EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 February 2014
EMA/CHMP/175692/2014
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

DuoResp Spiromax

International non-proprietary name:

Budesonide / formoterol

Procedure No. EMEA/H/C/002348

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Product information

Name of the medicinal product:	DuoResp Spiromax
Applicant:	Teva Pharma B.V. Computerweg 10 3542DR Utrecht NETHERLANDS
Active substance:	BUDESONIDE / FORMOTEROL FUMARATE DIHYDRATE
International Non proprietary Name:	Budesonide / formoterol
Pharmaco-therapeutic group (ATC Code):	Formoterol and other drugs for obstructive airway diseases (R03AK07)
Therapeutic indication(s):	DuoResp Spiromax is indicated in adults 18 years of age and older only. Asthma DuoResp Spiromax is indicated in the regular treatment of asthma, where use of a combination (inhaled corticosteroid and long-acting β2 adrenoceptor agonist) is appropriate: -in patients not adequately controlled with inhaled corticosteroids and “as needed” inhaled short-acting β2 adrenoceptor agonists. or -in patients already adequately controlled on both inhaled corticosteroids and long-acting β2 adrenoceptor agonists. COPD Symptomatic treatment of patients with severe COPD (FEV1 < 50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators.
Pharmaceutical form(s):	Inhalation powder

Strength(s):	160 µg / 4.5 µg and 320 µg / 9 µg
Route(s) of administration:	Inhalation use
Packaging:	inhaler
Package size(s):	1 inhaler (120 doses), 1 inhaler (60 doses), 2 inhalers (2x120 doses), 2 inhalers (2x60 doses), 3 inhalers (3x120 doses), 3 inhalers (3x60 doses)

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List of abbreviations

ABS	acrylonitrile butadiene styrene
AE	adverse event
API	active pharmaceutical ingredient
APSD	aerodynamic particle size distribution
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ATC	anatomical therapeutic chemical (classification system)
AUC_{0-inf}	area under the plasma concentration time curve from time zero (pre-dose) to infinity
AUC_{0-t}	area under the plasma concentration time curve from time zero (pre-dose) to the time of the last quantifiable concentration
AUC_{last}	area under the plasma concentration time curve from time zero (pre-dose) to the last measurable concentration
bpm	beats per minute
BE	bioequivalence
BUD	budesonide
BF Spiromax	fixed-dose combination of budesonide and formoterol fumarate in the Spiromax Inhaler
CDA	critical device attribute
CEP	certificate of suitability to the monographs of the European Pharmacopoeia
CMA	critical material attribute
COPD	chronic obstructive pulmonary disease
CQA	critical quality attribute
CSR	clinical study report
C_{max}	maximum plasma concentration
CI	confidence interval
DBP	diastolic blood pressure
DoE	design of experiments
DPI	dry powder inhaler/multi-dose powder inhaler
EC	European Commission
ECG	electrocardiogram
EDQM	European Directorate for the Quality of Medicines and Healthcare
EMA	European Medicines Agency
FPD	fine particle dose
FDC	fixed-dose combination
FEV_1	forced expiratory volume in one second
FOR	formoterol fumarate
GCP	good clinical practice
GLP	good laboratory practice
GMP	good manufacturing practice
GSD	geometric standard deviation
HPA	hypothalamic pituitary adrenocortical
HPLC	high performance liquid chromatography
HR	heart rate

ICH	The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS	inhaled corticosteroid
IP	inlet port
ITT	intent-to-treat population
KF	Karl Fischer titration
LC	label claim
LS	least squares
LABA	long-acting β_2 adrenergic agonist
LC-MS/MS	liquid chromatography-mass spectrometry/mass spectrometry
LLGR	lower leg growth rate
LLOQ	lower limit of quantification
MO	Major Objection
MMAD	mass median aerodynamic diameter
MedDRA	Medical dictionary for regulatory activities
MUC	modified urine cortisol
NGI	next generation impactor
OIP	orally inhaled product
PAPP	polyester/aluminium/polyester/polypropylene
PD	pharmacodynamics
PEF	peak expiratory flow
PET	polyethylene terephthalate
Ph. Eur.	European Pharmacopoeia
PIFR	peak inspiratory flow rate
PIL/PL	patient information leaflet/package leaflet
PK	pharmacokinetics
PP	per protocol population
PP	polypropylene
PS	pre-separator
PSD	particle size distribution
QTc	corrected QT interval
QTcB	corrected QT interval using the Bazzett correction formula
QTcF	corrected QT interval using the Fridericia correction formula
QTPP	quality target product profile
RH	relative humidity
RMP	risk management plan
RMS	root mean square
SAE	serious adverse event
SmPC	summary of product characteristics
SBP	systolic blood pressure
$T_{1/2}$	terminal phase half-life
T_{max}	time to maximum plasma concentration
TD	total dose
TEAR	treatment-emergent adverse events
TSE	transmissible spongiform encaphalopathy
UC	urine cortisol
UDD	uniformity of delivered dose
UV	ultra violet

WHO-DD	World Health Organisation-Drug Dictionary
µg	microgram

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Teva Pharma B.V. submitted on 29 January 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for DuoResp Spiromax, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 20 May 2010. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of interest of patients at Community level.

The application concerns a hybrid medicinal product as defined in Article 10(3) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in a Member State on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Asthma

DuoResp Spiromax is indicated in the regular treatment of asthma, where use of a combination (inhaled corticosteroid and long-acting beta2-adrenoceptor agonist) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and "as needed" inhaled short-acting beta2-adrenoceptor agonists.

or

- patients already adequately controlled on both inhaled corticosteroids and long-acting beta2-adrenoceptor agonists.

COPD

Symptomatic treatment of patients with severe COPD (FEV1 < 50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators.

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Information on the reference product

The chosen reference medicinal product is:

- Medicinal product which is or has been authorised in accordance with Community provisions in accordance with Community provisions in force for not less than 6/10 years in the EEA:

Product name, strength, pharmaceutical form:	Symbicort Turbuhaler, 160 mikrogram/4,5 mikrogram/inhalation, inhalationspulver
Marketing authorisation holder:	AstraZeneca AB
Date of authorisation:	25-08-2000
Marketing authorisation granted by:	Sweden
Community Marketing authorisation number:	16047

- Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

Product name, strength, pharmaceutical form:	Symbicort mite Turbuhaler, 80 mikrogram/4,5 mikrogram/inhalation, inhalationspulver Symbicort Turbuhaler, 160 mikrogram/4,5 mikrogram/inhalation, inhalationspulver Symbicort forte Turbuhaler, 320 mikrogram/9 mikrogram/inhalation, inhalationspulver
Marketing authorisation holder:	AstraZeneca AB
Date of authorisation:	25-08-2000 (80/4,5 mcg and 160/4,5 mcg)/ 28-12-2001(320/9mcg)
Marketing authorisation granted by:	Sweden
Community Marketing authorisation number:	16048/16047/17443

- Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

Study reference number/EudraCT number:	BFS-AS-101 / 2008-006163-36
Product name, strength, pharmaceutical form:	Symbicort Turbohaler 400/12 mcg, Inhalation powder
Marketing authorisation holder:	AstraZeneca UK Limited

Marketing authorisation granted by:	United Kingdom
Community Marketing authorisation number:	PL 17901/0200
Member State of source	United Kingdom
Study reference number/EudraCT number:	BFS-AS-102 / 2008-006185-28
Product name, strength, pharmaceutical form:	Symbicort Turbohaler 100/6 mcg, Inhalation powder
Marketing authorisation holder:	AstraZeneca UK Limited
Marketing authorisation granted by:	United Kingdom
Community Marketing authorisation number:	PL 17901/0091
Member State of source	United Kingdom
Study reference number/EudraCT number:	BFS-AS-103 / 2009-014496-48
Product name, strength, pharmaceutical form:	Symbicort Turbohaler 100/6 Mikrogramm/Dosis Pulver zur Inhalation
Marketing authorisation holder:	AstraZeneca GmbH
Marketing authorisation granted by:	Germany
Community Marketing authorisation number:	50703.00.00
Member State of source	Germany
Study reference number/EudraCT number:	BFS-AS-104 / 2010-021663-32
Product name, strength, pharmaceutical form:	Symbicort Turbohaler 160/4.5 Mikrogramm/Dosis Pulver zur Inhalation
Marketing authorisation holder:	AstraZeneca GmbH
Marketing authorisation granted by:	Germany
Community Marketing authorisation number:	50703.01.00
Member State of source	Germany
Study reference number/EudraCT number:	BFS-AS-105 / 2009-014499-23
Product name, strength, pharmaceutical form:	Symbicort Turbohaler 320/9 Mikrogramm/Dosis Pulver zur Inhalation
Marketing authorisation holder:	AstraZeneca GmbH
Marketing authorisation granted by:	Germany
Community Marketing authorisation number:	50703.02.00
Member State of source	Germany

Study reference number/EudraCT number:	BFS-AS-106 / 2010-021655-64
Product name, strength, pharmaceutical form:	Symbicort Turbohaler 80/4.5 Mikrogramm and Symbicort Turbohaler 320/9 Mikrogramm/Dosis Pulver zur Inhalation
Marketing authorisation holder:	AstraZeneca GmbH
Marketing authorisation granted by:	Germany
Community Marketing authorisation number:	50703.00.00; 50703.02.00
Member State of source	Germany

Study reference number/EudraCT number:	BFS-AS-107 / 2010-021656-25
Product name, strength, pharmaceutical form:	Symbicort Turbohaler 320/9 Mikrogramm/Dosis Pulver zur Inhalation
Marketing authorisation holder:	AstraZeneca GmbH
Marketing authorisation granted by:	Germany
Community Marketing authorisation number:	50703.02.00
Member State of source	Germany

Study reference number/EudraCT number:	BFS-AS-108 / 2012-000486-20
Product name, strength, pharmaceutical form:	Symbicort Turbohaler 200/6 mcg, Inhalation powder
Marketing authorisation holder:	AstraZeneca UK Limited
Marketing authorisation granted by:	United Kingdom
Community Marketing authorisation number:	PL 17901/0092
Member State of source	United Kingdom

Study reference number/EudraCT number:	BFS-AS-109 / 2012-000485-37
Product name, strength, pharmaceutical form:	Symbicort Turbohaler 400/12 mcg, Inhalation powder
Marketing authorisation holder:	AstraZeneca UK Limited
Marketing authorisation granted by:	United Kingdom
Community Marketing authorisation number:	PL 17901/0200
Member State of source	United Kingdom

Study reference number/EudraCT number:	BFS-AS-110 / 2011-004207-20

Product name, strength, pharmaceutical form:	Symbicort Turbohaler 200/6 mcg, Inhalation powder
Marketing authorisation holder:	AstraZeneca UK Limited
Marketing authorisation granted by:	United Kingdom
Community Marketing authorisation number:	PL 17901/0092
Member State of source	United Kingdom
Study reference number/EudraCT number:	BFS-AS-305 / 2010-019082-29
Product name, strength, pharmaceutical form:	Symbicort Turbohaler 80/4.5 Mikrogramm/Dosis Pulver zur Inhalation
Marketing authorisation holder:	AstraZeneca GmbH
Marketing authorisation granted by:	Germany
Community Marketing authorisation number:	50703.00.00
Member State of source	Germany

Scientific Advice

The applicant received Scientific Advice from the CHMP on 24/9/2009, 6/11/2009, 8/12/2009, 9/4/2010, 22/4/2010, 18/11/2010, 22/9/2011 and 16/2/2012. The Scientific Advice pertained to quality and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturers responsible for batch release

Norton (Waterford) Limited T/A Teva Pharmaceuticals Ireland
Unit 27/35, IDA Industrial Park
Cork Road
Waterford
Republic of Ireland

Teva Pharmaceuticals Europe B.V.
Swensweg 5
NL-2031 GA Haarlem
The Netherlands

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Greg Markey **Co-Rapporteur: David Lyons**

- The application was received by the EMA on 29 January 2013.
- The procedure started on 27 March 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 17 June 2013. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 14 June 2013.
- During the PRAC meeting on 11 July 2013, the PRAC agreed on a PRAC RMP advice and assessment overview.
- During the meeting on 25 July 2013, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 25 July 2013.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 October 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 25 November 2013.
- During the PRAC meeting on 5 December 2013, the PRAC agreed on a PRAC RMP advice and assessment overview.
- During the CHMP meeting on 19 December 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 20 January 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 29 January 2014.
- During the PRAC meeting on 6 February 2014, the PRAC agreed on a PRAC RMP advice and assessment overview.
- During the meeting on 20 February 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to DuoResp Spiromax.

2. Scientific discussion

2.1. Introduction

DuoResp Spiromax is an orally inhaled fixed-dose combination product containing the active substances budesonide, an inhaled glucocorticosteroid with anti-inflammatory activity in the lungs, and formoterol fumarate dihydrate, a selective long-acting inhaled β_2 adrenoceptor agonist. This combination of active substances is already approved at national level in several EU countries. This well-known combination is indicated for use in the regular treatment of adults, adolescents and children six years of age and older with asthma where the use of the combination of an inhaled corticosteroid and an inhaled long-acting β_2 adrenoceptor agonist is appropriate (maintenance and reliever therapy) and in the symptomatic treatment of adults with severe chronic obstructive pulmonary disease (COPD).

The fixed-dose combination of budesonide and formoterol fumarate has been shown to provide greater improvement in pulmonary function and overall asthma control than either drug administered alone and its use does not result in any untoward interaction that might affect the pharmacokinetic, pharmacodynamic or safety profiles of the individual drugs.

Budesonide is an orally inhaled glucocorticosteroid with high local anti-inflammatory activity and a lower incidence of adverse effects than is seen with oral corticosteroids. Budesonide has been shown to decrease airways reactivity to histamine and methacholine in patients with hyper reactive airways. Inhaled budesonide is recommended for use in the management of patients with asthma.

Formoterol fumarate dihydrate is a selective long-acting β_2 adrenergic agonist and exerts a preferential effect on β_2 adrenergic receptors on bronchial smooth muscle to produce relaxation and bronchodilatation. Formoterol is used via the orally inhaled route in the management of patients with reversible airways obstruction. Formoterol produces bronchodilatation within 1-3 minutes following inhalation, bronchodilatation which lasts for 12 hours following a single dose. Formoterol is particularly useful in patients with reversible airways obstruction who continue to experience symptoms despite treatment with an anti-inflammatory agent such as an inhaled corticosteroid. Guidelines for the management of reversible airways obstruction and particularly asthma recommend the addition of a long-acting β_2 agonist to the treatment regimen in these patients and studies have shown that the addition of a long-acting β_2 agonist provides better control of asthma than increasing the dose of inhaled corticosteroid.

The mechanisms of action of the two drugs, budesonide and formoterol fumarate dihydrate are different but complementary. Budesonide and formoterol fumarate demonstrate additive effects.

The clinical pharmacology of budesonide and formoterol fumarate has been investigated extensively in the past, is well known and has been the subject of many publications. The Applicant has not presented a review of the literature with regard to the pharmacokinetics (and pharmacodynamics) of budesonide and formoterol fumarate but cites relevant literature as required and as appropriate.

The Applicant has submitted an application through the Centralised Procedure for an orally inhaled fixed-dose combination product in three strengths formulated as an inhalation powder and administered via a novel inhalation-driven, multi-dose dry powder inhaler (DPI) device known as the Spiromax Inhaler:

- DuoResp Spiromax 80/4.5 µg per dose, inhalation powder
- DuoResp Spiromax 160/4.5 µg per dose, inhalation powder and
- DuoResp Spiromax 320/9 µg per dose, inhalation powder

The proposed indication is in the regular treatment of adults and adolescents with asthma where the use of the combination of an inhaled corticosteroid and an inhaled long-acting β_2 adrenoceptor agonist is appropriate and in the symptomatic treatment of adults with severe chronic obstructive pulmonary disease. Budesonide and formoterol are well-known active substances and a fixed dose combination of budesonide and formoterol has well-documented and demonstrated positive benefit-risk in the claimed indications.

This application has been submitted in accordance with Directive 2001/83/EC Article 10(3) – hybrid application – application for a medicinal product referring to a so-called reference

medicinal product with a Marketing Authorisation in a Member State or in the Community on the basis of a complete dossier in accordance with the provisions of Article 8 of Directive 2001/83/EC and which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA.

The reference medicinal products, in respect of the combination of these two active substances, are:

- Symbicort mite Turbohaler 80 Mikrogramm /4.5 Mikrogramm pro Dosis Pulver zur Inhalation,
- Symbicort Turbohaler 160Mikrogramm/4.5 Mikrogramm pro Dosis Pulver zur Inhalation and
- Symbicort forte Turbohaler 320 Mikrogramm/9 Mikrogramm pro Dosis Pulver zur Inhalation

The Marketing Authorisation Holder is AstraZeneca AB. The lower two strengths were authorised on 25th August 2000 and the highest strength was authorised on 28 December 2001.

