Apart from paracetamol/acetaminophen, hormone replacement therapy and systemic contraceptives, no concomitant medication or therapy will be allowed. The subjects should be instructed that no other medication is allowed, including herbal remedies, vitamin supplements and OTC products, without the consent of the investigator.

When any medication is required, it should be prescribed by the investigator. Following consultation with AstraZeneca Lead Physician, the investigator must determine whether or not the subject should continue in the study.

8.9. Treatment Compliance

Dosing will take place at the PAREXEL Early Phase Clinical Unit. Compliance will be assured by direct supervision and witnessing of study drug administration.

Administration of IMP/NIMP will be recorded in ClinBase™.

8.10. Randomisation

8.10.1. Subject enrolment and randomisation

The PI will ensure:

- Signed informed consent is obtained from each potential subject before any study specific procedures are performed.
- Each potential subject is assigned a unique enrolment number, beginning with "E", at screening upon signing the ICD.
- The eligibility of each subject is in accordance with the inclusion and exclusion criteria.
- Each eligible subject is assigned a unique randomisation/sequence code (subject number).

Randomisation will be performed on the morning of first dosing (Day 1, Treatment Period 1).

Randomisation codes will be assigned strictly sequentially as subjects become eligible for randomisation, starting from e.g., 1001 (no leading zero[s]).

When using the unique enrolment number, the specific format must be followed (i.e., reduced enrolment number, e.g., "1001" in ClinBase and on labels, full enrolment number, e.g., "E0001001" for outputs).

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

Procedures for randomisation

Upon completion of the randomisation requirements specifications form, the randomisation will be produced by PAREXEL according to the AstraZeneca randomisation (AZRand) process.

For this study, a total of 56 subject identifiers will be randomly assigned to one of the following 8 possible treatment sequences: AB CD, AB DC, BA CD, BA DC, CD AB, CD BA, DC AB or DC BA. These treatment sequences allow for subjects who might drop out after 2 treatment periods only to be included in the statistical analysis of the PK.

Subjects will be assigned a randomisation number for dosing in consecutive order per the randomisation list.

Once a randomisation number has been allocated to 1 subject, it may not be assigned to another subject.

8.10.2. Procedures for handling incorrectly randomised subjects

Subjects who fail to meet the inclusion criteria or meet any exclusion criterion should not, under any circumstances, be randomised into the study. There can be no exceptions to this rule.

Where a subject, who does not meet the selection criteria, is randomised in error and this is identified before dosing, the subject should be withdrawn from the study.

If a subject, who does not meet the selection criteria, has been dosed before the error is identified, the subject should be advised to continue safety assessments to ensure their safety.

8.11. Blinding

This is an open-label study.

8.12. Device and Inhalation Training

In order to ensure that the subjects are able to perform inhalation according to instructions and to achieve reproducibility in inhalation techniques, inhalation techniques will be practiced. Device and inhalation training will be conducted on admission to each treatment period, and prior to dosing on Day 1 of each treatment period. Details of the training content will be described in a separate instruction sheet (refer to Appendix 15.4). Device and inhalation training will be conducted using a placebo containing pMDI. The training material will be provided by AstraZeneca.

9. MEASUREMENTS AND METHODS OF ASSESSMENTS

9.1. Appropriateness of Measurements

Standard measures to assess PK, safety and tolerability apply during the study. For the single doses of Symbicort planned to be given during this study, no safety issues are expected.

For timing of assessments refer to Table 2.

9.2. Pharmacokinetics

9.2.1. Sample collection and handling

Blood samples for the determination of plasma concentrations of budesonide and formoterol will be collected for each treatment period as specified in the schedule of assessments (Table 2). Before dosing, an indwelling venous cannula will be inserted. The registered nurse will decide when to remove or replace the venous cannula based on the time (since insertion of the cannula) or if clotting occurs. If the cannula is removed, the subsequent blood samples will be collected by venipuncture or the cannula will be replaced.

Samples will be collected, handled, labelled, stored and shipped as detailed in the Laboratory Manual. Plasma samples will be analysed for budesonide and formoterol using a validated assay.

The rooms in the clinical unit used for blood and urine sampling, and handling of blood, plasma and urine samples must not be used for drug administration.

9.2.2. Pharmacokinetic drug assays

Blood samples for determination of budesonide and formoterol concentrations in plasma will be analysed by Covance Bioanalytical Alliance (CBioA) on behalf of AstraZeneca Research and Development (R&D), using a validated assay.

Full details of the analytical method and analyses performed used will be described in a separate Bioanalytical Report.

9.2.3. Disposal of pharmacokinetic samples

Pharmacokinetic samples will be disposed of after finalization of the Bioanalytical Report or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

Pharmacokinetic samples may be disposed of or destroyed and anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further

evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will be reported separately in a Bioanalytical Report appended to the final CSR.

9.2.4. Pharmacokinetic parameters

Where possible, the following PK parameters will be assessed for budesonide and formoterol of Symbicort pMDI using plasma concentrations.

Primary PK parameters

C_{max}	Maximum observed plasma concentration
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration

Secondary PK parameters

AUC	Area under plasma concentration-time curve from time zero to infinity
t_{max}	Time to reach maximum observed plasma concentration
$t_{½\lambda z}$	Half-life associated with terminal slope (λ_z) of a semi-logarithmic concentration-time curve
λ_z	Terminal elimination rate constant
V_z/F	Apparent volume of distribution during the terminal phase (extravascular administration)
CL/F	Apparent total body clearance of drug from plasma after extravascular administration
t_{last}	Time of last quantifiable plasma concentration

In addition, the ratio of $C_{max(B)}$:$C_{max(A)}$ and $C_{max(D)}$:$C_{max(C)}$, $AUC_{0-t(B)}$:$AUC_{0-t(A)}$ and $AUC_{0-t(D)}$:$AUC_{0-t(C)}$, and $AUC_{(B)}$:$AUC_{(A)}$ and $AUC_{(D)}$:$AUC_{(C)}$ (using non log-transformed data) will be determined for Symbicort pMDI administered through a spacer device : Symbicort pMDI delivered without a spacer device, both with no charcoal (total systemic exposure) and both with charcoal (lung exposure).

The following diagnostic parameters for plasma PK analysis will be listed, but not summarised:

λ_z upper and λ_z lower	The time interval (h) of the log-linear regression to determine $t_{½\lambda z}$
λ_z, N	Number of data points included in the log-linear regression analysis
Rsq_adj	Regression coefficient adjusted for n observations, Goodness of fit statistic for calculation of λz
$AUC_{\%extrap}$	Percentage of AUC obtained by extrapolating the area under the plasma concentration-time curve from the time of the last quantifiable concentration to infinity

Additional PK parameters may be determined where appropriate.

9.2.5. Derivation of pharmacokinetic parameters

The PK analyses of the plasma concentration data for budesonide and formoterol will be performed by Covance CPKA, on behalf of AstraZeneca R&D.

PK parameters will be derived using non-compartmental methods with Phoenix® WinNonlin® Version 6.2, or higher.

PK analysis will, where possible, be carried out using actual elapsed times determined from the PK sampling and dosing times recorded in the database. If actual elapsed times are missing, nominal times may be used at the discretion of the PK Scientist.

Plasma concentrations that are NQ from the time of pre-dose sampling (t=0) up to the time of the first quantifiable concentration will be set to a value of zero. After this time point, NQ plasma concentrations will be set to missing for all concentration profiles. Where two or more consecutive concentrations are NQ at the end of a profile, the profile will be deemed to have terminated and therefore any further quantifiable concentrations will be set to missing for the calculation of the PK parameters unless it is considered to be a true characteristic of the profile of the drug.

If an entire concentration-time profile is NQ, the profile will be excluded from the PK analysis.

C_{max}, t_{max} and t_{last} will be determined by inspection of the concentration-time profiles.

Where possible λ_z will be calculated by log-linear regression of the terminal portion of the concentration-time profiles where there are sufficient data and $t_{½\lambda z}$ will be calculated as $\ln 2/\lambda_z$. For the determination of λ_z, the start of the terminal elimination phase for each subject will be defined by visual inspection and will be the first time point at which there is no systematic deviation from the log-linear decline in plasma concentrations (λ_z lower) and the last point (λ_z upper) will be the time of the last measurable plasma concentration.

A minimum of 3 data points will be used in calculating λ_z, and the duration of time over which λ_z is recommended to be at least 3 times the subsequently estimated terminal half-life. Where an elimination half-life is estimated over less than 3 times the subsequently estimated terminal half-life, it will be flagged and commented upon in the study report.

AUCs (including AUC and AUC_{0-t}) will be calculated using the linear trapezoidal method when concentrations are increasing and the logarithmic trapezoidal method when concentrations are decreasing (linear up, log down). AUC is estimated by $AUC_{0-t} + C_{last}/\lambda_z$ where C_{last} is the observed last quantifiable drug concentration. The AUC values where $AUC_{\%extrap}$ is greater than 20% will be flagged in the data listings.

The minimum requirement for the calculation of AUC will be the inclusion of at least 3 consecutive plasma concentrations above the lower limit of quantification (LLOQ), with at least 1 of these concentrations following C_{max}.

The apparent clearance (CL/F) will be determined from the ratio of dose/AUC.

9.3. Safety Variables

After informed consent was obtained, screening procedures will be performed as listed in the schedule of assessments (Table 2).

On admission to Treatment Period 1, eligibility will be confirmed. Clinical procedures will be performed on admission to each treatment period as listed in the schedule of assessments (Table 2).

Subjects will be randomised before dosing on Day 1 of Treatment Period 1. Data on AEs and concomitant medication will be collected during each treatment period. Reporting of AEs is the safety endpoint of the study.

Post-study visit procedures will be performed, after subjects completed all 4 treatment periods or in the event of early withdrawal, as listed in the schedule of assessments (Table 2).

9.3.1. Adverse events

Refer to Section 12.2.3.

9.3.2. Vital signs

The following variables will be collected after the subject has rested in the supine position for at least 5 minutes:

- Systolic BP (mmHg)

- Diastolic BP (mmHg)
- Pulse (beats per minute [bpm])

The measurement of vital signs will be carried out according to the relevant PAREXEL standard operating procedures (SOPs).

9.3.3. Resting 12-lead electrocardiogram

A 12-lead ECG will be obtained after the subject has rested in the supine position for at least 10 minutes at each of the time points specified in the schedule of assessments (Table 2) using the site's own ECG machines.

At each time point, the investigator will judge the overall ECG as normal or abnormal and this evaluation will be reported in ClinBase. If abnormal, it will be further documented as to whether or not the abnormality is clinically significant by the investigator. For all abnormalities (regardless of clinical significance) the specific type and nature of the abnormality will be documented in ClinBase. Clinically significant findings should also be documented on the AE page of the CRF if applicable.

The investigator may add extra 12-lead resting ECG safety assessments if there are any abnormal findings or if the investigator considers it is required for any other safety reason. These assessments should be entered as an unscheduled assessment.

All ECG readings will be digitally stored as source documents.

9.3.4. Physical examination

Full

The complete physical examinations will include an assessment of the general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculoskeletal and neurological systems.

Brief (Abbreviated)

The brief physical examinations will include an assessment of the general appearance, skin, abdomen, cardiovascular system and respiratory.

9.3.5. Laboratory assessments

9.3.5.1. Haematology

White blood cell (WBC) count
Red blood cell (RBC) count
Haemoglobin (Hb)
Neutrophils absolute count
Lymphocytes absolute count
Monocytes absolute count

Haematocrit (HCT)
Mean corpuscular volume (MCV)
Mean corpuscular haemoglobin (MCH)
Mean corpuscular haemoglobin concentration (MCHC)
Eosinophils absolute count
Basophils absolute count
Platelets

9.3.5.2. Serum clinical chemistry

Sodium
Potassium
Urea
Creatinine
Albumin
Calcium
Phosphate
Glucose(fasting)
Alkaline phosphatase (ALP)
Alanine aminotransferase (ALT)*
Aspartate aminotransferase (AST)*
Gamma glutamyl transpeptidase (GGT)
Total bilirubin*
Unconjugated bilirubin
Conjugated bilirubin
Follicle-stimulating hormone (FSH) (post-menopausal women only)

* In case a subject shows an AST or ALT ≥3xULN or total bilirubin ≥ 2xULN please refer to Appendix 15.3 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

9.3.5.3. Urinalysis

Glucose
Protein
Blood
Microscopy (if positive for protein or blood): RBC, WBC, Casts (Cellular, Granular, Hyaline)

9.3.5.4. Pregnancy testing

β human chorionic gonadotropin (β-hCG) (females only)

9.3.5.5. Viral serology

Human immunodeficiency virus (HIV) I and II
Hepatitis B surface antigen (HBsAg)
Hepatitis C virus antibody

9.3.5.6. Drugs of abuse, alcohol and cotinine

Amphetamine	Benzodiazepines
Alcohol	Methadone
Tetrahydrocannabinol (THC)	Barbiturates
Cocaine	Phencyclidine
Opiates	Urine creatinine
Tricyclic anti-depressants (TCA)	Cotinine

9.3.6. Spirometry

Spirometry will be performed at the screening visit, in accordance with American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines [3]. Predicted values will be calculated using the Quanjer 2012 reference equations [4].

All subjects will perform a minimum of 3 technically acceptable measurements. The highest FEV_1 % predicted value and FEV_1/FVC ratio value will be used to ensure the inclusion criteria are met (refer to Section 7.4.1).