The development of DuoResp Spiromax follows the CHMP Guideline on OIPs (CPMP/EWP/4151/00 Rev. 1) and aims to demonstrate therapeutic equivalence of this new product to the reference product. The development is based on the demonstration of pharmacokinetic equivalence between each strength of this fixed-dose combination, BF Spiromax[1] and the corresponding strength of the reference product, Symbicort Turbohaler. One pharmacodynamic study and one safety study has been carried out, but no Phase 3 clinical efficacy or safety studies have been conducted comparing the test and reference products in adults or adolescents.

2.2. Quality aspects

2.2.1. Introduction

DuoResp Spiromax is a fixed-dose combination product presented as dry powder for oral inhalation containing budesonide and formoterol fumarate dihydrate. Three strengths were initially proposed: budesonide 80 µg and formoterol (as fumarate dihydrate) 4.5 µg, budesonide 160 µg and formoterol (as fumarate dihydrate) 4.5 µg and budesonide 320 µg and formoterol (as fumarate dihydrate) 9 µg. During the procedure, the lowest strength was withdrawn since neither *in vitro* equivalence, nor bioequivalence with the originator product was demonstrated. The only other ingredient is lactose monohydrate. The product is administered via a novel inhalation-driven multi-dose dry powder inhaler (DPI) with active dose metering known as the Spiromax inhaler. Each inhaler contains either 60 doses (high strength) or 120 doses (middle strength) and is foil-wrapped.

[1] BF Spiromax – The Applicant refers to this fixed-dose combination of budesonide and formoterol fumarate as BF Spiromax. The CHMP uses the same term in order to avoid confusion across documents.

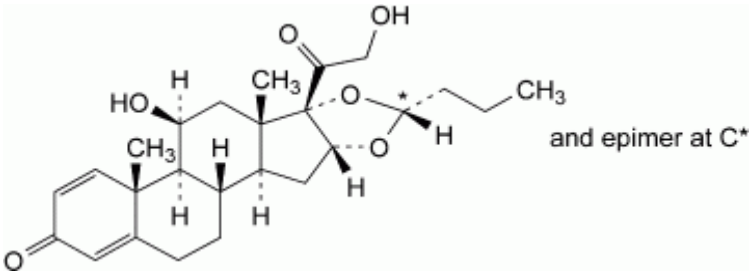
2.2.2. Active Substance

The finished product contains two known active substances, formoterol fumarate dihydrate (a long-acting β_2 agonist), and budesonide (a corticosteroid anti-inflammatory), which are described in Ph. Eur. As there are monographs for budesonide and formoterol fumarate dihydrate in the European Pharmacopoeia, the manufacturers of the active substances have been granted Certificates of Suitability of the European Pharmacopoeia (CEP) which have been provided within the current Marketing Authorisation Application. The information provided regarding the manufacturing processes and the control of the active substances was assessed and approved by the European Directorate for the Quality of Medicines. Satisfactory quality of the active substances is ensured through the CEPs. Budesonide is supplied by a single manufacturer and formoterol fumarate dihydrate is supplied by a further manufacturer. Both active substances are micronized by a separate manufacturer before formulation.

Budesonide

Budesonide is a corticosteroid designated chemically as a mixture of the C*-22*S* (epimer A) and the C*-22*R* (epimer B) epimers of 16α,17-[(1*RS*)-butylidenebis(oxy)]-11β,21-dihydroxypregna-1,4-diene-3,20-dione. The active ingredient budesonide has nine chiral centres. Budesonide is a white to almost white crystalline powder that is practically insoluble in water, sparingly soluble in ethanol, and freely soluble in dichloromethane.

The chemical structure of budesonide is:



The release specifications include tests for residual solvents and particle size distribution in addition to all controls specified in the Ph. Eur. monograph. The specifications comprise tests for appearance (Ph. Eur.), solubility (Ph. Eur.), identification (Ph. Eur.), related substances (Ph. Eur.), epimer A (Ph. Eur.), loss on drying (Ph. Eur.), assay (Ph. Eur.), residual solvents (CEP) and particle size (laser diffraction). The method used for quantification of methanol is described in Annex I of the CEP and no validation data is presented since it was already assessed by EDQM. The laser diffraction method has been adequately described and validated. The particle size distribution is crucial to achieving the required delivered dose and lung deposition characteristics.

The characterisation of the active substance and its impurities and the in-process controls are considered adequate. The specifications and control methods for intermediate products, starting materials and reagents have been assessed by the EDQM before issuing the Certificate of Suitability. Analytical data demonstrating compliance with the drug substance specification have been provided for 3 batches of budesonide.

Budesonide is packaged in a double layer of polyethylene bags, then stored in either fibre drums or Moplen containers.

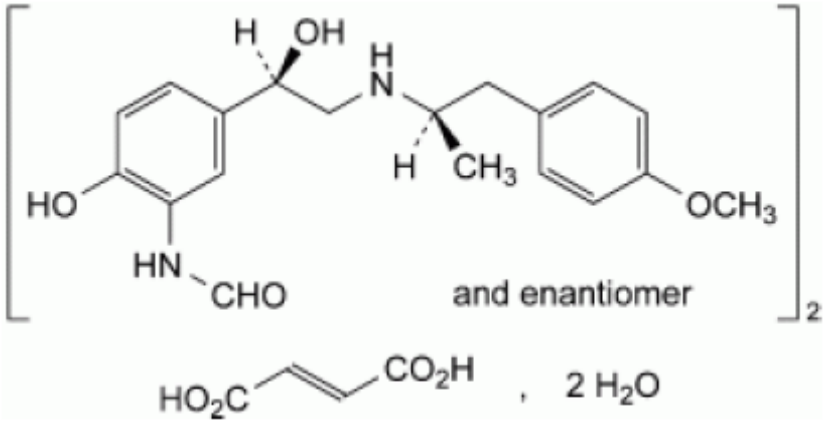
Stability data on 10 pilot and commercial scale batches of budesonide from the proposed manufacturer stored in the intended commercial packaging for up to 60 months under long term conditions (25 ºC / 60% RH) and on 7 pilot and commercial scale batches stored for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The following parameters were tested: appearance, identity, loss on drying, assay, purity, related substances, epimer A content and microbial quality. The analytical methods used were the same as for release, except for microbiological testing and particle size. Both methods have been validated. No trends were observed and all results comply with the current specifications.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container. The applicant commits to placing 1 batch of budesonide on long-term stability on an annual basis as per ICH guidelines.

Formoterol Fumarate Dihydrate

Formoterol fumarate dihydrate is 2:1 salt of formoterol and fumaric acid associated with 2 molecules of water. It is a selective and long-acting β_2 adrenergic receptor agonist and has 2 chiral centres. It's chemical name is *N*-[2-Hydroxy-5-[(1*RS*)-1-hydroxy-2-[[(1*RS*)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide (*E*)-butenedioate dihydrate. Formoterol fumarate dihydrate is a white to almost white or slightly yellow crystalline powder that is slightly soluble in water, soluble in methanol, slightly soluble in 2-propanol and practically insoluble in acetonitrile.

The chemical structure of formoterol fumarate dihydrate is:



The release specifications include tests for residual solvents (methanol and 2-propanol) and particle size distribution in addition to all controls specified in the Ph. Eur. monograph. The specifications comprise tests for appearance (Ph. Eur.), identification (Ph. Eur.), pH (Ph. Eur.), optical rotation (Ph. Eur.), related substances (Ph. Eur.), impurity I (Ph. Eur.), water (Ph. Eur.), residual solvents (CEP) and particle size (laser diffraction). The method used for quantification of methanol and 2-propanol is described in the CEP and no validation data is presented since it was already assessed by EDQM. The laser diffraction method has been adequately described and validated. The particle size distribution is crucial to achieving the required delivered dose and lung deposition characteristics.

The characterisation of formoterol fumarate dihydrate and its impurities and the in-process controls are considered adequate. The specifications and control methods for intermediate

products, starting materials and reagents have been assessed by the EDQM before issuing the Certificate of Suitability. Analytical data demonstrating compliance with the drug substance specification have been provided for 3 batches of formoterol fumarate dihydrate.

Formoterol fumarate dihydrate is packaged in an amber borosilicate glass bottle inside a thermally welded polyester/aluminium/polyester/polypropylene (PAPP) bag.

Stability data on 3 production scale batches of formoterol fumarate dihydrate from the proposed manufacturer stored in the intended commercial packaging for up to 60 months and a further 3 production scale batches for up to 40 months under long term conditions (25 ºC / 60% RH) and on 6 production scale batches stored for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The following parameters were tested: appearance, identity, water, assay, related substances, impurity I, particle size, degree of crystallinity and microbial quality. The analytical methods used were the same as for release, except for microbiological testing and degree of crystallinity. Both methods have been validated. No trends were observed and all results comply with the current specifications.

The stability results indicate that the drug substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container. The applicant commits to placing 1 batch of formoterol fumarate dihydrate on long-term stability on an annual basis as per ICH guidelines.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The objective was to develop a dry powder for inhalation containing a fixed dose combination of formoterol fumarate dihydrate, a selective and long acting β_2-agonist bronchodilator, and budesonide, a corticosteroid anti-inflammatory, to treat the symptoms of asthma and COPD. The product is to be delivered via the Spiromax inhaler, an inhalation-driven multi-dose dry powder delivery device. The product is designed to have an equivalent performance to the reference product, Symbicort Turbohaler. As such, DuoResp Spiromax has been developed following the EMA "Guideline on the requirements for clinical documentation for orally inhaled products including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease in adults and for the use in the treatment of asthma in children and adolescents" (CPMP/EWP/4151/00 Rev. 1). Akin to the reference product, the formulation is a simple combination of the two active substances and lactose.

The principles of Quality by Design were applied to the pharmaceutical development, although no design space was applied for and manufacture and validation are carried out classically. The applicant defined key parameters of the reference product (flow resistance, uniformity of delivered dose (UDD) and aerodynamic particle size distribution (APSD). Pharmacokinetic studies were carried out to establish relationships between these parameters and the *in vivo* performance (bioequivalence) of each active substance. A quality target product profile (QTPP) was then defined for DuoResp Spiromax as follows: it should closely match the quality profile of Symbicort Turbohaler; it should produce equivalent lung deposition and total systemic exposure to Symbicort Turbohaler as demonstrated by equivalent *in vivo* PK performance; it should meet the quality requirements as per EMA Guidance "Guideline on the Pharmaceutical Quality of Inhalation

and Nasal Products" (CHMP/QWP/49313/2005 Corr), as well as other relevant quality guidelines.

Flow resistance and dependence, UDD, and APSD were defined as critical quality attributes (CQAs). Critical material attributes (CMAs) are particle size distribution (PSD) including fine particle dose (FPD) of both active substances and lactose and critical process parameters are mixing time and speed during blending. The relationship between APSD and lung deposition was determined and used to guide development. Limits for the various CQAs and CPPs required to ensure the desired APSD were established using Design of Experiments methodology (DoE). In addition, critical device attributes (CDAs) were compared with those of the reference product to ensure equivalent performance of the inhaler.

A series of trial formulations using micronized budesonide, micronized formoterol, and lactose of varying PSD were manufactured and their performance evaluated, first *in vitro*, and then by PK studies *in vivo*. Once the final formulation had been decided, a further pivotal *in vivo* PK study was carried out on the medium and high strength products to demonstrate bioequivalence to Symbicort. Bioequivalence was not demonstrated for the low strength product which is therefore not authorised for marketing at this time.

Lactose is a well-known pharmaceutical ingredient and its quality is compliant with Ph. Eur. standards. Its compatibility with the active substances is already known from experience with the innovator product. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The primary packaging is a white inhaler with a translucent wine red mouthpiece cap. The inhaler is made of different plastic materials; acrylonitrile butadiene styrene (ABS), polyethylene terephthalate (PET), and polypropylene (PP). Each inhaler contains either 60 doses (high strength) or 120 doses (middle strength) and is foil-wrapped. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and Veterinary Medicinal Products.

Manufacture of the product

The manufacturing process consists of 4 main steps: blending of the 2 micronized active substances with pre-sieved lactose monohydrate; filling of the homogeneous powder blend into the device sub-assembly, followed by assembly of the entire device; equilibration of the filled device; packaging and labelling. The manufacturing process is considered to be non-standard.

Controls are applied to critical steps of the manufacturing process as follows: blend homogeneity testing by NGI on multiple samples to ensure adequate blending; measurement of net powder weight in each device to ensure correct fill weight; check to ensure each device is assembled correctly; actuation check on each device to ensure correct functionality; dose counter check; leak testing to ensure foil pouch seal integrity.

Major steps of the manufacturing process have been validated according to the Note for Guidance on Process Validation (CPMP/QWP/848/96) and Annex II to Note for Guidance on Process Validation – Non-standard Processes (CPMP/QWP/2054/03). Validation data was provided for three batches each of the middle and high strength products manufactured according to the registered process description. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for the production of this dry powder inhaler.

Product specification

The finished product release specifications for each strength include appropriate tests for this kind of dosage form including appearance of powder (visual description), appearance of inhaler (visual inspection), identification (HPLC, UV), related substances (HPLC), formoterol impurity I (HPLC), assay of inhaler content (HPLC) moisture content (KF), microbiological contamination (Ph. Eur.), uniformity of delivered dose (Ph. Eur.), aerodynamic assessment of fine particles (Ph. Eur.) and number of actuations per device (visual inspection).

Batch analysis results provided for 6 commercial scale batches of high (320/9 μg) strength product, along with 3 commercial scale batches of the medium (160/4.5 μg) strength product confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of 3 commercial scale batches each of the medium and high strengths of finished product stored under long term conditions (25 ºC / 60% RH) for up to 18 months and under accelerated conditions (40 ºC / 75% RH) for up to 6 months according to the ICH guidelines were provided. The batches of DuoResp Spiromax are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

In addition, in-use stability was tested using unwrapped samples stored under long term conditions (25 ºC / 60% RH) for up to 6 months. An in-use shelf-life of 6 months when stored below 25 ºC is granted.

Samples were tested according to the release specifications except that slightly wider limits are allowed for aerodynamic assessment of fine particles and assay of inhaler content. No relevant change or trend to any of the measured parameters was observed under either condition. The analytical procedures used are stability indicating. The applicant will complete the on-going stability studies on pivotal batches up to the proposed shelf-life. In addition, a commitment is made to place a further production batch of each strength on stability as per GMP requirements.

Based on available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out

indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The Applicant has not conducted or sponsored any non-clinical studies using budesonide and formoterol to support this Marketing Authorisation Application as the pharmacological and toxicological effects of both budesonide and formoterol are documented in the published literature. The Applicant has chosen to rely on the literature on the non-clinical characterisation of budesonide and formoterol and their known clinical properties.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Budesonide

***In vitro*:** Budesonide is a glucocorticoid with high affinity for specific glucocorticoid receptors that were characterised by interaction with cortisol. When administered systemically, budesonide bound to these receptors with an affinity approximately 200 times that of cortisol and was shown to have a 1000-fold greater topical anti-inflammatory activity than cortisol (Dollery, 1999; Clissold, 1984; Szefler, 1999). Budesonide was shown to have a high ratio of topical to systemic activity when compared to other corticosteroids (e.g. beclomethasone, fluocinolone and triamcinolone). This high ratio is due to the 16, 17-acetal side chain of budesonide. Inhaled budesonide was shown to rapidly induce pulmonary vasoconstriction, suggesting a nongenomic mechanism probably related to the disposition of noradrenaline at the neuromuscular junction. In an isolated and perfused rat lung model, vasoconstriction was more pronounced after inhalation of 10 to 50 µg budesonide than a lower dose of 2 µg (Ewing, 2010).

Budesonide was shown to inhibit the adhesion of neutrophils and monocyte/macrophages to the capillary endothelial cells in inflamed tissue, block the effect of macrophage migration

inhibitory factor and inhibit phospholipase A2 activity, thereby reducing the formation of prostaglandins and leukotrienes in the local tissue.

Inhaled budesonide was also shown to reduce the indices of eosinophil activation in asthma. These effects were considered a likely result of the inhibition of transcription of several cytokines that are overexpressed in asthma, in particular the interleukin (IL)-3, IL-4 and IL-5 and granulocyte-macrophage colony stimulating factor (GM-CSF), especially from activated T cells. Glucocorticoids are known to inhibit plasma exudation through the endothelial barrier of the bronchial vasculature and therefore reduce airway oedema (Dollery, 1999).

***In vivo*:** In early studies in rats, budesonide administered intratracheally or by inhalation was found to counteract the pathophysiological changes (bronchial and interstitial infiltration of eosinophils and mononuclear cells) associated with the intratracheal administration of Sephadex beads (Clissold, 1984).

In a model of late allergic reaction of the lower airways of minipigs sensitised to *Ascaris suum* (roundworms), animals were administered topical or intravenous doses of 10.2 and 5 µg/kg budesonide, respectively. Inhalation of budesonide 1 hour prior to challenge altered the airway reactions and mediator release observed after challenge (Fornhem, 1996).