Spirometry assessments may be performed up to 8 times to obtain 2 reproducible readings according to ATS/ERS guidelines [3].

9.3.7. Concomitant medication

Refer to Section 8.8.

9.4. Procedures for Handling of Biological Samples

9.4.1. Storage and destruction of biological samples

Samples will be disposed of, on instruction from AstraZeneca, after the CSR has been finalized.

9.4.1.1. Pharmacokinetic samples

For disposal of PK samples, refer to Section 9.2.3.

9.4.2. Labelling and shipment of biohazard samples

Samples will be labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria) (for International Airline Transportation Association [IATA] guidance, see Appendix 15.2 of this clinical study protocol).

Any samples identified as Infectious Category A materials will not be shipped and no further samples will be taken from the subject unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.

9.4.3. Chain of custody of biological samples

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

The PI will ensure full traceability of collected biological samples from the subjects while in storage at the clinical unit until shipment and will keep documentation of receipt of arrival.

The sample receiver will keep full traceability of samples while in storage and during use, until used, disposed of, or until further shipment or disposal (where appropriate) and will keep documentation of receipt of arrival.

Samples retained for further use will be registered in the AstraZeneca bio-bank system during the entire life cycle.

9.4.4. Withdrawal of informed consent for donated biological samples

If a subject withdraws consent to the use of donated biological samples, the samples will be disposed if not already analysed and the action documented. As collection of donated biological samples is an integral part of the study, consent withdrawal implies that the subject is withdrawn from further study participation.

AstraZeneca ensures the laboratory holding the samples is informed about the withdrawn consent immediately and that samples are disposed of or destroyed, the action documented and the signed document returned to the clinical unit.

10. QUALITY ASSURANCE AND DATA MANAGEMENT

The AstraZeneca – PAREXEL Relationship is based on a solid quality foundation that is focused on the highest quality standards. The Quality Agreement describes the quality strategies in establishing criteria to ensure that controls are in place to comply with applicable global and local regulatory requirements and guidelines, legal requirements, and pertinent AstraZeneca/PAREXEL standards for clinical studies jointly undertaken. The Quality Agreement does not supersede any procedural documents or contractual plans, but should be followed by AstraZeneca and PAREXEL to ensure a high level of quality.

10.1. Quality Control and Source Data Verification

Source data verification will be conducted with due regard to subject confidentiality.

The clinical unit will allow the study monitor and sponsor representative direct access to all study documents, medical files and source documents to enable verification of the study data, whilst maintaining the anonymity of the subject and confidentiality of the data.

Internal quality control will be performed at all stages of the study by the clinical unit.

10.2. Audit/Inspections

The clinical unit facilities and all study data/documentation may be audited/inspected by independent auditor/inspector/any representatives of regulatory authorities. The investigator must allow the applicable persons access to all relevant facilities and data/documents. The investigator must be available to discuss any findings/issues.

If an audit was performed, the audit certificate will be included in the CSR.

10.3. Study Monitoring

The conduct of the study will be monitored by an independent PAREXEL monitor or a subcontracted monitor to ensure compliance with applicable regulatory requirements and GCP. The summary of the documentation of the monitoring visits will form part of the study documentation and will be archived as such.

10.4. Data Collection

The ClinBase system is an electronic source data capturing and information management system. The system combines all aspects of source data capturing with process control and clinical study management. All clinical and laboratory data, except those which are paper-based or provided by external vendor, will be collected in ClinBase. Only paper-based data will be subject to data entry. For electronic source data, no data entry will be performed.

The responsible study monitor will check data at the monitoring visits to the clinical unit. The investigator will ensure that the data collected are accurate, complete and legible. Data will be monitored within ClinBase by the study monitor before being exported. Any changes made during monitoring will be documented with a full audit trail within ClinBase.

10.4.1. Case report forms and source documents

All data obtained using paper collection methods during the clinical study will be recorded in ClinBase. All source documents from which ClinBase entries are derived should be placed in the subject's personal records.

The original ClinBase entries for each subject will be checked against source documents by the study monitor. Instances of missing or uninterpretable data will be discussed with the investigator for resolution.

10.4.2. Access to source documents

During the course of the clinical study, a study monitor will make clinical unit visits to review protocol compliance, compare ClinBase entries and individual subject's personal records, assess IMP/NIMP accountability and ensure that the clinical study is being conducted according to pertinent regulatory requirements. ClinBase entries will be verified against source documents. The review of medical records will be handled confidentially to ensure subject anonymity.

Checking of the ClinBase entries for completeness and clarity and verifying with source documents, will be required to monitor the clinical study for compliance with GCP and other regulations. Moreover, regulatory authorities of certain countries, IECs/IRBs may wish to carry out source data inspections on-site, and the sponsor's clinical quality assurance group may wish to carry out audits. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and subject confidentiality. The investigator assures the sponsor of the necessary support at all times.

10.5. Data Management

PAREXEL will utilize standardized and validated procedures and systems to collect, process and file the clinical data of this study. Any system used will be compliant with FDA 21 CFR Part 11 requirements.

A data management plan (DMP) will be prepared to describe the processes and data-flow within the clinical study. Timelines, versions for the computer systems and the coding will

be defined in the DMP, and if applicable, sponsor specific requests will also be documented within. The DMP will be finalized before first dose where possible but before database lock.

A data validation specification (DVS) will be created to outline the validation checks to be performed during the study. The DVS must be finalized before data validation.

After the data has been monitored by the responsible study monitor all data received will be reviewed, logged and filed.

The raw data intended for further processing will be checked by standard routines or according to the DVS and queries will be generated and sent to the investigator for review and resolution. Corrections resulting from these queries will be confirmed on the data clarification forms (DCFs). This process will be repeated until no further discrepancies are found. The data will then be declared as clean. Applicable documentation will be stored in the study files.

Only trained study staff will have access to the clinical database and every change in data will have a full audit trail.

11. STATISTICAL METHODS

11.1. Overview

The statistical methodology below describes the statistical analysis as it is foreseen when the study is being planned.

If circumstances should arise during the study rendering the analysis inappropriate, or if in the meantime improved methods of analysis should come to light, different analyses may be performed. A separate statistical analysis plan (SAP) will not be written for the study. Any deviations from the statistical methodology defined in this protocol, reasons for such deviations and all alternative/additional statistical analyses that may be performed will be described in the CSR. Such changes to analyses may be written into an abbreviated SAP, if appropriate. The verification and review of all statistical modelling assumptions will be documented appropriately.

11.2. General Statistical Methodology

All original and derived parameters as well as demographic and disposition data will be listed and described using summary statistics. All safety data (scheduled and unscheduled) will be presented in the data listings.