In dogs, pre-treated with inhalation doses of 2.7 mg/day budnesonide for 7 days, significant reductions in eosinophils in bronchiolar lavage were associated with a reduction in allergen-induced airway hyperresponsiveness (Woolley, 1994a).

Inhibition of induced plasma extravasation in the nasal mucosa of rats has been reported. Intra-nasal doses of 0.1 to 50 µg budesonide, twice daily for 2 days, resulted in a dose-dependent inhibition of capsaicin-induced extravasation in the nasal cavity.

Like other corticosteroids, budesonide was ineffective at resolving established sustained airway hyperresponsiveness, even though they were shown to be effective at reducing inflammation-associated airway hyperresponsiveness and sustained airway hyperresponsiveness when administered continuously prior to the development of airway dysfunction (Southam, 2008).

There is evidence that circulating inflammatory cell progenitors may contribute to the airway inflammation seen in asthma. The effect of allergen inhalation on bone marrow progenitor cell production was investigated in dogs with allergen-induced airway hyperresponsiveness. The inhalation of approximately 100 µg/kg/day budesonide for 7 days significantly reduced the number of bone marrow granulocyte-macrophage progenitors (Woolley, 1994).

Unlike the glucocorticoids beclomethasone and fluticasone, budesonide conjugates with intracellular fatty acids in airway and lung tissue to form lipophilic esters which are unable to bind to the glucocorticoid receptor. In studies in rats administered 10^{-8} to 10^{-5} M [^{3}H]-budesonide into the airways, 70 to 80% of budesonide retained in the airways was conjugated by 20 minutes post dose. The fatty acid conjugation was reversible and the conjugates slowly hydrolysed to free budesonide. It was suggested that the prolonged airway retention of budesonide, as a result of this conjugation and subsequent slow release, contributes to the relatively long duration of its local anti-inflammatory activity (Miller-Larsson, 1998).

Formoterol

***In vitro*:** *In vitro* studies have shown that formoterol has more than 200-fold greater agonist activity at ß2-receptors than at ß1-receptors.

In [^{125}I]iodocyanopindolol-labeled bronchial membranes, formoterol and salmeterol (a β2-adrenergic receptor agonist) induced high-affinity states of the ß2-receptor, the former inducing a higher percentage (57 versus 28). Formoterol and salmeterol were highly selective for the ß2- versus ß1-subtype (pK_i values were 8.2 and 6.25, and 8.3 and 5.7, respectively). Albuterol (a β2-adrenergic receptor agonist) and fenoterol (a β2-adrenergic agonist) were less selective for the ß2- versus ß1-subtype (pKI values were 5.83 and 4.71, and 6.33 and 5.67, respectively; Roux, 1996).

Increased cAMP levels caused the relaxation of bronchial smooth muscle and inhibited the release of mediators of immediate hypersensitivity from cells, especially mast cells. *In vitro* tests showed that formoterol is an inhibitor of the release of mast cell mediators, such as histamine and leukotrienes, from human lung tissue. The relevance of these *in vitro* findings to humans is unknown (PDR, 2012).

Results of an *in vitro* study indicated that the increased lipophilicity of the long acting ß2-agonists, including formoterol, was associated with binding in the smooth muscle membrane adjacent to the ß-receptor (Faulds, 1991).

In *in vitro* studies, using both animal and human muscle preparations, formoterol showed a greater pharmacological maximal effect than salmeterol. Results from severely constricted bronchial smooth muscle preparation indicated that salmeterol was a partial agonist of the β2-receptor in relation to formoterol. Formoterol was shown to have a rapid onset of action and high intrinsic activity (Lötvall, 2002).

***Ex vivo*:** Inhaled formoterol is known to act locally in the lung as a bronchodilator. The biological activities of salmeterol and formoterol on isolated guinea pig tracheal spirals and their receptor binding to guinea pig bronchial and ventricular membranes were characterised. The long-acting -β2-agonists salmeterol and formoterol, were equipotent in relaxing 100 µM histamine-induced maximally contracted guinea pig tracheal spirals. Both agonists were 10 times more potent than L-isoproterenol (a β1 and β2-adrenergic agonist) and fenoterol and 100 times more potent than albuterol. A comparison was also made of the relaxation achieved with 200 µM aminophylline (a bronchodilator). L-isoproterenol and fenoterol induced >90% relaxation (percentage of maximal aminophylline relaxation). Formoterol and albuterol were equally efficacious. Formoterol was more efficacious (86%) than salmeterol (62%) or the bronchodilator soterenol (59%). In 10 µM histamine-induced minimally contracted tissues, all agonist potencies increased 10-fold and complete relaxation was achieved (Roux, 1996).

In vivo: A series of experiments were conducted to investigate whether the anti-plasma leakage action of ß2-adrenoceptor agonists in rat airways was subject to tolerance. Rats were pretreated with intraperitoneal doses of 0.1, 1 or 10 µg/kg formoterol for 7 days; and 24 hours later the effectiveness of a single intravenous dose of up to 10 µg/kg formoterol was tested against substance P-induced plasma leakage. The anti-leakage effect of formoterol was not subject to tolerance with the low or intermediate pretreatment dose. Pretreatment with 10 µg/kg formoterol reduced the effectiveness of the 1 µg/kg acute dose but not the 10 µg/kg acute dose. These results suggested that tolerance to the anti-leakage effect of formoterol could occur with repeated higher doses (Bowden, 1997).

The effects of formoterol on rat and guinea pig hypersensitivity reactions and on mouse IgE antibody formation were investigated. The inhibitory effect of intravenously and orally administered formoterol on (mouse) IgE-mediated 24-hour passive cutaneous anaphylaxis (PCA) in rats was 6.3 and 33 times, respectively, more potent than that of salbutamol (a

short-acting β2-adrenergic receptor agonist). This action was antagonised by pretreatment with propranolol (a sympatholytic non-selective β blocker). The dose of formoterol which inhibited PCA had no effect on histamine- and 5-hydroxytryptamine (5HT)-induced skin reactions. Formoterol, administered intravenously or orally, inhibited (guinea pig) IgE-mediated 8-day PCA in guinea pigs. In the isolated guinea pig lung, both formoterol and salbutamol exhibited dose-dependent inhibition of antigen-induced histamine release. However, in the isolated rat mesenterium these two drugs showed only partial inhibition of antigen-induced mast cell degranulation. Neither formoterol nor salbutamol affected the hapten-specific IgE antibody response in female mice (Tomioka, 1981).

Formoterol was also shown to inhibit histamine-induced plasma albumin extravasation in anaesthetised guinea pigs and allergen-induced eosinophil influx in dogs with airway hyperresponsiveness. The relevance of these findings to humans is unknown (PDR, 2012).

Combination studies

The exact mechanisms for the enhanced efficacy of inhaled corticosteroids and long acting β2-agonist combinations are still under investigation but likely include interactions at the receptor level and interwoven signalling pathways. Data from preclinical studies provided evidence of additive, compensatory, complementary and synergistic effects of inhaled corticosteroids and long acting β2-agonist in the control of inflammation, airway and lung remodelling. These effects were considered to contribute to the improved efficacy seen when treating asthma and COPD with inhaled corticosteroids and long acting β2-agonist combinations in clinical studies (Miller-Larsson, 2006).

The anti-inflammatory, anti-remodeling and anti-bronchoconstriction effects of budesonide and formoterol when used in combination include the inhibition of the following activities: granulocyte macrophage-colony stimulating factor (GM-CSF) release in human bronchial epithelial cells, expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) in human lung fibroblasts, oxidative burst in human eosinophils stimulated by bronchial epithelial cell-derived conditioned medium, inflammation-induced lung oedema, proliferation of airway smooth muscle cells, production of proteoglycans by lung fibroblasts and the bronchoconstriction response to provocation. These effects provide evidence that the combination of budesonide and formoterol delivers a greater benefit compared to either drug administered alone (FDA, 2006).

Furthermore, formoterol, when added to budesonide in human lung fibroblasts exerted an additive effect of the inhibition of IL-1β (Sharafkhaneh, 2002).

In mouse tracheal smooth muscle, β2-receptors mRNA was not affected by cytokines (IL-1 β at 10 ng/mL) but increased with budesonide (1 μM) exposure. However, the cytokines markedly increased cyclooxygenase (COX)-2 mRNA expression, which may lead to heterologous desensitisation of β2-receptors. The cytokine-induced increase of COX-2 was blocked by concomitant budesonide. This suggested that heterologous desensitisation of β2-receptors by cytokines may be prevented by budesonide treatment. Budesonide also prevented cytokine-induced impairment of tracheal relaxation and β2-receptors/cAMP signaling for formoterol but not salmeterol. These results suggested that differences exist between formoterol and salmeterol in β2-receptors coupling/activation and/or signal transduction upstream of cAMP. They also implied that maximal bronchodilator effects of formoterol, but not salmeterol, are maintained by budesonide treatment during periods of increased inflammation, such as asthma exacerbations (Adner, 2010).

IL-6 is produced in response to inflammatory stress, and regulates the expression of acute-phase proteins such as C-reactive protein and plasma fibrinogen. In clinical studies, serum IL-6 was consistently linked with an increased risk of cardiovascular disease. In a study using a mouse model of lung injury, a single pretreatment with budesonide and formoterol combined reduced IL translocation and the systemic increase of IL-6 expression and prevented the endothelial and cardiac dysfunction related to lipopolysaccharide-induced acute lung injury (Suda, 2011).

A study was conducted to investigate the effect of inhaled corticosteroids and long acting β2-agonist combination therapy on the immune-inflammatory, structural, and physiological processes associated with chronic aeroallergen (house dust mite) exposure. The effect of budesonide and/or formoterol treatment with allergen avoidance was investigated in a murine model of sustained eosinophil inflammation and airway remodeling. It was shown that a budesonide/formoterol combination therapy suppressed established airway inflammation, goblet cell hyperplasia and subepithelial anti-α-smooth muscle actin expression, even with ongoing allergen exposure (Johnson, 2008).

In rats administered salmeterol (route of administration not specified) for 1 week, down regulation of pulmonary β2-receptors density (by up to 70%) and desensitisation of β receptors activity were observed. However, the addition of corticosteroids attenuated this effect. Dexamethasone increased the number and rate of synthesis of β2-receptors in human lung tissue by increasing the transcription of β receptors gene. Similar results were found when hamster smooth muscle cells were treated with corticosteroid (triamcinolone acetonide). In some studies, the effective doses of budesonide and formoterol when used in combination were much lower than required when used individually (Sharafkhaneh, 2002).

In asthma and COPD, activation of Gq-protein-coupled receptors causes bronchoconstriction. The management of moderate-to-severe disease uses inhaled corticosteroid and long acting β2-agonist combination therapies, which are more efficacious than either monotherapy alone. In primary human airway smooth muscle cells, inhaled corticosteroid and long acting β2-agonist combinations synergistically induced the expression of the regulator of G-protein signalling 2 (RGS2). Functionally, RGS2 reduced intracellular free calcium flux elicited by histamine, methacholine, leukotrienes and other spasmogens. Protection against spasmogen-increased intracellular free calcium, following treatment for 6 hours with long acting β2-agonist plus corticosteroid, was dependent on RGS2. RGS2-deficient mice revealed enhanced broncho-constriction to spasmogens and an absence of long acting β2-agonist -induced broncho-protection (Holden, 2011).

Secondary pharmacodynamic studies

Racemic formoterol is an equimolar mixture of (R,R)- and (S,S)-formoterol. Several studies have shown (S,S)- formoterol to have proinflammatory effects. It was hypothesised that (S,S)-formoterol promoted asthma by enhancing IL-4 production in mast cells of the asthmatic airway. To investigate this, murine and human mast cells were pretreated with either (R,R)- or (S,S)-formoterol and then stimulated by high affinity IgE receptor cross-linking or with phorbol myristate acetate (PMA; an activator of protein kinase C)/A23187 (a calcium ionophore). In addition, T cells were stimulated with only PMA. (S,S)-formoterol enhanced the production of IL-4, histamine and prostaglandin D2 (PGD2) in mast cells, whereas (R,R)-formoterol had no effect. Neither (S,S)- nor (R,R)-formoterol had an effect on IL-4 production in T cells.

Ovalbumin (OVA)-sensitised mice were pretreated with (R,R)- or (S,S)-formoterol before each daily intranasal OVA challenge for 10 days. (S,S)-formoterol increased IL-4 secretion, whereas (R,R)-formoterol had no effect. (S,S)-formoterol enhanced the inflammatory changes in the peribronchial and perivascular areas without affecting early and late allergic responses or airway hyperresponsiveness. (R,R)-formoterol reduced early and late allergic responses and airway hyperresponsiveness as well as cellular infiltration in lung tissue. It was concluded that (S,S)-formoterol may exert adverse effects in asthma control by activating mast cells to produce proinflammatory mediators such as IL-4 (Abraha, 2004).

Safety pharmacology programme

No safety pharmacology studies with budesonide or formoterol were included in this application which is acceptable in view of the well-known clinical use of budesonide and formoterol.

Pharmacodynamic drug interactions

The pharmacodynamic interactions of budesonide and formoterol are known from the clinical use of the two components and therefore no drug interaction studies were included in this application.

2.3.3. Pharmacokinetics

Pharmacokinetic studies

The pharmacokinetics, absorption, distribution, metabolism and excretion of budnesonide and formoterol were investigated through a series of *in vitro*, *ex vivo* and *in vivo* studies in the mouse, rat, rabbit, dog and human. Budesonide and formoterol were administered either as [H^3]-labelled or unlabelled drug. The routes of administration used were intravenous, oral, inhalation, nasal instillation and intratracheal. The doses of drugs and species used in a number of the pharmacokinetics studies reported were not specified.

Methods of analysis

High performance liquid chromatography or column liquid chromatoghaphy and electrospray tandem mass spectrometry were used to determine the plasma levels of budesonide and formoterol in plasma samples.

Absorption

A study was conducted to determine the pulmonary disposition of budesonide, formoterol or terbutaline (a β2- adrenergic receptor agonist). Isolated and perfused rat lung was exposed to respirable dry particle aerosols of budesonide, formoterol or terbutaline for approximately 1 minute. Each short inhalation of the aerosols delivered 1 or 3 mg of budesonide, formoterol or terbutaline as powder. The inhaled drugs appeared rapidly in the perfusate. The concentration of budesonide peaked at a significantly shorter Tmax than that of formoterol, for both the low and high dose exposures (Ewing, 2008).

An isolated and perfused rat lung model with negative pressure ventilation was used in further lung absorption experiments. The total recovery of budesonide in the perfusate, trachea and lung tissue was 94% of the administered dose. The high absorption rate of budesonide, in combination with a relatively low extent of air-to-blood absorption, suggested that the drug was bound to the lung tissue. The lung-tissue affinity of budesonide was

demonstrated and measured using the isolated and perfused lung model, but was not detected from the Caco-2 cell monolayer apparent permeability values obtained from *in vitro* transport studies. The lung affinity of budesonide after intratracheal administration to isolated perfused rat lungs was also reported (Tronde, 2003).

In other experiments using isolated and perfused rat lungs, 45% of budesonide administered via airways was absorbed within 30 minutes. The remaining fraction was bound to lung tissue compartments and released slowly into the circulatory system (FDA, 2001).

Animal studies have confirmed a relatively rapid and complete availability of budesonide after inhalation or nasal instillation. Rats that received [^{3}H]-budesonide intratracheally showed peak plasma levels of unchanged compound at approximately 3 minutes post dose; concentrations then declined rapidly but were still detectable 4 hours after dosing. The plasma AUC of unchanged budesonide accounted for 61% of the radioactivity AUC; only one minor metabolite was detected 45 minutes post dose (Chanoine, 1991).

In an inhalation study in rats, exposure to 5 and 500 µg/kg [^{3}H]-budesonide produced between 37 to 81% of deposited radioactivity in the upper respiratory and gastrointestinal tracts at 30 minutes post-dose. Only 0.7 to 2.0% was recovered from the lung (FDA, 2001).

Formoterol was shown to be readily absorbed following oral and inhalation administration. The bioavailability of formoterol following oral and intratracheal administration was high, although there was evidence of extensive metabolism. Peak concentrations of formoterol were achieved 0.5 to 1 hour post oral and intratracheal administration (FDA, 2006).

Distribution

The *in vitro* plasma protein binding of budesonide in rat and dog was found to be approximately 90% (FDA, 2001).

The *in vitro* protein binding of formoterol in human plasma was determined at 0.1 to 100 ng/mL and was 61% to 64 %. The *in vitro* binding of formoterol to human serum albumin was determined at 5 to 500 ng/mL and was 31 to 38%. The concentrations of formoterol used to assess the plasma protein binding were higher than those achieved in plasma following inhalation of a single 120 mg dose (PDR, 2012).

The relatively long tissue retention (lungs) of both budesonide and formoterol in rats has been reported. Formoterol had markedly longer tissue retention in the lungs than terbutaline (a short acting β2-agonist). The Applicant attributes the increased duration of clinical effect of formoterol, compared with terbutaline, to its higher lipophilicity. The Applicant states that a possible mechanism of the delayed clearance of budesonide is intracellular fatty acid esterification coupled with the high lipophilicity. This reversible esterification was reported to have the potential to prolong the anti-inflammatory effect of budesonide and improve its airway selectivity (Ewing, 2008).