Demographic and baseline data will be summarised for all randomised subjects. Pharmacokinetic data will be summarised by treatment. Safety and tolerability data will be summarised by treatment, if applicable.

Frequency counts (number of subjects [n] and percentages) will be made for each qualitative variable. Descriptive statistics (n, mean, standard deviation [SD], median, minimum and maximum) will be calculated for each quantitative variable (unless otherwise stated). Descriptive statistics will only be presented if $n \geq 3$.

The following rules will apply to any repeated safety assessments occurring within each treatment period (applicable to all treatment periods):

- If the repeated measurement of a specific parameter occurs prior to IMP/NIMP administration (Day 1), then the last obtained value prior to dosing will be used in the descriptive statistics;
- If the repeated measurement of a specific parameter occurs after IMP/NIMP administration (Day 1), then the first (non-missing) value after dosing will be used in descriptive statistics.

For safety assessments performed at screening and the follow-up, the following rules will apply for any repeated assessments:

- If the repeated assessment occurs at screening the last available value will be used in the summary statistics;
- If the repeated assessment occurs at the follow-up visit the first non-missing assessment will be used in the summary statistics.

All statistical analyses and production of tables, figures and listings will be performed using SAS® version 9.2 or later.

11.2.1. Missing Data

Missing dates and times in the AE data will be handled as described in Section 11.10.1. Concentrations that are NQ in the PK data will be handled as described in Section 9.2.5.

There will be no imputations of other missing data. All subjects will be included into the safety analyses as far as the data permit.

11.3. Study populations

11.3.1. Safety analysis set

The safety analysis set will include all subjects who received at least 1 dose of Symbicort pMDI and for whom any safety post-dose data are available.

Unless otherwise stated the safety analysis set will be used for the presentation of all demographic and disposition data, as well as all safety analyses. Exposure to IMP/NIMP will also be presented using the safety analysis set.

11.3.2. Pharmacokinetic analysis set

The PK analysis set will consist of all subjects in the safety analysis set for whom at least 1 of the primary PK parameters for a given analyte can be calculated and who have no important protocol deviations thought to impact on the analysis of the PK data.

Subjects may be excluded from the PK analysis for a specific comparison as a result of the following:

- The subject had an AE on the day of PK sampling or took an inadmissible concomitant medication, either of which were deemed to impact on the PK assessments, or received the incorrect IMP/NIMP dose. The subject may be excluded from the analysis for the specific treatment comparison only.

- The pre-dose concentration is > 5% of C_{max} for budesonide or formoterol in a specific treatment period.

Individual plasma concentrations may be excluded from the PK analysis at the discretion of the PK Scientist and the reason documented. Data from subjects excluded from the PK analysis will be included in the data listings, but not in the descriptive statistics or in the inferential statistics. Any PK samples that deviate by >10% from the protocol scheduled collection time will be excluded from the summary tables and related figures but the data will be used in the PK analysis to determine the PK parameters. It may not be possible to determine all the PK parameters for all the subjects and these will be returned as No Result (NR) or Not Calculable (NC) and therefore not included in the PK parameter summary tables and related figures and the reasons documented by the PK Scientist.

Clinical PK of Symbicort pMDI are described in Section 5.2.

The available concentration data and PK parameter data for any subjects excluded from the PK analysis will be listed only. Concentration data for subjects excluded from the PK analysis will be included in the individual figures of concentration versus time plots.

11.4. Determination of Sample Size

This study has been sized to estimate the difference between budesonide and formoterol PK parameters with and without a spacer in the presence and absence of a charcoal block.

The purpose of this study is to estimate any difference in the PK of budesonide and formoterol with adequate precision; there have been no pre-determined success limits defined as this study is considered to be descriptive in nature. To determine an adequate level of variability of the estimated relative bioavailability it was decided to use the same logic and require the same precision as would have been relevant for a bio-equivalence study.

Assuming an intra-subject coefficient of variation (CV) of 33% (based on the variability of AUC_{0-12} for budesonide and AUC_{0-12} and C_{max} for formoterol observed in a similarly designed crossover study in healthy adults), 44 evaluable subjects will give at least 80% power to show that the 90% confidence interval (CI) for the treatment effects (Treatment B vs Treatment A and Treatment D vs Treatment C) lies entirely within the range 0.8 to 1.25, i.e., would rule out a 20% change (on a log scale) in exposure to budesonide and formoterol. It is considered appropriate to base the sample size on AUC_{0-12} for budesonide rather than C_{max} (which has higher variability) since the effects of inhaled corticosteroids are more likely related to total systemic exposure (i.e., AUC) rather than to acute exposure (i.e., C_{max}).

Additional subjects may be randomised to ensure that at least 44 evaluable subjects complete the study.

nQuery was used for the sample size calculations.

11.5. Protocol Deviations

Protocol deviations are considered any deviation from the clinical study protocol relating to a subject, and include the following:

- Inclusion/exclusion criteria deviations
- Dosing deviations (e.g., incorrect treatment received subject was not fasted as per the protocol requirements prior to and after dosing)
- Time window deviations for safety and/or PK assessments
- Subjects receiving prohibited concomitant medications
- Other procedural and study conduct deviations recorded by the clinical unit on a protocol deviation log

The criteria for the assessment and reporting of protocol deviations will be stipulated in a separate study specific protocol deviation specification (PDS) document. This will include a Windows Allowance Document (WAD) which stipulates tolerance windows for safety and PK assessments. Measurements performed within these tolerance windows will not be considered as protocol deviations and will not be reported.

All protocol deviations will be discussed at the data review meeting prior to database hard lock in order to define the analysis sets for the study.

Important protocol deviations will be listed by subject.

Protocol deviations will be handled in accordance with PAREXEL SOPs.

For handling of protocol amendments, see Section 3.6.

11.6. Subject Disposition

A randomisation listing will be presented and include the following: each subject's randomisation number, the subject's full enrolment number, the treatment to which the subject has been randomised and the country where the study centre is located.

Subjects and/or data excluded from the PK analysis set will be listed including the reason for exclusion. Subject disposition will be summarised and will include the following information: number of subjects randomised and dosed, number and percentage of subjects completing the study and the number and percentage of subjects who were withdrawn (including reasons for withdrawal). Disposition data will be presented based on all subjects randomised.

Subject discontinuations will be listed including the date of study exit, duration of treatment and reason for discontinuation. A listing of informed consent response will also be presented.

11.7. Demographic and Baseline Data

Demographic variables (age, gender, race, ethnicity, height, weight and BMI) will be listed by subject. Demographic characteristics (age, gender, race and ethnicity) and subject characteristics (height, weight and BMI) will be summarised separately for all subjects in the safety analysis set. The denominator for percentages will be the number of subjects in the safety analysis set.