Investigation of the pharmacokinetics of budesonide and its major ester metabolite, budesonide-21-oleate, in rats following inhalation and intravenous administration of unlabelled and [^{3}H]-budesonide showed that budesonide oleate was formed in the trachea, lung and skeletal muscle tissues but not in plasma; the half-life in the trachea was 18 to 20 hours. Accumulation of the ester in the trachea gave rise to high and persistent concentrations of active budesonide. Budesonide oleate appeared to have no effect on plasma levels of budesonide (Jendbro, 2001).

The distribution of formoterol following inhalation exposure (species not specified) was reported to be in the following order: trachea- lung- kidney- liver- plasma- heart- brain. Half-lives of the drug ranged from 2 to 4 hours (FDA, 2006).

Formoterol was shown to readily cross the placenta of pregnant rats (FDA, 2006).

Metabolism

Budesonide was rapidly metabolised in *in vitro* liver preparations from mice, rats and humans. Apart for the metabolic pathway involving cleavage of the nonsymmetric 16α, 17α-acetal moiety which is unique to budesonide, its biotransformation is similar to that for other synthetic glucocorticoids (Edsbacker, 1987).

The formation of the metabolites, 16α-hydroxyprednisolone and 6β-hydroxybudesonide, in the liver was shown to be catalysed by cytochrome P450 (CYP) 3A enzymes (Jönsson, 1995). Both metabolites were shown to have very little pharmacological activity (less than 1% of budesonide) (Dollery, 1999).

Formoterol was shown to be extensively metabolised by glucuronide conjugation and o-demethylation as the major pathways. Following oral administration, there was evidence of a hepatic first pass effect. Following intratracheal administration, there was some evidence of a first pass metabolic effect in the lung (FDA, 2006).

Excretion

In rats and dogs, elimination of [^{3}H]-budesonide administered by various routes was mainly via faeces. In the rabbit, approximately equal amounts of drug-related radioactivity were eliminated in urine and faeces. Analysis of urine and bile samples revealed only trace amounts of unchanged budesonide demonstrating its extensive biotransformation. In humans, budesonide is excreted in urine and faeces in the form of inactive metabolites (FDA, 2001).

Formoterol was shown to be primarily eliminated in urine and smaller quantities by biliary excretion. There was evidence of enterohepatic recirculation in rats and dogs. In rats, small amounts of formoterol were excreted in milk (FDA, 2006).

Pharmacokinetic drug interactions

No pharmacokinetic drug interaction studies have been included in this application since these interactions of budesonide and formoterol are known from the clinical use of the two components.

Other pharmacokinetic studies

No other pharmacokinetic studies have been reported in this application.

2.3.4. Toxicology

The toxicology studies were taken from the FDA Pharmacology Reviews (FDA, 2001; FDA 2006) cited unless otherwise specified. The doses of drugs and species used in a number of the toxicology studies reported were not specified.

Single dose toxicity

Rat: In a single dose inhalation toxicity study, rats were exposed to air or dry powder consisting of 97 mg/kg budesonide and 3 mg/kg formoterol combined for 1 hour and observed for 14 days after exposure. Deposited doses of budesonide and formoterol were 7.9 and 0.24 mg/kg, respectively. There were no deaths. Body weight gain in male rats decreased to 40% of the air-control animals. Female rats showed an 8.3% reduction of the initial body weight gain. Decreased absolute and relative weights of the spleen, thymus and adrenal glands were observed in both sexes. These changes were attributed to the pharmacological action of budesonide.

Dog: In a single dose inhalation toxicity study, male and female dogs were exposed to dry powder consisting of 737 µg/kg budesonide and 22 µg/kg formoterol. Deposited doses of budesonide and formoterol were 117 and 3.3 µg/kg, respectively. There were no deaths. Clinical signs observed included mucosal redness, body tremor, vomiting, loose stools, increased salivation, nasal catarrh, abdominal respiration and redness of intact skin. Sinus tachycardia was observed in all dogs immediately after dosing and up to 4 hours post dose. Ventricular tachycardia was observed in a male (at 24 and 48 hours post dose) and a female (at 24 hours post dose) dog.

The LD_{50} values of budesonide and formoterol are as follows (taken from the Applicant's Non-clinical Overview):

BUDESONIDE

Species	LD_{50}	Route	Effects
mouse	124 mg/kg	intravenous	altered sleep time, somnolence, convulsions
mouse	4750 mg/kg	oral	altered sleep time, somnolence
mouse	1700 mg/kg	oral	somnolence, weight loss
mouse	179 mg/kg	intraperitoneal	altered sleep time, somnolence
mouse	113.8 mg/kg	intraperitoneal	somnolence, weight loss
mouse	53.6 mg/kg	subcutaneous	altered sleep time, somnolence
rat	96.9 mg/kg	intravenous	altered sleep time, convulsions
rat	2435.9 mg/kg	oral	somnolence, weight loss
rat	>3200 mg/kg	oral	weight loss
rat	138 mg/kg	intraperitoneal	altered sleep time, changes in spleen
rat	58.4 mg/kg	subcutaneous	altered sleep time, changes in spleen
dog	173 mg/kg	subcutaneous	ulceration or bleeding from stomach, diarrhea, changes in spleen

FORMOTEROL

Species	LD_{50}	Route	Effects
mouse	71 mg/kg	intravenous	cardiac arrhythmia, acute pulmonary edema, dyspnea
mouse	6700 mg/kg	oral	cardiac arrhythmia, acute pulmonary edema, dyspnea
mouse	210 mg/kg	intraperitoneal	cardiac arrhythmia, acute

			pulmonary edema, dyspnea
mouse	640 mg/kg	subcutaneous	cardiac arrhythmia, acute pulmonary edema, dyspnea
rat	3130 mg/kg	oral	cardiac arrhythmia, acute pulmonary edema, dyspnea
rat	98 mg/kg	oral	cardiac arrhythmia, acute pulmonary edema, dyspnea
rat	170 mg/kg	intraperitoneal	cardiac arrhythmia, acute pulmonary edema, dyspnea
rat	1 g/kg	subcutaneous	cardiac arrhythmia, acute pulmonary edema, dyspnea

The lowest published toxic inhalation dose of budesonide in rats was reported to be 1.2 mg/m3 in 4 hours. The lowest published toxic dose of budesonide intratracheally administered to rabbits was reported to be 0.5 mg/kg (RTECS, 2011).

Repeat dose toxicity

Budesonide: In 6-month repeated dose studies, rats were administered subcutaneous doses of 0.01 to 80 µg/kg budesonide. Decreased body weight gain and food consumption were observed in the 20 and 80 µg/kg/day dose groups. The haematology effects observed included increased red blood cell counts, a decrease in circulating lymphocytes and their reduced numbers in lymph nodes. Mammary hyperplasia was also observed. At 80 µg/kg/day, hepatocyte vacuolation and thymic atrophy were observed microscopically. Although a dose-related reduction in adrenal weights was observed at 5 to 80 µg/kg/day, no histopathological changes were reported. The no-toxic-effect level was reported to be 5 µg/kg/day and the no-observed-effect-level (NOEL) was 0.1 µg/kg/day (Ekman, 1987).

Formoterol: Subchronic and chronic toxicology studies with formoterol were conducted in both rats and dogs. Studies in rats included 3-, 6-, and 24-month inhalation studies. The longest duration inhalation toxicology study in dogs was 1 month. A 1-year oral toxicology study was conducted in dogs. The Applicant states that the 6-month inhalation toxicology study in rats was considered sufficient to bridge the systemic toxicology studies of formoterol because deposited doses in rats greatly exceeded those that could be achieved in dogs, and neither species seemed particularly sensitive to the local effects of formoterol. Thus, the studies conducted were considered adequate to evaluate the toxicity of formoterol in terms of its local (respiratory) and systemic effects.

The lowest published toxic inhalation dose of formoterol in monkeys was reported to be 0.14 µg/kg in a period of 10 months (RTECS, 2010).

Budesonide and formoterol combined: In 3 month inhalation toxicity studies in rats and dogs administered budesonide and formoterol combined, the findings observed (not specified) were primarily attributable to budesonide. The tachycardia observed in dogs was attributed to formoterol. When administered in combination, no potentiation of toxic effects of budesonide and formoterol was observed.

Genotoxicity

In a series of genotoxicity studies, including the Ames test, recessive lethal test in *Drosophila melanogaster*, mouse lymphoma test, chromosome aberration test in human lymphocytes, DNA repair analysis in rat hepatocytes and mouse micronucleus assay, budesonide was not shown to be genotoxic.

In a series of genotoxicity studies, including the Ames test, chromosome aberration assay in human lymphocytes, mouse lymphoma assay and rat micronucleus assay, formoterol was not shown to be genotoxic.

Carcinogenicity

In a 91-week oral carcinogenicity study in mice orally administered 200 µg/kg budesonide, no carcinogenic effects were reported. Three 2-year oral carcinogenicity studies with budesonide were conducted in rats. In one study, 50 µg/kg budesonide produced an increased incidence of glioma. However, this was not confirmed in two subsequent carcinogenicity studies. Budesonide also produced hepatocellular tumours, which were reported to be a finding typically observed with other glucocorticoids.

In a 2 year study, rats dosed with 5 µg/mL budesonide in drinking water showed an increased incidence of liver tumors. Additional groups of rats were dosed with the synthetic glucocorticoids prednisolone (40 µg/mL) and triamcinolone (1.5 µg/mL). Reduced survival and body weight gain was observed in all drug-treated groups. An increased incidence of combined hepatocellular adenomas/carcinomas occurred with all three compounds. The findings were therefore regarded as a class effect of glucocorticoids (Ryrfeldt, 1992).

In 2-year carcinogenicity studies conducted with formoterol in mice (orally dosed up to 2.5 mg/kg/day) and rats (inhalation doses of up to 130 µg/kg/day), there were findings of increased incidences of ovary and/or uterine leiomyomas. These findings were reported to be typical effects observed with other β2-agonists, however, a reference to support this statement was not provided. The Applicant should cite a reference to support this statement in a revised Non-clinical Overview.

Reproduction Toxicity

Reproductive and developmental toxicity studies were conducted in rats and rabbits.

Fertility and early embryonic development

Budesonide was shown to have no effect on fertility when administered subcutaneously (species and doses used were not specified). In male rats, the oral administration of formoterol reduced fertility, although the dose at which this occurred was not specified.

Embryo-fœtal development

Budesonide: In rats and rabbits, subcutaneous doses (not specified) of budesonide was teratogenic and embryocidal. These effects were not seen in rats that received inhalation doses of up to 250 µg/kg/day budesonide. Epidemiological data indicated that budesonide had no risk to humans during pregnancy.

Formoterol: Oral doses (not specified) of formoterol was teratogenic in both rats and rabbits. No teratogenic effects were reported in rats following inhalation exposure to doses of up to 91 µg/kg/day formoterol.

Combination: The budesonide and formoterol combination was shown to be teratogenic in rats following inhalation exposure to high doses. In an embryo-fetal development study, rats were exposed to a combination of budesonide/formoterol (in a Symbicort HFA pMDI formulation) by nose-only inhalation at actual doses of 2.5/ 0.14, 12/0.66 and 80/4.4 µg/kg/day from Days 6 to 16 of gestation. Deposited doses of budesonide/formoterol for low, mid, and high dose groups were 0.24/0.014, 1.01/0.057 and 6.8/0.39 µg/kg/day, respectively. The mid and high doses were found to be teratogenic. An external

malformation, umbilical hernia, was observed in a single fetus at the mid dose and 2 fetuses at the high dose. These incidences (of 0.4 and 0.9%) exceeded the mean historical control incidence of 0.01%. A visceral malformation, aortic arch: right sided, was observed in one fetus in the high dose group. Fused stemebra was also observed in a single fetus in the high dose group. The relationship of these findings to treatment was unclear. Incidences of no or incomplete ossification were increased in the high dose group. The incidence of a 14th right rib was reported to be higher in the treatment groups. Maternal toxicity was evident in the high dose group.

Prenatal and postnatal development, including maternal function

No pre and postnatal development studies with budesonide and formoterol were reported.

Studies in which the offspring (juvenile animals) are dosed and/or further evaluated

No juvenile toxicity studies with budesonide or formoterol have been included in the application, which is considered acceptable by the CHMP.

Toxicokinetic data

Toxicokinetic analyses were not reported for any of the toxicology studies. This is acceptable in view of the many years clinical use of budesonide and formoterol.

Local Tolerance

No local tolerance studies conducted with budesonide were reported. This is acceptable as no concerns appear to have arisen from its clinical use that warrants the necessity of these studies. In dogs, formoterol caused slight reactive changes at sites of subcutaneous injection.

Other toxicity studies

Haemolysis: The haemolytic/protein flocculation potential of formoterol was assessed *in vitro*. Formoterol did not produce haemolysis or protein flocculation. No haemolysis or protein flocculation studies with budnesonide were reported.

Antigenicity, immunotoxicity, dependence, metabolites: No antigenicity, immunotoxicity, dependence and metabolite studies with budesonide or formoterol have been reported. This is acceptable as no concerns have arisen during the many years of their clinical use that warrant the need for these studies.

Impurities: The impurity profiles of the Symbicort Turbohaler 80 microgram/4.5 microgram/inhalation, inhalation powder and budesonide/formoterol Spiromax 80/4.5, 160/4.5, 320/9 µg per dose, inhalation powder products are reported to be similar. The impurities levels were reported to be below the qualification threshold, as defined by the ICH Note for Guidance on Impurities in New Drug Products (CPMP/ICH/2738/99) and should not cause any safety concerns.

Excipients: Safety assessment studies of excipients were conducted. The only excipient used in budesonide/formoterol Spiromax formulation is lactose monohydrate which is a standard compendial excipient, commonly used in pharmaceutical preparations. There are no toxicological concerns with lactose monohydrate at the doses used in the proposed product.

Phototoxicity: No phototoxicity studies with budesonide and formoterol were reported, which is acceptable as no concerns have arisen during the many years of their clinical use that warrant the need for these studies.

2.3.5. Ecotoxicity / environmental risk assessment

In accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human use [EMEA/CHMP/SWP4447/00], a justification for the absence of an environmental risk assessment (ERA) has been provided. The applicant states that the proposed budesonide/formoterol Spiromax 80/4.5, 160/4.5, 320/9 µg per dose, inhalation powder products would replace the currently marketed medicinal products and hence the exposure of the environment to budesonide and formoterol is not likely to increase. Therefore, the absence of ERA is considered acceptable.

2.3.6. Discussion on non-clinical aspects

Pharmacology, pharmacokinetics and toxicology studies *in vitro*, *ex vivo* and *in vivo* have been conducted with budesonide and formoterol alone and in combination.

No safety pharmacology studies and pharmacodynamic drug interactions have been provided by the applicant. This is considered acceptable by the CHMP since this information is already known from the clinical use of the two components and since being a hybrid application it can rely on the results of pre-clinical tests of the reference product.

The pharmacokinetics, absorption, distribution, metabolism and excretion of budnesonide and formoterol were investigated through a series of *in vitro*, *ex vivo* and *in vivo* studies in the mouse, rat, rabbit, dog and human. Budesonide and formoterol were administered either as [H^3]-labelled or unlabelled drug. The routes of administration used were intravenous, oral, inhalation, nasal instillation and intratracheal.

The toxicology studies were taken from the FDA Pharmacology Reviews (FDA, 2001; FDA 2006) cited unless otherwise specified.

The justification for the absence of an environmental risk assessment ERA is acceptable and an ERA is not deemed necessary. The proposed budesonide/formoterol Spiromax 80/4.5, 160/4.5, 320/9 µg per dose, inhalation powder products are considered unlikely to present a risk to the environment when use as prescribed.

Therefore on the basis of the considerable amount of published scientific evidences on budesonide/formoterol combination, the CHMP concluded that Budesonide/Formoterol inhalation powder produces the claimed pharmacological activity and can be safely administered within therapeutic indications.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical program performed by the Applicant was considered adequate to support this hybrid application for the treatment of asthma and chronic obstructive pulmonary disease.

2.4. Clinical aspects

2.4.1. Introduction

The development of this new fixed-dose combination orally inhaled product (OIP) follows the CHMP Guideline on OIPs (CPMP/EWP/4151/00 Rev. 1) and aims to demonstrate therapeutic equivalence of this new product to the reference product authorised in a

Member State or in the Community on the basis of a complete dossier. The development is based on the demonstration of pharmacokinetic equivalence between each strength of this fixed-dose combination, BF Spiromax[2] and the corresponding strength of the reference product, Symbicort Turbohaler.

The applicant applied for the following indication:

Asthma

DuoResp Spiromax is indicated in the regular treatment of asthma, where use of a combination (inhaled corticosteroid and long-acting beta2-adrenoceptor agonist) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and "as needed" inhaled short-acting beta2-adrenoceptor agonists.

or

- patients already adequately controlled on both inhaled corticosteroids and long-acting beta2-adrenoceptor agonists.