Medical history data will be listed by subject including visit, description of the disease/procedure, Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC), MedDRA Preferred Term (PT), start date and stop date (or ongoing if applicable).

FSH results will be listed.

Spirometry results will be listed for each subject.

The results of viral serology and the drugs of abuse, alcohol and cotinine screen will not be listed in the CSR.

11.8. Prior and Concomitant Medication and Drug Administration

11.8.1. Prior and concomitant medication

Prior medications are those that started and stopped prior to the first dose of IMP/NIMP; all medications taken after first dosing are considered as concomitant (including medications that started prior to dosing and continued after).

Prior and concomitant medication will be listed by subject and will include the following information: reported name, PT, the route of administration, dose, frequency, start date/time, duration and indication. Prior and concomitant medication will be coded according to the sponsor's drug dictionary.

The duration will be calculated as:

Duration = end date/time – start date/time

The duration may be presented in hours or days in the listing depending on the applicability to the emerging data. For medications with partial or completely missing start date/times and/or end date/times, the duration will not be calculated.

Medications with missing or partial start date/time and/or end date/time such that it is not possible to classify as prior or concomitant will be considered as concomitant in the listings.

11.8.2. Drug administration

Drug administration dates and times will be listed for each subject and treatment period.

11.9. Pharmacokinetic analysis

11.9.1. Presentation of pharmacokinetic data

A listing of PK blood sample collection times with actual elapsed times as well as derived sampling time deviations will be provided for budesonide and formoterol. Plasma concentrations will be summarised by treatment for each analyte presenting the following summary statistics in accordance with AZ Best Practice Reference Guidelines for PK Evaluations in Clinical Studies: n, n above LLOQ, G_{mean}, G_{mean}+SD, G_{mean}-SD, GCV(%), median, minimum and maximum.

All primary and secondary PK parameters will be listed for each subject, analyte and treatment using descriptive statistics in accordance with AZ Best Practice Reference Guidelines for PK Evaluations in Clinical Studies as follows:

- C_{max}, AUC_{0-t} and AUC will present n, G_{mean}, G_{mean}+SD, G_{mean}-SD, GCV(%), median, minimum and maximum.
- All relative values of C_{max}, AUC_{0-t} and AUC will present n, arithmetic mean (A_{mean}), SD, G_{mean}, G_{mean}+SD, G_{mean}-SD, GCV(%), median, minimum and maximum.
- $t_{½,\lambda z}$, λ_z, CL/F and Vz/F will present n, A_{mean}, SD, median, minimum and maximum.
- t_{max} and t_{last} will present only n, median, minimum and maximum.

Diagnostic parameters will be listed only.

The geometric mean is calculated as the exponential of the arithmetic mean calculated using log-transformed data.

The geometric mean ± SD at a given time point is calculated using the formula exp[mean[ln(concentration)] ± SD[ln(concentration)]].

GCV(%) is calculated as $100.\sqrt{(\exp(s^2) - 1}$, where *s* is the SD of the log-transformed data.

Data from subjects excluded from the PK analysis will be included in the data listings, but not in the descriptive statistics or in the inferential statistics.

Individual plasma concentrations versus actual time will be plotted in linear and semi-logarithmic scale with all treatments overlaid on the same plot and separate plots for each subject and analyte.

Combined individual plasma concentration versus actual times will be plotted in linear and semi-logarithmic scale. Separate plots will be presented for each treatment and analyte. Plots will be based on the PK analysis set.

Plasma concentration (showing G_{mean}±SD error bars) versus nominal sampling time will be plotted in linear and semi-logarithmic scale with treatments A and B overlaid on the same figure and separate plots for each analyte. The same plots will be provided for treatments C and D. Any PK samples that deviate by > 10% from the protocol scheduled collection time will be excluded from the summary figures.

For mean plots, Not Quantifiable (NQ) values will be handled as described for the summary tabulations (Section 11.9.1.2); for individual plots plasma concentrations which are NQ prior to the first quantifiable concentration will be set to a value of zero (linear plots only). After the first quantifiable concentration, any NQ plasma concentrations will be regarded as missing.

Additional line plots showing C_{max}, AUC_{0-t} or AUC on the y-axis as a continuous parameter versus Treatment on the x-axis as a categorical parameter (separate plots for Treatment A vs Treatment B and for Treatment C vs Treatment D) will be presented. Plots would include all individual subject data and the G_{mean} for each treatment with lines drawn to connect the Treatment A and Treatment B data or the Treatment C and Treatment D data for each subject and the G_{mean}. The plots will be presented for both analytes.

Scatter plots will also be presented showing individual C_{max}, AUC_{0-t} or AUC ratios of non-transformed data on the y-axis as a continuous parameter (1 plot per parameter) versus Treatment Ratio on the x-axis as a categorical parameter (showing Treatment B:A ratio and Treatment D:C ratio on the same plot). The plots will be presented for both analytes.

All plots will be based on the PK analysis set, with the exception of individual plots of the plasma concentration-time data by subject which will be based on the safety analysis set.

11.9.1.1. Precision and rounding rules for PK data

For PK concentration data, the listings will be presented to the same number of significant figures as the data received from the bioanalytical laboratory; for PK parameters, the listings will be presented according to the following rules:

- C_{max} – will be presented to the same number of significant figures as received from the bioanalytical laboratory
- t_{max}, t_{last}, λ_z upper and λ_z lower time limit – will be presented as received in the data, usually to 2 decimal places
- AUC, AUC_{0-t}, $t_{1/2,\lambda z}$, CL/F, V_z/F, Rsq_adj and ratios of C_{max}, AUC_{0-t} or AUC – will be presented to 3 significant figures
- λ_z – will be presented to 4 significant figures
- λ_z, N – will be presented as an integer (no decimals)
- $AUC_{\%extrap}$ – will be presented to 2 decimal places

For PK concentration data, all descriptive statistics will be presented to 4 significant figures with the exception of the minimum and maximum which will be presented to 3 significant figures.

For PK parameters data, the descriptive statistics will be presented according to the following rules:

- C_{max}, AUC_{0-t}, AUC, $t_{1/2,\lambda z}$, CL/F, V_z/F and ratios of C_{max}, AUC_{0-t} or AUC – will be presented to 4 significant figures with the exception of the minimum and maximum which will be presented to 3 significant figures
- λ_z – will be presented to 5 significant figures with the exception of the minimum and maximum which will be presented to 3 significant figures
- t_{max}, t_{last} – will be presented as received in the data, usually to 2 decimal places

Source data shall be used in all derived PK parameter calculations without prior rounding.

11.9.1.2. Handling of values that are below the limit of quantification

Plasma concentrations that are NQ or if there are missing values (e.g., NR) will be handled as follows:

- Where there is NR, these will be set to missing.
- At a time point where less than or equal to 50% of the values are NQ, all NQ values will be set to the LLOQ, and all descriptive statistics will be calculated accordingly.
- At a time point where more than half (but not all) of the values are NQ, the G_{mean} and GCV% will be set to NC. The maximum value will be reported from the individual data, and the minimum and median will be set to NQ.