DuoResp Spiromax 80 micrograms/4.5 micrograms per dose is not appropriate in patients with severe asthma.

COPD (DuoResp Spiromax 160/4.5 micrograms per dose and DuoResp Spiromax 320/9 micrograms per dose only)

Symptomatic treatment of patients with severe COPD (FEV1 < 50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators.

The therapeutic indications stated are identical to the therapeutic indications of the reference fixed-dose combination products containing the same active substances and formulated as an inhalation powders in the UK (Symbicort Turbohaler 100 micrograms/6 micrograms/inhalation, inhalation powder, Symbicort Turbohaler 200 micrograms/6 micrograms/inhalation, inhalation powder and Symbicort Turbohaler 400 micrograms/12 micrograms/inhalation, inhalation powder).

The proposed route of administration is for inhalation use.

One pharmacodynamic study has been carried out but no Phase 3 clinical efficacy or safety studies have been conducted comparing the test and reference products in adults or adolescents.

The applicant received Scientific Advice from the CHMP on several occasions pertaining to quality and clinical aspects of the dossier.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

[2] BF Spiromax – The Applicant refers to this fixed-dose combination of budesonide and formoterol fumarate as BF Spiromax. The CHMP uses the same term in order to avoid confusion across documents.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of control	Test Product(s); Dosage Regimen; Route of Administration	Number of subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study status; Type of Report
Pilot PK	BFC-AS-101	5.3.1.2	Assess the PK profiles of BUD and FOR after administration of two inhalations from two batches (each with a different fine particle dose) of BF Spiromax vs. two inhalations of Symbicort Turbohaler	Randomized, open-label, 3-way, crossover	BF Spiromax® Batch A 400/12 mcg metered dose (320/9 mcg delivered dose) BF Spiromax® Batch B 400/12 mcg metered dose (320/9 mcg delivered dose) Symbicort Turbohaler 400/12 mcg metered dose Single dose (2 inhalations) of each treatment	18	Non-smoking healthy volunteers aged 18-45 years	Subjects received each treatment on 1 occasion in 3 treatment periods. Each treatment dose required approximately 1 minute for administration of 2 inhalations per subject	Complete; Full

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of control	Test Product(s); Dosage Regimen; Route of Administration	Number of subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study status; Type of Report
Pilot PK	BFC-AS-102	5.3.1.2	Assess the PK profiles of BUD and FOR after administration of two inhalations from two batches (each with a different fine particle dose) of BF Spiromax vs. two inhalations of Symbicort Turbohaler	Randomized, open-label, 3-way, crossover	BF Spiromax® Batch A 100/6 mcg metered dose (80/4.5 mcg delivered dose) BF Spiromax® Batch B 100/6 mcg metered dose (80/4.5 mcg delivered dose) Symbicort Turbohaler 100/6 mcg metered dose Single dose (2 inhalations) of each treatment	18	Non-smoking healthy volunteers aged 18-45 years	Subjects received each treatment on 1 occasion in 3 treatment periods. Each treatment dose required approximately 1 minute for administration of 2 inhalations per subject	Complete; Full
PK	BFS-AS-103	5.3.1.2	To compare the PK profiles of BUD and FOR after administration of two inhalations of BF Spiromax and Symbicort Turbohaler with and without charcoal block	Randomized, open-label 4-period crossover study	BF Spiromax 80/4.5 mcg delivered dose with and without charcoal Symbicort Turbohaler 100/6 mcg metered dose with and without charcoal Single dose (2 inhalations) of each treatment	88	Non-smoking healthy volunteers aged 18-45 years	4 to 8 weeks	Complete; Full

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of control	Test Product(s); Dosage Regimen; Route of Administration	Number of subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study status; Type of Report
PK	BFS-AS-104	5.3.1.2	To compare the PK profiles of BUD and FOR after administration of two inhalations of BF Spiromax and Symbicort Turbohaler with and without charcoal block and assess intra-subject variability via a replicate Symbicort Turbohaler without charcoal treatment arms	Randomized, open-label 5-period crossover study	BF Spiromax 160/4.5 mcg delivered dose with and without charcoal Symbicort Turbohaler 200/6 mcg metered dose with and without charcoal (x2) Single dose (2 inhalations) of each treatment	90 (to ensure 80 complete dosing and all critical assessments)	Non-smoking healthy volunteers aged 18-45 years	6 to 9 weeks	Complete; Full
PK	BFS-AS-105	5.3.1.2	To compare the PK profiles of BUD and FOR after administration of two inhalations of BF Spiromax and Symbicort Turbohaler with and without charcoal block	Randomized, open-label 4-period crossover	BF Spiromax 320/9 mcg delivered dose with and without charcoal Symbicort Turbohaler 400/12 mcg metered dose with and without charcoal Single dose (2 inhalations) of each treatment	88	Non-smoking healthy volunteers aged 18-45 years	4 to 8 weeks	Complete; Full

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of control	Test Product(s); Dosage Regimen; Route of Administration	Number of subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study status; Type of Report
PK	BFS-AS-107	5.3.1.2	To compare the PK profiles of BUD and FOR after administration of two inhalations of BF Spiromax and Symbicort Turbohaler with and without charcoal block and assess intra-subject variability via replicate BF Spiromax and Symbicort Turbohaler 1 treatment arm	Randomized, open-label 4-period crossover, replicate	BF Spiromax 320/9 mcg delivered dose Symbicort Turbohaler 400/12 mcg metered dose Single dose (2 inhalations) of each treatment replicated	72 (to ensure a minimum of 66)	Non-smoking healthy volunteers aged 18-45 years	4 to 8 weeks	Complete; Full
PK	BFS-BE-108	5.3.1.2	To assess the PK profiles of BUD and FOR powder combination product administered as two inhalations from BF Spiromax and two inhalations from Symbicort Turbohaler with and without charcoal, and assess intra-subject variability via a replicate Symbicort Turbohaler without charcoal treatment arms	Open-label, single-dose, randomized, five-way crossover	BF Spiromax 160/4.5 mcg delivered dose Symbicort Turbohaler 200/6 mcg metered dose Single dose (2 inhalations) of each treatment	90 (to ensure 80 subjects will complete all dosing periods and all critical assessments)	Non-smoking healthy volunteers aged 18-45 years	9 to 14 weeks	Complete; Full

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of control	Test Product(s); Dosage Regimen; Route of Administration	Number of subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study status; Type of Report
PK	BFS-BE-109	5.3.1.2	To assess the PK profiles of BUD and FOR powder combination product administered as two inhalations from BF Spiromax and two inhalations from Symbicort Turbohaler with and without charcoal, and assess intra-subject variability via a replicate Symbicort Turbohaler without charcoal treatment arms	Open-label, single-dose, randomized, five-way crossover	BF Spiromax 320/9 mcg delivered dose Symbicort Turbohaler 400/12 mcg metered dose Single dose (2 inhalations) of each treatment	90 (to ensure 80 subjects will complete all dosing periods and all critical assessments)	Non-smoking healthy volunteers aged 18-45 years	9 to 14 weeks	Complete; Full
Pilot PK	BFS-BE-110	5.3.1.2	To assess the pharmacokinetic (PK) profiles BUD and FOR following two inhalations from each of four batches of BF Spiromax® vs. two inhalations from a single batch of Symbicort® Turbohaler®	Open-label, single-dose, randomized, five way crossover.	BF Spiromax 320/9 mcg delivered dose Symbicort Turbohaler 400/12 mcg metered dose Single dose (2 inhalations) of each treatment	20	Non-smoking healthy volunteers aged 18-45 years	9 to 14 weeks	Complete; Full

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of control	Test Product(s); Dosage Regimen; Route of Administration	Number of subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study status; Type of Report
PD	BFS-AS-106	5.3.4.1	To evaluate the pharmacodynamic (extra-pulmonary) effects of BF Spiromax relative to Symbicort Turbohaler on QTcc, heart rate, blood pressure, glucose and potassium	Randomized, double-blind, double-dummy, cumulative-dose, 4-period crossover	BF Spiromax cumulative delivered doses of 36 mcg and 72 mcg FOR Symbicort Turbohaler cumulative metered doses of 48 mcg and 96 mcg FOR Cumulative dosing of 1+1+2+4 inhalations from each device	56 (to ensure 52 complete dosing and all critical assessments)	Non-smoking healthy volunteers aged 18-45 years	6 to 8 weeks	Complete; Full
Safety	BFS-AS-305	5.3.5.1	To demonstrate non-inferiority of BF Spiromax relative to Symbicort Turbohaler on change in the growth rate of the right lower leg as messured by knemometry.	Randomized, double-blind, double dummy, placebo- and active-controlled 3-way crossover study.	BF Spiromax 80/4.5 mcg delivered dose Symbicort Turbohaler 100/6 mcg metered dose 14 days of each treatment comprising 1 inhalation morning and evening	78 (to ensure 72 complete dosing and all critical assessments)	Male and female prepubescent subjects (Tanner stage 1) aged 6 -11 with persistent asthma.	12 weeks	Complete; Full

2.4.2. Pharmacokinetics

Absorption

- Bioavailability

No bioavailability studies were submitted since the clinical pharmacology of budesonide and formoterol fumarate has been investigated extensively in the past, is well known and has been the subject of many publications. The development of this new fixed-dose combination OIP aims to demonstrate therapeutic equivalence of these new products to appropriate reference products and the development is based on the demonstration of pharmacokinetic and/or pharmacodynamic equivalence between each strength of this fixed-dose combination, BF Spiromax and the corresponding strength of the reference

product, Symbicort Turbohaler.

- Bioequivalence

Three pilot studies, three supportive bioequivalence studies and three pivotal bioequivalence studies, one at each of three strengths, were presented to characterise the pharmacokinetic profile of BF Spiromax (test product) and to compare this with that of Symbicort Turbohaler (reference product) to assess whether these two fixed-dose combination products are therapeutically equivalent.

All studies saw the recruitment of male and female healthy volunteers and were of similar design: single centre, single dose, open-label, crossover studies. Volunteers recruited were aged 18 to 45 years, inclusive, had a body mass index of 19 to 30kg/m2 and a body weight ≥50kg. Subjects were non-smokers for at least 1 year prior to the screening visit and had a maximum smoking history of 5-pack years (equivalent of one pack per day for five years). Pregnant women, women trying to become pregnant and women who were breast feeding were excluded. All subjects recruited underwent appropriate training in the proper use of both the BF Spiromax and the Symbicort Turbohaler devices and had to demonstrate an adequate inspiratory flow rate of greater than or equal to 60 litres per minute.

All studies used the same sampling schedules, pharmacokinetic endpoints and analyses for comparison of all pharmacokinetic profiles. All pharmacokinetic parameters for budesonide and formoterol fumarate were calculated by non-compartmental analysis methods from the concentration-time data. Area under the curve, AUC0-t and AUC0-inf, Cmax, tmax and t½ were calculated for both budesonide and formoterol fumarate in each study.

The primary endpoints were AUC0-t (calculated using the trapezoidal rule) and Cmax. Data were natural log-transformed prior to statistical analysis. Comparisons between BF Spiromax and Symbicort Turbohaler were carried out using a parametric ANOVA model with terms for sequence, period, treatment group and a random effect of subject within sequence. The treatment difference and the associated 90% CI estimated from the ANOVA analysis on the log scale were back-transformed to obtain the estimated ratio of geometric means between treatment groups and the 90% CI for this ratio. BF Spiromax and Symbicort Turbohaler were to be considered similar if the 90% CIs of the ratios of geometric means for both budesonide and formoterol fumarate were contained within the acceptance range of 0.8 to 1.25. However, if the RMS error for Cmax in the ANOVA crossover model exceeded 0.30, indicating high intra-subject variability, the acceptance criteria for Cmax could be widened to a maximum of (0.6984, 1.4319) in line with the CHMP Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr 2012). Comparison of tmax between treatment groups was primarily based on the Wilcoxon signed rank test applied to the period differences.

The pharmacokinetic bioequivalence studies in the BF Spiromax clinical development programme were all single centre, open-label, single dose, crossover studies, with washout periods ranging across the studies from at least 5 days to between 7 and 14 days in duration, set up to compare the pharmacokinetic profiles of budesonide and formoterol fumarate administered as BF Spiromax with budesonide and formoterol fumarate administered as Symbicort Turbohaler. All studies saw recruitment of male and female healthy volunteers, aged 18 to 45 years, inclusive, with no history or current evidence of clinically significant concomitant disease.

In each study, subjects had to complete a training period and demonstrate an adequate

inspiratory flow rate of ≥ 60 L/min, ability to use both the BF Spiromax and Symbicort Turbohaler devices and have no tolerability issues with the active drug substances in either BF Spiromax or Symbicort Turbohaler prior to entering the treatment phase of the study.

The pharmacokinetic profiles of budesonide and formoterol fumarate were characterised in each study after single doses of two inhalations of study treatments in each treatment period. Two inhalations of both the test and reference products were administered in order to optimise the ability to detect budesonide and formoterol fumarate over their entire pharmacokinetic profile. Where subjects were randomised to receive co-administration of activated charcoal, a suspension of 5g activated charcoal in water was administered 2 minutes before and 2, 62, 122, and 242 minutes after dose inhalation.

In each study plasma samples were obtained pre-dose, and at 2, 5, 10, 15, 20, 25, 30, 45 minutes and at 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0, 18.0 and 24.0 hours post-dose. Plasma concentrations of budesonide and formoterol were determined using validated assay procedures as described.

The primary pharmacokinetic endpoints in the bioequivalence studies for both budesonide and formoterol fumarate were:

- area under the plasma concentration-time curve from time zero to the last quantifiable concentration as measured up to 24 hours post-dose (AUC_{0-t})

and

- maximum observed plasma concentration (Cmax)

In each study, safety was monitored by clinical laboratory examinations, 12-lead electrocardiograms (ECGs), physical examination, vital signs and recording of adverse events (AEs).

Each strength of BF Spiromax was developed and evaluated in separate pharmacokinetic studies. Pharmacokinetic equivalence was not achieved initially for one or both drug moieties and therefore changes to the dose cup size or formulation were made to better match the performance of the Spiromax Inhaler to the Turbohaler at a given strength.

A) High Strength – DuoResp Spiromax 320/9 µg per dose, inhalation powder

Four pharmacokinetic equivalence studies were presented in the dossier, one pilot study (BFC-AS-101), two supportive studies (BFS-AS-105 and BFS-AS-107) and one pivotal study (BFS-BE-109). These are presented below:

Pilot and supportive pharmacokinetic studies:

Study BFC-AS-101 (n=18) – pilot study at the high strength not powered for formal bioequivalence assessments

This study, an early pilot study not powered for formal bioequivalence but set up to evaluate the in vitro/*in vivo* relationship for BF Spiromax relative to Symbicort Turbohaler, compared two batches of BF Spiromax 320/9µg, each with a different fine particle dose (FPD), with Symbicort Turbohaler 400/12µg. Based on the in vitro/*in vivo* relationship observed in this pilot study, a pharmacokinetic bioequivalence study was carried out to evaluate whether the

device and formulation selected for BF Spiromax at the high strength could be shown to be bioequivalent to Symbicort Turbohaler.
For both batches of BF Spiromax, the systemic availability of plasma budesonide was comparable with that from Symbicort Turbohaler and the 90% CIs for the ratios of AUClast were contained within the acceptance limits of 0.8, 1.25. For the secondary endpoints AUC0-inf and Cmax, the 90% CIs for the ratios were also contained within these acceptance limits (0.8, 1.25) but with the exception of Cmax for Batch B, which was slightly higher for BF Spiromax than for Symbicort Turbohaler (0.97, 1.31).
The systemic availability of plasma formoterol fumarate was higher for BF Symbicort Batch A than for Symbicort Turbohaler for all endpoints. For Batch B, the systemic availability of formoterol fumarate was contained within the acceptance limits (0.8, 1.25) but with the exception of Cmax which was slightly higher for BF Spiromax than for Symbicort Turbohaler with the 90% CI for the ratio just outside the acceptance range (0.95, 1.30).

Study BFS-AS-105 (n=88) – initial pharmacokinetic bioequivalence study – a supportive study at the high strength

This study was a single dose, four-period crossover study set up to compare the pharmacokinetic profiles of budesonide and formoterol fumarate following administration of BF Spiromax 320/9µg and Symbicort Turbohaler 400/12µg, with and without charcoal blockade, in healthy volunteers. The primary pharmacokinetic endpoints were evaluated for the intent-to-treat (ITT) population – 88 subjects were randomised to treatment, 83 completed all four treatment periods, all 88 subjects were included in the ITT and safety populations.

Five subjects were withdrawn from the study as follows:

- Subject 10002 (Treatment Period 1; Male; BF Spiromax) was withdrawn from the study due to over volunteering on 08JAN2010. The subject screened for a study with another CRO while he confirmed for admission for Treatment Period 1 of this study. Study drug administration for Treatment Period 1 was on 05JAN2010.

- Subject 10003 (Treatment Period 4; Male; Symbicort Turbohaler + charcoal) was withdrawn from the study due to a sleep disorder (cataplexy) on 26JAN2010. Study drug administration for Treatment Period 4 was on 26JAN2010, but the subject did not receive the last 2 charcoal doses.

- Subject 10053 (Treatment Period 1; Male; Symbicort Turbohaler) was withdrawn due to the use of concomitant medication (antibiotics) on 12FEB2010. Study drug administration for Treatment Period 1 was on 06FEB2010.

- Subject 10056 (Treatment Period 3; Female; BF Spiromax + charcoal) was withdrawn due to an adverse event (toothache) on 26FEB2010. Study drug administration for Treatment Period 3 was on 20FEB2010.

- Subject 10087 (Treatment Period 3; Female; BF Spiromax + charcoal) was withdrawn due to an adverse event (acute gastroenteritis) on 03MAR2010. Study drug administration for Treatment Period 3 was on 24FEB2010.

Statistical Comparison of PK Parameters of BUD in Study BFS-AS-105 (ITT population)

Comparison	Parameter	Ratio[b]	90% Confidence Interval		RMS Error	BE (yes/no)
			Lower	Upper		
BF Spiromax (320/9 mcg) vs. Symbicort Turbohaler (400/12 mcg)	AUC_{0-t} (h·pg/mL)	114.4	108.3	121.0	0.221	Yes
	AUC_{0-inf} (h·pg/mL)	113.7	107.7	120.0	0.215	Yes
	C_{max} (pg/mL)	122.3	112.8	132.6	0.323	No
	t_{max} (min)[a]	-0.63	-1.73	0.04	NA	Yes
BF Spiromax (320/9 mcg) + charcoal vs. Symbicort Turbohaler (400/12 mcg) + charcoal	AUC_{0-t} (h·pg/mL)	96.0	90.8	101.6	0.221	Yes
	AUC_{0-inf} (h·pg/mL)	95.9	90.8	101.3	0.215	Yes
	C_{max} (pg/mL)	112.2	103.3	121.7	0.323	Yes
	t_{max} (min)[a]	-0.5	-1.45	0.2	NA	Yes

BE = bioequivalence
a From Wilcoxon Signed Rank test.
b For tmax, this represents the estimated treatment difference.

In the absence of charcoal blockade, bioequivalence was demonstrated for AUC0-t and AUC0-inf for budesonide as the 90% CIs for the ratios were both within the accepted bioequivalence range (0.8, 1.25) – see the table above. However Cmax for budesonide was slightly higher for BF Spiromax 320/9µg than for Symbicort Turbohaler 400/12µg and the 90% CIs for the ratio were not contained within (0.8, 1.25).

In the presence of charcoal blockade equivalence for AUC0-t, AUC0-inf and Cmax was demonstrated – 90% CIs for the ratios were all within the accepted bioequivalence range (0.8, 1.25).

No statistically significant differences between the products in terms of time to reach peak budesonide concentration in plasma were seen either following charcoal blockade or without charcoal blockade.

Statistical Comparison of PK Parameters of FOR in Study BFS-AS-105 (ITT population)

Comparison	Parameter	Ratio[b]	90% Confidence Interval		RMS Error	BE (yes/no)
			Lower	Upper		
BF Spiromax (320/9 mcg) vs. Symbicort Turbohaler (400/12 mcg)	AUC_{0-t} (h·pg/mL)	120.4	113.0	128.4	0.255	No
	AUC_{0-inf} (h·pg/mL)	120.5	113.0	128.6	0.258	No
	C_{max} (pg/mL)	123.7	115.4	132.5	0.275	No
	t_{max} (min)[a]	0.07	-0.05	0.18	NA	Yes
BF Spiromax (320/9 mcg) + charcoal vs. Symbicort Turbohaler (400/12 mcg) + charcoal	AUC_{0-t} (h·pg/mL)	94.8	88.8	101.1	0.255	Yes
	AUC_{0-inf} (h·pg/mL)	95.1	89.0	101.5	0.258	Yes
	C_{max} (pg/mL)	101.0	94.2	108.3	0.275	Yes
	t_{max} (min)[a]	-0.06	-0.25	0.13	NA	Yes

BE = bioequivalence
a From Wilcoxon Signed Rank test.

b For tmax, this represents the estimated treatment difference.

In the absence of charcoal blockade, bioequivalence was not demonstrated for AUC0-t, AUC0-inf or Cmax for formoterol fumarate as the 90% CIs for all ratios were marginally outside the accepted bioequivalence range (0.8, 1.25) – see the table above. However, in the presence of charcoal blockade, bioequivalence was demonstrated for all three variables (90% CIs for the ratios were all contained within (0.8, 1.25).

No statistically significant differences between the products in terms of time to reach peak formoterol fumarate concentration in plasma were seen either following charcoal blockade or without charcoal blockade.

Systemic Exposure in BFS-AS-105 (ITT population)

Data shown are Geometric Mean (CV%)		BUD		FOR	
	N	AUC_{0-t} (h.pg/mL)	C_{max} (pg/mL)	AUC_{0-t} (h.pg/mL)	C_{max} (pg/mL)
BF Spiromax (320/9 mcg)	87	4357.1 (23.68)	2761.9 (37.94)	96.4 (25.36)	44.6 (32.96)
+ charcoal	86	3773.5 (23.39)	2851.5 (39.97)	76.5 (29.31)	43.0 (33.01)
% change		-13.4%	+3.2%	-20.6%	-3.6%
Symbicort Turbohaler (400/12 mcg)	87	3801.0 (28.29)	2253.5 (38.06)	79.7 (31.96)	35.9 (36.95)
+ charcoal	84	3921.8 (29.01)	2539.0 (38.94)	80.6 (34.82)	42.5 (36.43)
% change		+3.2%	+12.7%	+1.1%	+18.4%

Minimal change in Cmax and a decrease in AUC were observed for budesonide (13.4%) and formoterol fumarate (20.6%) in the presence versus the absence of charcoal blockade following BF Spiromax administration.

In contrast, while AUC0-t was essentially unchanged, Cmax increased by 12.7% for budesonide and 18.4% for formoterol fumarate in the presence of charcoal blockade following Symbicort Turbohaler administration. The Applicant considered this finding unexpected in that charcoal blockade should not affect Cmax which is almost entirely due to pulmonary absorption of OIPs. There is no physiological reason why Cmax for formoterol fumarate would be higher in the presence versus the absence of charcoal blockade as the charcoal block is designed to reduce orally available drug absorption. Furthermore AUC should be reduced for both drugs following charcoal blockade due to each having measurable oral bioavailability. The expected pattern was observed for BF Spiromax but not for Symbicort Turbohaler; according to the Applicant this was believed to be due to dose to dose variability from the Turbohaler device. This explanation was acknowledged by the CHMP.

Study BFS-AS-107 (n=72) – second pharmacokinetic bioequivalence study – a supportive study at the high strength

In order to confirm bioequivalence between BF Spiromax and Symbicort Turbohaler at the high strength following the completion of Study BFC-AS-105 above, Study BFS-AS-107 was set up to further evaluate the pharmacokinetic profiles of budesonide and formoterol fumarate in the absence of charcoal blockade.

This was an open-label, randomised, four-period crossover, replicate treatment, single-dose study to compare the pharmacokinetic profile of BF Spiromax 320/9µg with Symbicort Turbohaler 400/12µg in healthy volunteers. This study was designed to further evaluate pharmacokinetic parameters as measured in Study BFS-AS-105 in which bioequivalence was not established. In addition, this study was designed to assess intra-subject variability since high dose-to-dose variability with Symbicort Turbohaler was believed to have contributed to the findings in Study BFS-AS-105. In this regard, the intrasubject variability with BF Spiromax 320/9µg and Symbicort Turbohaler 400/12µg was also determined from replicate treatment arms for both treatments. The primary pharmacokinetic endpoints were evaluated for both the ITT and the per protocol (PP) population – 72 subjects were randomised to treatment, 70 completed all four treatment periods, all 72 subjects were included in the ITT and safety populations and 71 were included in the PP population. This approach followed the written scientific advice received from CHMP.

Statistical Comparison of PK Parameters of BUD in Study BFS-AS-107 (PP population)

Comparison	Parameter	Ratio[b]	90% Confidence Interval		RMS Error		BE (yes/no)
			Lower	Upper	BFS	ST	
BF Spiromax (320/9 mcg) vs. Symbicort Turbohaler (400/12 mcg)	AUC_{0-t} (h·pg/mL)	108.67	104.45	113.06	0.149	0.189	Yes
	AUC_{0-inf} (h·pg/mL)	108.61	104.50	112.88	0.149	0.183	Yes
	C_{max} (pg/mL)	113.91	106.31	122.04	0.371	0.327	Yes
	t_{max} (min)[a]	0.30	-0.33	1.02			
	$t_{1/2}$ (h)[a]	0.24	0.03	0.46			

BE = bioequivalence

[a] From Wilcoxon Signed Rank test.

[b] For t_{max} and $t_{1/2}$, this represents the estimated treatment difference.

Statistical Comparison of BUD after First and Second Administration of BF Spiromax and Symbicort Turbohaler in Study BFS-AS-107 (PP population)

Comparison	Parameter (Geometric mean)	Administration		Ratio	90% Confidence Interval		BE (yes/no)
		1st	2nd		Lower	Upper	
BF Spiromax (320/9 mcg) 1st vs 2nd administration	AUC_{0-t} (h·pg/mL)	3913.86	3755.67	104.40	100.17	108.80	Yes
	C_{max} (pg/mL)	2532.89	2739.13	94.28	84.44	105.27	Yes
Symbicort Turbohaler (400/12 mcg) 1st vs 2nd administration	AUC_{0-t} (h·pg/mL)	3630.72	3423.15	105.40	99.89	111.21	Yes
	C_{max} (pg/mL)	2196.99	2364.94	92.72	84.25	102.04	Yes

BE = bioequivalence

Statistical Comparison of PK Parameters of FOR in Study BFS-AS-107 (PP population)

Comparison	Parameter	Ratio[b]	90% Confidence Interval		RMS Error		BE (yes/no)
			Lower	Upper	BFS	ST	
BF Spiromax (320/9 mcg) vs. Symbicort Turbohaler (400/12 mcg)	AUC_{0-t} (h·pg/mL)	117.17	112.55	121.97	0.156	0.215	Yes
	AUC_{0-inf} (h·pg/mL)	117.98	112.85	123.34	0.159	0.217	Yes
	C_{max} (pg/mL)	120.42	114.38	126.78	0.218	0.296	No
	t_{max} (min)[a]	0.06	-0.30	0.32			
	$t_{1/2}$ (h)[a]	0.07	-0.33	0.45			

BE = bioequivalence
a From Wilcoxon Signed Rank test.
b For tmax and t1/2, this represents the estimated treatment difference.

Statistical Comparison of FOR after First and Second Administration of BF Spiromax and Symbicort Turbohaler in Study BFS-AS-107 (PP population)

Comparison	Parameter (Geometric mean)	Administration		Ratio	90% Confidence Interval		BE (yes/no)
		1st	2nd		Lower	Upper	
BF Spiromax (320/9 mcg) 1st vs 2nd administration	AUC_{0-t} (h·pg/mL)	118.63	122.17	96.61	92.17	101.27	Yes
	C_{max} (pg/mL)	45.55	45.85	99.26	93.34	105.56	Yes
Symbicort Turbohaler (400/12 mcg) 1st vs 2nd administration	AUC_{0-t} (h·pg/mL)	102.92	102.55	100.43	94.33	106.91	Yes
	C_{max} (pg/mL)	39.40	37.80	104.79	96.15	114.20	Yes

BE = bioequivalence

As in the earlier studies, again bioequivalence for formoterol fumarate through Cmax was not achieved between BF Spiromax and Symbicort Turbohaler. The clinical relevance of this finding was evaluated in the pharmacodynamic study, Study BFS-AS-106 (described under section 2.4.3 Pharmacodynamics below).

PIVOTAL pharmacokinetic study

Study BFS-BE-109 (n=90) – third pharmacokinetic bioequivalence study – a pivotal study at the high strength

Based on the findings in respect of Cmax for formoterol fumarate (which were similar across all three strength products – see Studies BFS-AS-105 and BFS-AS-107, above and Studies BFS-AS-104 and BFS-AS-103 below) the Applicant considered that a common cause maybe responsible for the lack of bioequivalence. *In vitro* evaluation of possible solutions to achieve pharmacokinetic bioequivalence for formoterol fumarate with regard to Cmax, suggested that a change in the micronization process for the drug substance, to produce a larger particle size, might enable the achievement of pharmacokinetic bioequivalence for the formoterol fumarate comparisons of test and reference products. This hypothesis was tested and validated in a pilot study carried out with the middle strength of BF Spiromax and Symbicort Turbohlaer (see study BFS-BE-110 below). Based on the findings of this pilot study the high strength product was modified by inclusion of coarser formoterol fumarate particles and a repeat pivotal pharmacokinetic study with the high strength was carried out with and without charcoal blockade.

This was a single-centre, open-label, randomized, five-period crossover, single dose study to assess the pharmacokinetic profiles of budesonide and formoterol fumarate following administration of Spiromax 320/9µg and Symbicort Turbohaler 400/12µg with and without charcoal blockade. Subjects were randomised one of 10 treatment sequences and to ensure consistency all dosing occurred between 08.00hours and 10.00hours. The primary pharmacokinetic endpoints were AUC0-t and Cmax for both budesonide and formoterol fumarate for the PP population. A total of 90 subjects were randomised to treatment and 87 subjects completed all five treatment periods. All 90 subjects were included in the ITT and safety populations and 87 were included in the PP population.

There were 3 subject-withdrawals during the study:

- Subject No. 2019 was not able to attend scheduled study visit during Period 4 within timelines required by the protocol. This deviation was considered as major and the subject was withdrawn from the study.
- Subject No. 2081 withdrew his consent during the wash-out period between Period 4 and Period 5. He was withdrawn from the study before the fifth Treatment Period.
- Subject No. 2086 was withdrawn from the study because he took a concomitant treatment during the wash-out period between Period 3 and Period 4.

Statistical Comparison of PK Parameters of BUD in Study BFS-BE-109 (PP population)

Comparison	Parameter	Ratio[b]	90% Confidence Interval		RMS Error		BE (yes/no)
			Lower	Upper	BFS	ST	
BF Spiromax (320/9 mcg) vs. Symbicort Turbohaler (400/12 mcg)	AUC_{0-t} (h·pg/mL)	1.0135	0.9785	1.0498	0.125	0.220	Yes
	AUC_{0-inf} (h·pg/mL)	1.0167	0.9808	1.0538	0.129	0.217	Yes
	C_{max} (pg/mL)	1.0455	0.9818	1.1132	0.268	0.332	Yes
	t_{max} (h)[a]	-0.021	-0.046	0.000	NA	NA	NA
	$t_{1/2}$ (h)[a]	0.007	-0.180	0.181	NA	NA	NA
BF Spiromax (320/9 mcg) + charcoal vs. Symbicort Turbohaler (400/12 mcg) + charcoal	AUC_{0-t} (h·pg/mL)	1.0052	0.9568	1.0559	0.167	0.225	Yes
	AUC_{0-inf} (h·pg/mL)	1.0115	0.9617	1.0639	0.170	0.221	Yes
	C_{max} (pg/mL)	1.0447	0.9730	1.1217	0.286	0.286	Yes
	t_{max} (h)[a]	0.000	-0.042	0.000	NA	NA	NA
	$t_{1/2}$ (h)[a]	0.204	0.001	0.426	NA	NA	NA

BE = bioequivalence

a From Wilcoxon Signed Rank test.

b For tmax and t1/2 this represents the estimated treatment difference.

The results for the ITT population were virtually identical to those for the PP population.

Statistical Comparison of PK Parameters of FOR in Study BFS-BE-109 (ITT population)

Comparison	Parameter	Ratio[b]	90% Confidence Interval		RMS Error		BE (yes/no)
			Lower	Upper	BFS	ST	
BF Spiromax (320/9 mcg) vs. Symbicort Turbohaler (400/12 mcg)	AUC_{0-t} (h·pg/mL)	0.9784	0.9400	1.0184	0.160	0.228	Yes
	AUC_{0-inf} (h·pg/mL)	0.9889	0.9451	1.0348	0.171	0.233	Yes
	C_{max} (pg/mL)	0.9942	0.9485	1.0420	0.184	0.273	Yes
	t_{max} (h)[a]	0.000	0.000	0.000	NA	NA	NA
	$t_{1/2}$ (h)[a]	-0.488	-0.868	-0.074	NA	NA	NA
BF Spiromax (320/9 mcg) + charcoal vs. Symbicort Turbohaler (400/12 mcg) + charcoal	AUC_{0-t} (h·pg/mL)	0.9589	0.9089	1.0116	0.197	0.232	Yes
	AUC_{0-inf} (h·pg/mL)	0.9523	0.8951	1.0131	0.216	0.221	Yes
	C_{max} (pg/mL)	1.0199	0.9603	1.0832	0.228	0.256	Yes
	t_{max} (h)[a]	0.000	0.00	0.00	NA	NA	NA
	$t_{1/2}$ (h)[a]	0.063	-0.485	-0.640	NA	NA	NA

BE = bioequivalence

a From Wilcoxon Signed Rank test.

b For tmax and t1/2 this represents the estimated treatment difference.