- If all values are NQ at a time point, no descriptive statistics will be calculated for that time point. NC will be written in the field for G_{mean}±SD and GCV% and NQ will be written in fields for Gmean, minimum, median and maximum.
- The number of values above LLOQ (n above LLOQ) will be reported for each time point together with the total number of collected values.

Three observations > LLOQ are required as a minimum for a plasma concentration or PK parameter to be summarised. Two values are presented as a minimum and maximum with the other summary statistics as NC. For consistency, the same plasma concentration values are used in the mean data graphs as those given in the descriptive statistics summary table for each time point.

11.9.2. Statistical analysis of pharmacokinetic data

The treatment ratio of each of the test formulations (B and D) will be compared to the reference formulations (A and C) for budesonide and formoterol.

The statistical analysis will be conducted separately for the following:

- For total systemic exposure: Treatment B versus Treatment A
- For lung exposure: Treatment D versus Treatment C

Only the data for the comparison under investigation will be included in the statistical analysis, i.e., when comparing Treatment A and Treatment B, the data for Treatment C and Treatment D will be removed from the dataset.

Subjects must have a primary PK parameter available for both treatments for the given analyte under consideration in order to be included in a specific analysis. A subject may therefore be included in the analysis for one parameter and not for another.

Treatment ratio will be assessed on the ratio of log-transformed C_{max}, AUC_{0-t} and AUC of budesonide and formoterol using a 2-sided 90% CI approach based on a repeated measures analysis of variance (ANOVA) model including period and treatment as fixed effects, and subject as a random effect.

All PK parameters will be log-transformed prior to analysis. The estimated treatment differences and the 90% CIs on the log scale will be back-transformed to obtain the G_{mean} ratios for each pair of treatments. The least squares means (and 95% CIs), G_{mean} ratios and 90% CIs will be tabulated for each comparison and analyte (budesonide and formoterol).

11.10. Presentations and Analysis of Safety Variables

Safety data (scheduled and unscheduled) will be presented in the data listings. Continuous variables will be summarised using descriptive statistics (n, mean, SD, minimum, median, maximum) by treatment, if applicable. Categorical variables will be summarised in frequency tables (frequency and proportion) by treatment, if applicable. The analysis of the safety variables will be based on the safety analysis set.

11.10.1. Adverse events

All AEs will be coded using MedDRA vocabulary, and will be listed for each subject. A treatment-emergent adverse event (TEAE) is defined as an AE with onset (start date/time) after the first dose of IMP/NIMP; any AEs occurring in the washout between successive treatment periods will also be regarded as treatment-emergent.

Adverse events will be assigned to a treatment based on the start date/time of the AE in relation to dosing in that period; for tabulation purposes the AE will then be assigned to the treatment received in the respective treatment period as follows:

- Screening: all AEs with start date/time prior to dosing in Treatment Period 1.
- Treatment Period 1: AEs with start date/time at the time of or after dosing in Treatment Period 1 until the time of dosing in Treatment Period 2.
- Treatment Period 2: AEs with start date/time at the time of or after dosing in Treatment Period 2 until the time of dosing in Treatment Period 3.
- Treatment Period 3: AEs with start date/time at the time of or after dosing in Treatment Period 3 until the time of dosing in Treatment period 4.
- Treatment Period 4: AEs with start date/time at the time of or after dosing in Treatment Period 4 until the final follow-up visit.

Adverse events with missing start dates/times will be handled as follows:

- If the start date is completely missing but the end date is known and shows that the AE ended on or after the first dose date, then the start date will be imputed as the first day of dosing; if the end date is known and shows that the AE ended before the first dose date, then the screening date will be used for the start date. If the end date is non-informative (i.e., is missing or does not contain enough information), the start date will be imputed as the first date of dosing;
- If only the start day is missing the day will be imputed as the first day on which a dose was given in that month unless the end date is known and shows that the AE ended before

a dose was given in that month; in which case the date will be imputed as 01. If the end date is non-informative (i.e., is missing or does not contain enough information), the start date will be imputed as the first date of dosing in the known month. If the month is not a dosing month the date will be imputed as 01;

- If the start day and month are missing the date will be imputed as the first day of dosing in the known year unless the end date is known and shows that the AE ended before a dose was given in that year; in which case the start day and month will be imputed as 01Jan or with the date of screening if this is later. If the end date is non-informative (i.e., is missing or does not contain enough information), the start date will be imputed as the first date of dosing in the known year. If the year is not a year of dosing then the date will be imputed as 01Jan or with the date of screening if this is later;
- Missing times will be imputed as 00:00 h or with the time of dosing for events starting on a dosing day.

Adverse events will be summarised by treatment and overall, and presented by SOC and PT, with the exception of the causality and severity (mild, moderate and severe) tables, which will be presented by PT only. An overview of all AEs will be presented, separately for the number and percentage of subjects and the number of events. This will include categories for any AE, AEs leading to discontinuation of IMP/NIMP, AEs with outcome of death and SAEs. In addition, a separate tabulation will be presented showing the number of events by treatment and PT. Finally, listings of AEs that led to death, SAEs and AEs that led to discontinuation (DAEs) will also be presented.

The following information will be included in the listings: verbatim term, SOC, PT and lowest level term, start date/time, end date/time, time from last dose, causality, action taken, whether the AE was classified as serious and the outcome.

11.10.2. Vital signs

The results of the vital signs measurements will be listed by subject and time point including the date/time of the assessment and repeat/unscheduled measurements. Descriptive statistics will be presented by treatment and time point for observed values.

11.10.3. Resting 12-lead electrocardiogram

12-Lead ECG results will be listed for each subject and will include the overall assessment by the investigator and details of any abnormalities.

11.10.4. Physical examination

The results of the physical examination will be listed by body system for each subject.

11.10.5. Laboratory assessments

Haematology and clinical chemistry values will be listed by subject and time point and repeat/unscheduled measurements. Summary tabulations including absolute values will be presented by time point for the safety analysis set.

The listings will include the following information: test name, date of measurement, reference range, result and flags for any measurements that are outside the reference range (e.g., AstraZeneca, program, or laboratory ranges). Clinical laboratory data will be reported in System International units in the CSR.

Additional listings will be presented for the following:

- Urinalysis (macroscopic and microscopic, if applicable)
- Pregnancy testing

12. ADVERSE EVENTS

12.1. Definitions

12.1.1. Definition of adverse events

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 (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., ECG, laboratory findings).

In clinical studies an AE can include an undesirable medical condition occurring at any time after the subject has signed informed consent, including run-in or washout periods, even if no specific treatment has been administered.