The results for the ITT population are identical to those for the PP population.

Both in the absence of and in the presence of a charcoal blockade bioequivalence was demonstrated for AUC0-t, Cmax and AUC0-inf for both budesonide and formoterol fumarate, the 90% CIs for the ratios were all within the accepted range for bioequivalence (0.8, 1.25).

Confidence intervals generated for tmax demonstrated no statistically significant difference between the products in terms of time to reach either peak budesonide or peak formoterol fumarate concentrations in plasma both in the absence and in the presence of a charcoal blockade.

The following tables summarise the primary/key pharmacokinetic findings in the one pivotal and two supportive studies with the high strength of this new orally inhaled fixed-dose combination product:

Across Study Comparison of BUD Bioequivalence - High Strength

Study / Comparison	Parameter	Ratio[b]	90% CI		RMS Error			BE (yes/no)
			Lower	Upper	Overall	BFS	ST	
Study BFS-BE-109 – Pivotal Study BF Spiromax (320/9 µg) vs. Symbicort Turbohaler (400/12 µg)	AUC_{0-t} (h·pg/mL)	101.4	97.85	104.98		0.125	0.220	Yes
	C_{max} (pg/mL)	104.6	98.18	111.32		0.268	0.332	Yes
	t_{max} (h)[a]	-0.021	-0.046	0.000				
BF Spiromax (320/9 µg) + charcoal vs. Symbicort Turbohaler (400/12 µg) + charcoal	AUC_{0-t} (h·pg/mL)	100.5	95.68	105.59		0.167	0.225	Yes
	C_{max} (pg/mL)	104.5	97.30	112.17		0.286	0.286	Yes
	t_{max} (h)[a]	0.000	-0.042	0.000				
Study BFS-AS-105 BF Spiromax (320/9 µg) vs. Symbicort Turbohaler (400/12 µg)	AUC_{0-t} (h·pg/mL)	114.4	108.3	121.0	0.221			Yes
	C_{max} (pg/mL)	122.3	112.8	132.6	0.323			No
	t_{max} (min)[a]	-0.63	-1.73	0.04				
BF Spiromax (320/9 µg) + charcoal vs. Symbicort Turbohaler (400/12 µg) + charcoal	AUC_{0-t} (h·pg/mL)	96.0	90.8	101.6	0.221			Yes
	C_{max} (pg/mL)	112.2	103.3	121.7	0.323			Yes
	t_{max} (min)[a]	-0.5	-1.45	0.2				
Study BFS-AS-107 BF Spiromax (320/9 µg) vs. Symbicort Turbohaler (400/12 µg)	AUC_{0-t} (h·pg/mL)	108.67	104.45	113.06		0.149	0.189	Yes
	C_{max} (pg/mL)	113.91	106.31	122.04		0.371	0.327	Yes
	t_{max} (min)[a]	0.30	-0.33	1.02				

BFS represents BF Spiromax and ST represents Symbicort Turbohaler

a From Wilcoxon Signed Rank test

b For t_{max}, this represents the estimated treatment difference.

Across Study Comparison of FOR Bioequivalence - High Strength

Study / Comparison	Parameter	Ratio[b]	90% Confidence Interval		RMS Error			BE (yes/no)
			Lower	Upper	Overall	BFS	ST	
Study BFS-BE-109 – Pivotal Study BF Spiromax (80/4.5 µg) vs. Symbicort Turbohaler (100/6 µg)	AUC_{0-t} (h·pg/mL)	97.84	94.00	101.84		0.160	0.228	Yes
	C_{max} (pg/mL)	99.42	94.85	104.20		0.184	0.273	Yes
	t_{max} (h)[a]	0.00	0.00	0.00				
BF Spiromax (80/4.5 µg) + charcoal vs. Symbicort Turbohaler (100/6 µg) + charcoal	AUC_{0-t} (h·pg/mL)	95.89	90.89	101.16		0.197	0.232	Yes
	C_{max} (pg/mL)	101.99	96.03	108.32		0.228	0.256	Yes
	t_{max} (h)[a]	0.00	0.00	0.00				
Study BFS-AS-105 BF Spiromax (320/9 µg) vs. Symbicort Turbohaler (400/12 µg)	AUC_{0-t} (h·pg/mL)	120.5	113.0	128.4	0.255			No
	C_{max} (pg/mL)	123.7	115.4	132.5	0.275			No
	t_{max} (min)[a]	0.07	-0.05	0.18				
BF Spiromax (320/9 µg) + charcoal vs. Symbicort Turbohaler (400/12 µg) + charcoal	AUC_{0-t} (h·pg/mL)	94.8	88.8	101.1	0.255			Yes
	C_{max} (pg/mL)	101.0	94.2	108.3	0.275			Yes
	t_{max} (min)[a]	-0.06	-0.25	0.13				
Study BFS-AS-107 BF Spiromax (320/9 µg) vs. Symbicort Turbohaler (400/12 µg)	AUC_{0-t} (h·pg/mL)	117.17	112.55	121.97		0.156	0.215	Yes
	C_{max} (pg/mL)	120.42	114.38	126.78		0.218	0.296	No
	t_{max} (min)[a]	0.06	-0.30	0.32				

BFS represents BF Spiromax and ST represents Symbicort Turbohaler

a From Wilcoxon Signed Rank test

b For t_{max}, this represents the estimated treatment difference.

In the pivotal study (study BFS-BE-109), the study in which BF Spiromax contained a mix of the same two active substances but employed a change in the micronization process for the formoterol fumarate drug substance to produce a larger and more coarse formoterol fumarate particle size, BF Spiromax 320/9µg and Symbicort Turbohaler 400/12µg were shown to be bioequivalent in respect of both budesonide and formoterol fumarate pharmacokinetic parameters, when administered both with and without charcoal blockade.

B) Middle Strength – DuoResp Spiromax 160/4.5 µg per dose, inhalation powder

Three pharmacokinetic equivalence studies were presented in the dossier, one pilot (BFS-BE-110), one supportive (BFS-AS-104) and one pivotal study (BFS-BE-108).

Supportive and pilot pharmacokinetic studies

Study BFS-AS-104 (n=90) – fourth pharmacokinetic bioequivalence study – a supportive study at the middle strength

This was an open-label, randomised, five-period crossover study to compare the pharmacokinetic profiles of BF Spiromax 160/4.5µg with Symbicort Turbohaler 200/6µg administered with and without a charcoal blockade. The intra-subject variability with Symbicort Turbohaler was also to be determined by replicate treatment of the Symbicort Turbohaler without charcoal treatment arm.

Subjects were randomised one of 10 treatment sequences and to ensure consistency all dosing occurred between 07.00hours and 09.00hours.

The primary pharmacokinetic endpoints were AUC0-t and Cmax for both budesonide and formoterol fumarate for the PP population. A total of 90 subjects were randomised to treatment and 86 subjects completed all five treatment periods. All 90 subjects were included the safety population and 89 were included in the ITT and PP populations.

The root mean square error in the ANOVA crossover exceeded 0.30 for Symbicort Turbohaler, indicating high intra-subject variability, therefore the acceptance criteria for Cmax were widened to a maximum of (0.698, 1.43)3 for the comparison of BF Spiromax with Symbicort Turbohaler.

Statistical Comparison of PK Parameters of BUD in Study BFS-AS-104 (PP population)

Comparison	Parameter	Ratio[b]	90% Confidence Interval		RMS Error[c]	BE[d] (yes/no)
			Lower	Upper		
BF Spiromax (160/4.5 mcg) vs. Symbicort Turbohaler (200/6 mcg)	AUC_{0-t} (h·pg/mL)	147.95	138.67	157.85	0.480	No
	AUC_{0-inf} (h·pg/mL)	142.71	134.62	151.29	0.422	No
	C_{max} (pg/mL)	144.14	132.53	156.76	0.489	No
	t_{max} (min)[a]	-0.71	-1.50	0.14	NA	NA
	$t_{1/2}$ (h)[b]	0.50	0.27	0.76	NA	NA
BF Spiromax (169/4.5 mcg) + charcoal vs. Symbicort Turbohaler (200/6 mcg) + charcoal	AUC_{0-t} (h·pg/mL)	128.59	119.29	138.61	0.480	No
	AUC_{0-inf} (h·pg/mL)	125.81	118.09	134.03	0.422	No
	C_{max} (pg/mL)	129.21	117.42	143.73	0.489	No
	t_{max} (min)[a, b]	0.34	-0.16	1.93	NA	NA
	$t_{1/2}$ (h)[a, b]	0.31	0.12	0.51	NA	NA

BE = bioequivalence

[3] CHMP Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1)

a From Wilcoxon Signed Rank test.
b For tmax and t1/2 this represents the estimated treatment difference.
c RMS for Symbicort Turbohaler is shown.
d For BF Spiromax – Symbicort Turbohaler Cmax acceptance criteria were widened to (0.698-1.432), for all other comparisons the acceptance criteria were (0.80-1.25)

Statistical Comparison of PK Parameters of FOR in Study BFS-AS-104 (PP population

Comparison	Parameter	Ratio[b]	90% Confidence Interval		RMS Error[c]	BE[d] (yes/no)
			Lower	Upper		
BF Spiromax 160/4.5mcg vs. Symbicort Turbohaler 200/6 mcg	AUC_{0-t} (h·pg/mL)	174.53	161.14	189.03	0.585	No
	AUC_{0-inf} (h·pg/mL)	143.39	135.16	152.12	0.308	No
	C_{max} (pg/mL)	187.17	174.06	201.27	0.517	No
	t_{max} (min)[a]	-0.01	-0.18	0.15	NA	NA
	$t_{1/2}$ (h)[b]	-0.07	-0.70	0.56	NA	NA
BF Spiromax 160/4.5mcg + charcoal vs. Symbicort Turbohaler 200/6 mcg + charcoal	AUC_{0-t} (h·pg/mL)	155.87	140.68	172.70	0.585	No
	AUC_{0-inf} (h·pg/mL)	141.46	131.81	151.83	0.308	No
	C_{max} (pg/mL)	167.35	153.60	182.33	0.517	No
	t_{max} (min)[a]	0.05	-0.12	0.20	NA	NA
	$t_{1/2}$ (h)[b]	0.42	-0.22	0.98	NA	NA

BE = bioequivalence
a From Wilcoxon Signed Rank test.
b For tmax, this represents the estimated treatment difference.
c RMS for Symbicort Turbohaler is shown.
d For BF Spiromax – Symbicort Turbohaler Cmax acceptance criteria were widened to (0.698-1.432), for all other comparisons the acceptance criteria were (0.80-1.25)

Very similar results were obtained using the ITT population.

Bioequivalence was not demonstrated for any of AUC0-t, AUC0-inf or Cmax either in the presence or absence of charcoal for budesonide or formoterol fumarate. The CIs generated for tmax demonstrated no statistically significant difference between the test and reference products in terms of time to reach peak budesonide or formoterol fumarate concentration in plasma.

Study BFS-BE-110 (n=20) – pilot study

This was a pilot study and was not powered for formal bioequivalence assessments. The study was set up to evaluate the *in vitro*/*in vivo* correlation for BF Spiromax relative to Symbicort Turbohaler for the middle strength product, DuoResp Spiromax 160/4.5 µg per dose, inhalation powder and used four batches of BF Spiromax each with a different formulation and different *in vitro* performance characteristics. The study assessed key formulation parameters identified in the *in vivo* studies:

- Metered dose (device cup volume)
- Formulation blend strength

- Drug substance particle size and lactose particle size.

The formulation options are summarised in the table below:

BF Spiromax Formulation Options Investigated in Study BFS-BE-110

Option	Formulation change	Product/formulation details	Comments
Batch A	Blend strength	Current Middle Strength formulation and lower blend strength of both drug substances by 5%	To reduce blend strength to better match Symbicort delivered dose of both drug substances
Batch B	Blend strength, FOR particle size	Batch A but using FOR with a larger particle size	To further reduce FOR systemic and local exposures from Batch A
Batch C	Blend strength, FOR particle size, lactose particle size	Batch B but using lactose with a lower fine lactose	To further reduce systemic and local exposures of both drug substances from Batch B
Batch D	High strength formulation and half sized cup dose	High strength with 5% lower FOR blend strength delivered from Spiromax device equipped with half sized dose cup	To use the High Strength formulation for delivery from half-sized dose cup to achieve Middle Strength delivered dose

This was a single-centre, open-label, single-dose, five-way crossover study and to ensure consistency, all dosing occurred between 08.00hours and 10.00hours. Subjects were randomised to one of 10 treatment sequences.

The primary objective was to assess the pharmacokinetic profiles of budesonide and formoterol fumarate following two inhalations from four batches of BF Spiromax (Batch A, Batch B, Batch C and Batch D) and two inhalations from a single batch of Symbicort Turbohaler. The study used BF Spiromax 160/4.5µg and Symbicort Turbohaler 200/6µg.

A total of 20 subjects were randomised to treatment. Eighteen subjects completed all five treatment periods. One subject had a motor bike accident between treatment periods 4 and 5 and withdrew and one subject experienced mild cough between treatment period 2 and 3. The 18 subjects who completed the study were included in the PP population. All randomised subjects were included in the safety and ITT populations.

In vitro evaluation of possible solutions to achieve pharmacokinetic bioequivalence for formoterol fumarate with regard to Cmax, suggested that a change in the micronisation process for the drug substance, to produce a larger particle size, might enable the achievement of pharmacokinetic bioequivalence for the formoterol fumarate comparisons of test and reference products.

The findings were as follows:

- For batches A and C of BF Spiromax the systemic availability of plasma budesonide was not comparable with Symbicort Turbohaler and the 90% CIs for the ratios of AUC_{0-t}, AUC_{0-inf} and C_{max} were not contained within (0.8, 1.25)
- For batches B and D of BF Spiromax the systemic availability of plasma budesonide was comparable with Symbicort Turbohaler and the 90% CIs for the ratios of AUC_{0-t},

and AUC_{0-inf} were contained within (0.8, 1.25); however, C_{max}, for both batch B and batch D was not contained within (0.8, 1.25);

- For all four batches, there were no appreciable differences between BF Spiromax and Symbicort Turbohaler with respect to BUD t½ and t_{max}.
- For batches A and D of BF Spiromax, the systemic availability of plasma formoterol fumarate was comparable with Symbicort Turbohaler and the 90% CIs for the ratios of AUC_{0-t}, and AUC_{0-inf} were contained within (0.8, 1.25); however, C_{max}, for both batches was not contained within (0.8, 1.25). Both of these batches utilised the original formoterol fumarate drug substance;
- For batch B of BF Spiromax, the systemic availability of plasma formoterol fumarate was comparable with Symbicort Turbohaler and the 90% CIs for the ratios of AUC_{0-t}, AUC_{0-inf} and C_{max} were all contained within (0.8, 1.25);
- For batch C the systemic availability of plasma formoterol fumarate was not comparable with Symbicort Turbohaler and the 90% CIs for the ratios of AUC_{0-t}, AUC_{0-inf} and C_{max} were not contained within (0.8, 1.25).

  Both batch B and batch C used formoterol fumarate drug substance from the new micronization process which resulted in a larger particle size;
- For all four batches there were no appreciable differences between BF Spiromax and Symbicort Turbohaler with respect to FOR t½ and $t_{max.}$

A higher formoterol Cmax was observed with all three strengths for BF Spiromax (low, middle and high) compared with Symbicort Turbohaler. As explained above, subsequent further *in vitro* evaluation of BF Spiromax aiming at achieving pharmacokinetic bioequivalence for formoterol fumarate Cmax suggested that a change in the micronisation process for the formoterol fumarate drug substance, such that a larger particle would be produced, might help achieve bioequivalence for all formoterol fumarate comparisons. This hypothesis was tested and validated in this pilot pharmacokinetic study carried out with the middle strengths of BF Spiromax and Symbicort Turbohaler (study BFS-BE-110). The results indicated that the smaller the particle size the higher the formoterol fumarate Cmax and that a larger, coarser particle size produced a lower Cmax.

The use of formoterol fumarate drug substance micronised by an alternative micronisation process, resulting in larger particles, appeared to correct this difference between the test and reference products in Cmax for the high and middle strength products. Therefore, the Applicant stated their intention to use this new fomoterol fumarate formulation (with larger, coarser particles) for the low strength product as well as for the two higher strengths and believed that pharmacokinetic equivalence for formoterol fumarate could be extrapolated to the low strength product from the middle and high strength pharmacokinetic studies (studies BFS-BE-108 and BFS-BE-109).