The term AE is used generally to include any AE whether serious or non-serious.

12.1.2. Definitions of serious adverse event

A SAE is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils 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 or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent 1 of the outcomes listed above

For further guidance on the definition of a SAE, see Appendix 15.1 of this clinical study protocol.

12.1.3. Other significant adverse events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs or AEs leading to discontinuation of investigational product (DAEs) or AEs leading to withdrawal. Based on the expert's

judgment, significant AEs of particular clinical importance may, after consultation with the Global Safety Physician, be considered other significant adverse events (OAEs) and reported as such in the CSR. A similar review of other data from vital signs, ECGs, laboratory assessments and other safety assessments 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.

12.2. Recording of Adverse Events

12.2.1. Time period for collection of adverse events

Serious AEs will be collected from the signing of informed consent and AEs from randomisation until the final follow-up visit.

12.2.2. Follow-up of unresolved adverse events

Any AEs that are unresolved at the subject's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the ClinBase.

AstraZeneca retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

12.2.3. Variables

The following variables will be collected for each AE:

- AE diagnosis/description
- The date and time when the AE started and stopped
- Intensity
- Whether the AE is serious or not
- Investigator causality rating against the IMP/NIMP (yes or no)
- Action taken with regard to investigational product
- AE caused subject's withdrawal from study (yes or no)
- Outcome

Additional variables will be collected for all SAEs including treatment given for the event.

The following intensity ratings will be used:

1. Mild (awareness of sign or symptom, but easily tolerated)

2. Moderate (discomfort sufficient to cause interference with normal activities)

3. 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 12.1.2.

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 an SAE.

12.2.4. Causality collection

The investigator will assess causal relationship between IMP/NIMP 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 study procedures and other medication, if applicable. 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 15.1 of this clinical study protocol.

12.2.5. Adverse events based on symptoms and signs

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel: *"Have you had any health problems since you were last asked?"*, or revealed by observation will be collected and recorded in ClinBase.

When collecting AEs the recording of diagnoses is preferred (when possible) to recording a list of symptoms and signs. However, if a diagnosis is known and there are other symptoms or signs that are not generally part of the diagnosis, the diagnosis and each symptom or sign will be recorded separately.

12.2.6. Adverse events based on examinations and tests

The results from protocol-mandated safety assessments will be summarised in the CSR. Deterioration as compared to baseline in protocol-mandated safety assessments should therefore only be reported as AEs if they fulfil any of the SAE criteria.

If deterioration in vital sign or a laboratory value is associated with clinical symptoms and/or signs, the symptom or sign will be reported as an AE and the associated vital sign or laboratory result will be considered as additional information.

Wherever possible the reporting investigator should use the clinical, rather than the laboratory term (e.g., anaemia versus low haemoglobin value).

In the absence of clinical symptoms or signs, 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.

12.2.7. Hy's Law

Cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3xULN together with total bilirubin ≥ 2xULN may need to be reported as SAEs. Please refer to Appendix 15.3 for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

12.3. Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the IMP/NIMP, or to the study procedure(s). All SAEs will be recorded in the ClinBase.

If any SAE occurs in the course of the study, then investigators or other clinical unit personnel will inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work 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 will be undertaken immediately.

Investigators or other clinical unit personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE immediately, or **no later than 24 hours** of when he or she becomes aware of it.

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

In addition to recording of SAEs in ClinBase, the AstraZeneca Serious Adverse Event Report – Clinical Study form for reporting an SAE to the Data Entry Site (DES) will also be used.

All information provided for the SAE sent into the DES will be in English.

The following CRF modules will be completed for each SAE report:

- Demography
- Dosing
- AE (including start and stop date/time for the AE, the investigator's causality assessment to study drug, action taken with study drug, severity and outcome)
- SAE (including serious criteria, causality assessment to study procedure any investigations, the symptoms and course of the event and any treatments given)
- Medical history
- Concomitant medications
- LIVERRF (risk factors), LIVERSS (signs and symptoms) and LIVERDI (additional diagnostic with results) for all SAEs with a reported term of 'Potential Hy's Law' or 'Hy's Law' will be provided in a narrative form by the PI
- Any additional supporting information, e.g., vital signs, ECG assessments, laboratory test results

The 'AstraZeneca first aware date' for all SAEs reported is the date that any member of the Provider or AstraZeneca first become aware of the SAE and for regulatory reporting purposes this is the 'clock start date'.

Each SAE (as Portable Document Format [PDF]) should be sent to the DES Tata Consultancy Services (TCS) preferably via secure e-mail using the mailbox e-mail address:

The e-mail should contain the following information in the e-mail header:

Subject Title: New SAE; <study code>, <SAE text>, <Country>, <Center No>, <Enrolment code>, <Randomisation code>

The message in the e-mail itself should contain the following:

A NEW serious adverse event has been reported for the following subject:

Study Code:

Country: <country>

Centre No: <study site number>

Enrolment Code: <SUBJECT>

Randomisation Code: <SUBJECT>

SAE Description:

Seriousness Criteria:

Study Drug Causality/Additional Med Causality/other Med Causality/Study Procedure Causality

Date SAE met criteria for serious:

AZ (= PAREXEL investigator) first aware date:

13. LEGAL AND ADMINISTRATIVE ASPECTS

13.1. Archiving of Study Documents

All source documents generated in connection with the study will be retained in the limited access file storage area, respecting the privacy and confidentiality of all records that could identify the subjects. Direct access is allowed only for authorized people for monitoring and auditing purposes. Source documents will be handled, stored and archived according to in-house procedures. Electronic data will be collected and handled as described in Section 10.4.

Study documentation will be archived by the contract research organization (CRO) for 15 years. The documents could be retained for a longer period, if required by the regulatory requirements or by an agreement with AstraZeneca. It is the responsibility of AstraZeneca to inform the investigator as to when these documents no longer need to be retained.

13.2. Publication of Study Results

All of the study information and data collected during the study are confidential and the property of AstraZeneca. After completion of the study, the investigator may prepare a joint publication with AstraZeneca. The investigator must undertake not to submit any part of the individual data from this clinical study protocol for publication without prior consent of AstraZeneca at a mutually agreed time.

13.3. Clinical Study Report

An integrated CSR will be prepared in accordance with the standards of the ICH guideline for structure and content of clinical study reports (ICH E3). Copies of the CSR will be provided to the IEC/IRB and the national regulatory authority in accordance with regulatory requirements and PAREXEL SOPs. In the event of premature termination of the study or other conditions specified in ICH E3, an abbreviated CSR may be prepared.

14. REFERENCE LIST

1. Summary of Product Characteristics, AstraZeneca UK Limited. Available at http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1459748202982.pdf Date of access: May. 10, 2016.
2. Thorsson L, Edsbäcker S, Conradson T-B. Lung deposition of budesonide from Turbuhaler® is twice that from a pressurized metered-dose inhaler P-MDI. Eur Respir J 1994;7:1839–44.
3. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardization of spirometry. Eur Respir J 2005;26(2):319-38.
4. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J 2012;40(6):1324-43.
5. FDA Guidance for Industry 'Drug-induced liver injury: Premarketing clinical evaluation'. July 2009. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

15. APPENDICES

15.1. Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT

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 (e.g., hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself a SAE, although the reasons for it may be (e.g., 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 judgment 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, hospitalization, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent 1 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 judgment must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment.
- Hepatotoxicity caused by paracetamol/acetaminophen overdose requiring treatment with N-acetyl cysteine.
- Intensive treatment in an emergency room or at home for allergic bronchospasm.
- Blood dyscrasias (e.g., neutropenia or anaemia requiring blood transfusion) or convulsions that do not result in hospitalization.

- Development of drug dependency or drug abuse.

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

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

- **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 other 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?

  Note: 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 1 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 recognized 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.

15.2. International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

CATEGORY A

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

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

CATEGORY B

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

- UN 3373 – Biological Substance, Category B

Category B pathogens:

- Are to be packed in accordance with UN3373 and IATA Instruction 650.

EXEMPT

Exempt refers to all other materials with minimal risk of containing pathogens.

- Clinical trial samples will fall into Category B or Exempt under IATA regulations.
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging.

  (http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)

- **Biological samples transported in dry ice require additional dangerous goods specification for the dry ice content.**
- IATA compliant courier and packaging materials should be used for packing and transportation. Packing should be done by an IATA certified person, as applicable.
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

15.3. Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law

1. INTRODUCTION

During the course of the study the investigator will remain vigilant for increases in liver clinical chemistry. The investigator is responsible for determining whether a subject/patient meets PHL criteria at any point during the study.

The investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. The HL criteria are met if there is no alternative explanation for the elevations in liver clinical chemistry other than Drug Induced Liver Injury (DILI) caused by the IMP/NIMP.

The investigator is responsible for recording data pertaining to PHL/HL cases and for reporting AEs and SAEs according to the outcome of the review and assessment in line with standard safety reporting processes.

2. DEFINITIONS

Potential Hy's Law (PHL)

- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3x upper limit of normal (ULN) **and** total bilirubin (TBL) ≥ 2x ULN at any point during the study irrespective of an increase in alkaline phosphatase (ALP)
- The elevations do not have to occur at the same time or within a specified time frame

Hy's Law (HL)

- AST or ALT ≥ 3x ULN **and** TBL ≥ 2x ULN, where no other reason, other than the IMP/NIMP, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug
- The elevations do not have to occur at the same time or within a specified time frame

3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any subject/patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3x ULN
- AST ≥ 3x ULN

- TBL ≥ 2x ULN

The investigator will review without delay each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the subject/patient meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

4. FOLLOW-UP

4.1 Potential Hy's Law Criteria not met

If the subject/patient does not meet PHL criteria the investigator will:

- Inform the AstraZeneca representative that the subject/patient has not met PHL criteria
- Perform follow-up on subsequent laboratory results according to the guidance provided in the clinical study protocol

4.2 Potential Hy's Law Criteria met

If the subject/patient does meet PHL criteria the investigator will:

- Notify the AstraZeneca representative who will then inform the central study team.

The study physician contacts the investigator, to provide guidance, discuss and agree an approach for the study subjects'/patients' follow-up and the continuous review of data.

Subsequent to this contact the investigator will:

- Monitor the subject/patient until liver clinical chemistry variables and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated.
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the study physician.
- Complete the 3 Liver CRF Modules as information becomes available.

If at any time (in consultation with the study physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

5. REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

The instructions in this section should be followed for all cases where PHL criteria were met.

No later than 3 weeks after the clinical chemistry abnormality was initially detected, the study physician contacts the investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP/NIMP. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for an SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AstraZeneca standard processes

If it is agreed that there is **no** explanation that would clarify the ALT or AST and TBL elevations other than IMP causality:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review [5].

15.4. Instruction Sheet

(Place holder for Inhaler instruction sheet)

(Place holder for Inhaler instruction sheet)

(Place holder for Inhaler instruction sheet)

(Place holder for Inhaler instruction sheet)

16. SIGNATURES

16.1. Declaration of Sponsor or Responsible Medical Expert (Physician)

Protocol Title: A RANDOMISED, OPEN-LABEL, SINGLE-DOSE, SINGLE-CENTRE, CROSSOVER STUDY IN HEALTHY SUBJECTS TO ASSESS THE RELATIVE BIOAVAILABILITY OF SYMBICORT pMDI 160/4.5 μg ADMINISTERED WITH A SPACER (WITH AND WITHOUT CHARCOAL) AND SYMBICORT pMDI 160/4.5 μg ADMINISTERED WITHOUT A SPACER (WITH AND WITHOUT CHARCOAL)

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational medicinal product, as well as with the ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on Good Clinical Practice applicable to this clinical study.

Sponsor Signatory/Responsible Medical Expert

Signature	**Date of signature**

Medical Science Director

16.2. Declaration of Sponsor or Responsible Medical Expert (Biostatistician)

Protocol Title: A RANDOMISED, OPEN-LABEL, SINGLE-DOSE, SINGLE-CENTRE, CROSSOVER STUDY IN HEALTHY SUBJECTS TO ASSESS THE RELATIVE BIOAVAILABILITY OF SYMBICORT pMDI 160/4.5 μg ADMINISTERED WITH A SPACER (WITH AND WITHOUT CHARCOAL) AND SYMBICORT pMDI 160/4.5 μg ADMINISTERED WITHOUT A SPACER (WITH AND WITHOUT CHARCOAL)

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational medicinal product, as well as with the ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on Good Clinical Practice applicable to this clinical study.

Sponsor Signatory/Responsible Medical Expert

Signature	**Date of signature**

Global Product Statistician

16.3. Declaration of the Principal Investigator

Protocol Title: A RANDOMISED, OPEN-LABEL, SINGLE-DOSE, SINGLE-CENTRE, CROSSOVER STUDY IN HEALTHY SUBJECTS TO ASSESS THE RELATIVE BIOAVAILABILITY OF SYMBICORT pMDI 160/4.5 μg ADMINISTERED WITH A SPACER (WITH AND WITHOUT CHARCOAL) AND SYMBICORT pMDI 160/4.5 μg ADMINISTERED WITHOUT A SPACER (WITH AND WITHOUT CHARCOAL)

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational medicinal product, as well as with the ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on Good Clinical Practice applicable to this clinical study.

Principal/Coordinating Investigator

Signature	**Date of signature**

PAREXEL International Limited