Based on the findings of the pilot study (study BFS-BE-110), the middle strength BF Spiromax product was modified also by the use of the high strength formulation which was subsequently filled into a half-sized dose cup device and by a change in the micronisation process for the formoterol fumarate drug substance and a change in the grade of lactose, to produce a larger and coarser particle size. All other components and manufacturing processes were the same as in the (initial) supportive pharmacokinetic bioequivalence study at the middle strength (study BFS-AS-104).

Based on the outcome of this pilot study (study BFS-BE-110), the pivotal pharmacokinetic studies at the high and middle strengths were set up using the proposed changed/modified micronisation process to the larger, coarser particle size. Both studies confirmed that this change resulted in some slight lowering of Cmax, in the absence of charcoal blockade, for both formoterol fumarate (as required from earlier study results) and budesonide in BF Spiromax such that bioequivalence between BF Spiromax and Symbicort Turbohaler was demonstrated for all comparisons.

The studies with the low strength were carried out using the original drug micronisation specifications and in the pivotal study (study BFS-AS-103) in both the absence of and in the presence of a charcoal blockade. Cmax for formoterol fumarate was higher for BF Spiromax than for Symbicorrt Turbohaler and the 90% CIs for the ratios were not within the accepted range for bioequivalence. The Applicant expected that the use of the proposed modified micronisation process to the larger, coarser particle size would have a similar effect to that seen with the high and middle strengths with some slight lowering of Cmax for both actives such that all comparisons between BF Spiromax 80/4.5 µg and Symbicort Turbohaler 100/6 µg would demonstrate bioequivalence. However, the modification of the micronisation process resulted in a lowering of the CIs not only for formoterol fumarate but also for budesonide and for the middle strength product, with the exception of Cmax without charcoal for formoterol fumarate. The CIs did not include unity. The pharmacokinetic data generated were consistently lower for BF Spiromax than for the reference product, Symbicort Turbohaler, particularly for budesonide. The Applicant explained that the batches of the test and reference products used in this study differed within their specification range. The *in vitro* performance of the BF Spiromax batch was inferior to that of the Symbicort Turbohaler batch with regards to FPD.

Study BFS-BE-108 (n=90) – fifth pharmacokinetic bioequivalence study – a pivotal study at the middle strength

This was another single-centre, open-label, randomised, five-period crossover, single dose study to assess the pharmacokinetic profiles of budesonide and formoterol fumarate following administration of BF Spiromax 160/4.5µg and Symbicort Turbohaler 200/6µg with and without charcoal blockade. Subjects were randomised one of 10 treatment sequences and to ensure consistency all dosing occurred between 08.00hours and 10.00hours. The primary pharmacokinetic endpoints were AUC0-t and Cmax for both budesonide and formoterol fumarate for the PP population. A total of 90 subjects were randomised to treatment and 86 subjects completed all five treatment periods. Eighty-eight subjects were included in the ITT and safety populations and 86 were included in the PP population.

There were 4 subject-withdrawals during the study:

- Subject No. 3024 withdrew his consent on Period 1 Day 0 following randomisation and did not receive any randomised study medication.
- Subject No. 3029 was withdrawn from the study after taking randomised study medication on Period 1 Day 0 at the request of the Investigator due to a poor venous status.
- Subject No. 3040 was withdrawn from the study before dosing on Period 3 Day 0 due to the occurrence of a gastroenteritis reported as an AE.

- Subject No. 3080 was withdrawn from the study on Period 1 Day 0 following randomisation and did not receive any randomised study medication due to the occurrence of vagal faintness and vomiting reported as AEs.

Based on the findings of the pilot study (study BFS-BE-110), the middle strength BF Spiromax product was modified also, by the use of the high strength formulation which was subsequently filled into a half-sized dose cup device and by a change in the micronisation process for the formoterol fumarate drug substance to produce a larger and coarser particle size. All other components and manufacturing processes were the same as in the (initial) supportive pharmacokinetic bioequivalence study at the middle strength, (study BFS-AS-104) discussed above.

Statistical Comparison of PK Parameters of BUD in Study BFS-BE-108 (PP population)

Comparison	Parameter	Ratio[b]	90% Confidence Interval		RMS Error		BE (yes/no)
			Lower	Upper	BFS	ST	
BF Spiromax (160/4.5 mcg) vs. Symbicort Turbohaler (200/6 mcg)	AUC_{0-t} (h·pg/mL)	0.9050	0.8735	0.9377	0.149	0.186	Yes
	AUC_{0-inf} (h·pg/mL)	0.9121	0.8811	0.9443	0.141	0.183	Yes
	C_{max} (pg/mL)	0.9309	0.8726	0.9930	0.303	0.279	Yes
	t_{max} (h)[a]	-0.042	-0.063	-0.021	NA	NA	NA
BF Spiromax (160/4.5 mcg) + charcoal vs. Symbicort Turbohaler (200/6 mcg) + charcoal	AUC_{0-t} (h·pg/mL)	0.8563	0.8193	0.8950	0.157	0.193	Yes
	AUC_{0-inf} (h·pg/mL)	0.8572	0.8216	0.8943	0.150	0.184	Yes
	C_{max} (pg/mL)	0.9153	0.8512	0.9842	0.288	0.290	Yes
	t_{max} (h)[a]	-0.042	-0.067	0.000	NA	NA	NA

BE = bioequivalence
a From Wilcoxon Signed Rank test.
b For tmax, this represents the estimated treatment difference.

Statistical Comparison of PK Parameters of FOR in Study BFS-BE-108 (PP population)

Comparison	Parameter	Ratio[b]	90% Confidence Interval		RMS Error		BE (yes/no)
			Lower	Upper	BFS	ST	
BF Spiromax (160/4.5 mcg) vs. Symbicort Turbohaler (200/6 mcg)	AUC_{0-t} (h·pg/mL)	0.9633	0.9281	0.9998	0.159	0.191	Yes
	AUC_{0-inf} (h·pg/mL)	0.9520	0.9131	0.9927	0.135	0.200	Yes
	C_{max} (pg/mL)	0.9726	0.9221	1.0260	0.249	0.234	Yes
	t_{max} (h)[a]	0.000	0.000	0.000	NA	NA	NA
BF Spiromax (320/9 mcg) + charcoal vs. Symbicort Turbohaler (200/6 mcg) + charcoal	AUC_{0-t} (h·pg/mL)	0.8757	0.8310	0.9227	0.189	0.226	Yes
	AUC_{0-inf} (h·pg/mL)	0.8548	0.8057	0.9068	0.195	0.197	Yes
	C_{max} (pg/mL)	0.9348	0.8839	0.9885	0.208	0.236	Yes
	t_{max} (h)[a]	0.000	0.00	0.00	NA	NA	NA

BE = bioequivalence
a From Wilcoxon Signed Rank test.
b For t_{max}, this represents the estimated treatment difference.

The results for the ITT population are virtually identical to those for the PP population. Both in the absence of and in the presence of a charcoal blockade bioequivalence was demonstrated for AUC0-t, Cmax and AUC0-inf for both budesonide and formoterol fumarate, the 90% CIs for the ratios were all within the accepted range for bioequivalence (0.8, 1.25).

Confidence intervals generated for tmax demonstrated no statistically significant difference between the products in terms of time to reach either peak budesonide or peak formoterol fumarate concentrations in plasma both in the absence and in the presence of a charcoal blockade.

The following tables summarise the primary/key pharmacokinetic findings in the one pivotal study and one supportive study with the middle strength of this new orally inhaled fixed-dose combination product:

Across Study Comparison of BUD Bioequivalence - Middle Strength

Study / Comparison	Parameter	Ratio[b]	90% Confidence Interval		RMS Error			BE (yes/no)
			Lower	Upper	Overall	BFS	ST	
Study BFS-BE-108 BF Spiromax (80/4.5 µg) vs. Symbicort Turbohaler (100/6 µg)	AUC_{0-t} (h·pg/mL)	0.9633	0.9281	0.9998		0.159	0.191	Yes
	C_{max} (pg/mL)	0.9726	0.9221	1.0260		0.249	0.234	Yes
	t_{max} (h)[a]	0.000	0.000	0.000				
BF Spiromax (80/4.5 µg) + charcoal vs. Symbicort	AUC_{0-t} (h·pg/mL)	0.8757	0.8310	0.9227		0.189	0.226	Yes
	C_{max} (pg/mL)	0.9348	0.8839	0.9885		0.208	0.236	Yes

Study / Comparison	Parameter	Ratio[b]	90% Confidence Interval		RMS Error			BE (yes/no)
			Lower	Upper	Overall	BFS	ST	
Turbohaler (100/6 µg) + charcoal	t_{max} (h)[a]	0.000	0.00	0.00				
Study BFS-AS-104 BF Spiromax (320/9 µg) vs. Symbicort Turbohaler (400/12 µg	AUC_{0-t} (h·pg/mL)	174.53	161.14	189.03			0.585	No
	C_{max} (pg/mL)	187.17	174.06	201.27			0.517	No
	t_{max} (min)[a]	-0.01	-0.18	0.15				
BF Spiromax (320/9 µg) + charcoal vs. Symbicort Turbohaler (400/12 µg) + charcoal	AUC_{0-t} (h·pg/mL)	155.87	140.68	172.70			0.585	No
	C_{max} (pg/mL)	167.35	153.60	182.33			0.517	No
	t_{max} (min)[a]	0.05	-0.12	0.20				

a From Wilcoxon Signed Rank test

b For t_{max}, this represents the estimated treatment difference.

Across Study Comparison of FOR Bioequivalence - Middle Strength

Study / Comparison	Parameter	Ratio[b]	90% Confidence Interval		RMS Error			BE (yes/no)
			Lower	Upper	Overall	BFS	ST	
Study BFS-BE-108 BF Spiromax (80/4.5 µg) vs. Symbicort Turbohaler (100/6 µg)	AUC_{0-t} (h·pg/mL)	0.9633	0.9281	0.9998		0.159	0.191	Yes
	C_{max} (pg/mL)	0.9726	0.9221	1.0260		0.249	0.234	Yes
	t_{max} (h)[a]	0.000	0.000	0.000				
BF Spiromax (80/4.5 µg) + charcoal vs. Symbicort Turbohaler (100/6 µg) + charcoal	AUC_{0-t} (h·pg/mL)	0.8757	0.8310	0.9227		0.189	0.226	Yes
	C_{max} (pg/mL)	0.9348	0.8839	0.9885		0.208	0.236	Yes
	t_{max} (h)[a]	0.000	0.00	0.00				
Study BFS-AS-104 BF Spiromax (320/9 µg) vs. Symbicort Turbohaler (400/12 µg	AUC_{0-t} (h·pg/mL)	174.53	161.14	189.03			0.585	No
	C_{max} (pg/mL)	187.17	174.06	201.27			0.517	No
	t_{max} (min)[a]	-0.01	-0.18	0.15				
BF Spiromax (320/9 µg) + charcoal vs. Symbicort Turbohaler (400/12 µg) + charcoal	AUC_{0-t} (h·pg/mL)	155.87	140.68	172.70			0.585	No
	C_{max} (pg/mL)	167.35	153.60	182.33			0.517	No
	t_{max} (min)[a]	0.05	-0.12	0.20				

a From Wilcoxon Signed Rank test
b For t_{max}, this represents the estimated treatment difference.

In the pivotal study (study BFS-BE-108), the study in which BF Spiromax contained a mix of the same two active substances but employed a change in the micronisation process for the formoterol fumarate drug substance to produce a larger and more coarse formoterol fumarate particle size, and used the high strength formulation with a half dose cup size, BF Spiromax 160/4.5µg and Symbicort Turbohaler 200/6µg were shown to be bioequivalent in respect of both budesonide and formoterol fumarate pharmacokinetic parameters, when administered both with and without charcoal blockade.

C) Low Strength – DuoResp Spiromax 80/4.5 µg per dose, inhalation powder

Two pharmacokinetic equivalence studies were presented in the dossier, one pilot study (BFC-AS-102) and one pivotal study (BFS-AS-103).

Study BFC-AS-102 (n=18) – a pilot pharmacokinetic study at the low strength not powered for formal bioequivalence assessments

This study, a pilot study not powered for formal bioequivalence, was carried out to evaluate the *in vitro*/*in vivo* relationship for BF Spiromax relative to Symbicort Turbohaler. The primary objective was to assess the pharmacokinetic profiles of budesonide and formoterol

fumarate from two batches of BF Spiromax 80/4.5µg, each with a different fine particle dose (FPD) and from Symbicort Turbohaler 100/6µg.

The study was a single-centre, open-label, single dose, three-way crossover and the primary pharmacokinetic endpoint was AUClast for both budesonide and formoterol fumarate. A total of 18 subjects were randomised to treatment and 16 subjects completed all three treatment periods. All 18 subjects were included in the pharmacokinetic and safety analyses and 17 subjects were included in the inferential pharmacokinetic statistics.

Statistical Comparisons PK Parameters for BUD in Study BFC-AS-102

	BF Spiromax Batch A (80/4.5 mcg) vs Symbicort Turbohaler (100/6 mcg)		BF Spiromax Batch B (80/4.5 mcg) vs Symbicort Turbohaler (100/6 mcg)	
	% Geometric mean ratio	90% CI	% Geometric mean ratio	90% CI
Primary endpoint				
AUC_{last}	119.92	107.85-133.35	79.04	70.92-88.09
Secondary endpoints				
C_{max}	123.31	109.22-139.23	78.11	69.00-88.42
AUC_{0-inf}	118.11	106.05-131.54	80.77	72.48-90.01

The systemic availability of plasma budesonide was higher for BF Symbicort Batch A than for Symbicort Turbohaler for all endpoints based on the 90% CI for the ratios not being contained within (0.8, 1.25). For Batch B, the systemic availability was lower for BF Spiromax than for Symbicort Turbohaler for all endpoints also based on the 90% CI for the ratios not being contained within (0.8, 1.25).

Statistical Comparisons PK Parameters for FOR in Study BFC-AS-102

	BF Spiromax Batch A (80/4.5 mcg) vs Symbicort Turbohaler (100/6 mcg)		BF Spiromax Batch B (80/4.5 mcg) vs Symbicort Turbohaler (100/6 mcg)	
	% Geometric mean ratio	90% CI	% Geometric mean ratio	90% CI
Primary endpoint				
AUC_{last}	144.27	124.14-167.66	105.25	90.26-122.72
Secondary endpoints				
C_{max}	167.08	150.83-185.08	114.02	102.70-126.60
AUC_{0-inf}	134.85	113.19-160.67	98.23	82.30-117.24

Source: Module 5 Section 5.3.1.2 Study BFC-AS-102 CSR Table 14.2.2.8 and 14.2.2.9

The systemic availability of plasma formoterol fumarate was higher for BF Spiromax Batch A than for Symbicort Turbohaler for all endpoints based on the 90% CI for the ratios not being contained within (0.8, 1.25). For Batch B, the systemic availability of plasma formoterol fumarate was comparable with Symbicort Turbohaler and the 90% CI for the ratio of AUClast was contained within (0.8, 1.25). For the secondary endpoint, AUC0-inf, the 90% CI for the ratio was contained within(0.8, 1.25), but the 90% CI for the ratio of Cmax was slightly higher for BF Spiromax than for Symbicort Turbohaler and was not contained within (0.8,1.25).

Study BFS-AS-103 (n=88) – sixth pharmacokinetic bioequivalence study – a pivotal pharmacokinetic study at the low strength

The pharmacokinetic study BFC-AS-102, compared two batches of low strength BF Spiromax 80/4.5µg, each with a different FPD, with Symbicort Turbohaler 100/6µg. Based on the *in vitro*/*in vivo* relationship observed, Study BFS-AS-103 (a further pharmacokinetic study) was conducted to evaluate whether the device and formulation selected for BF Spiromax at low strength could be shown to be equivalent to Symbicort Turbohaler.

Study BFS-AS-103 was a single-centre, open-label, randomised, four-period crossover, single dose study to compare the pharmacokinetic profiles of budesonide and formoterol fumarate following administration of BF Spiromax 80/4.5µg and Symbicort Turbohaler 100/6µg with and without charcoal blockade. Subjects were randomised to receive BF Spiromax or Symbicort Turbohaler without charcoal blockade in treatment periods 1 and 2 followed by BF Spiromax or Symbicort Turbohaler with charcoal blockade in treatment periods 3 and 4 and to ensure consistency all dosing occurred between 06.00hours and 09.00hours. The primary pharmacokinetic endpoints were AUC0-t and Cmax for both budesonide and formoterol fumarate for the ITT population. A total of 88 subjects were randomised to treatment and 87 subjects completed all four treatment periods. All 88 subjects were included in the ITT and safety populations.

Statistical Comparison of PK Parameters of BUD in Study BFS-AS-103 (ITTpopulation)

Comparison	Parameter	Ratio[b]	90% Confidence Interval		RMS Error	BE (yes/no)
			Lower	Upper		
BF Spiromax (80/4.5 mcg) vs. Symbicort Turbohaler (100/6 mcg)	AUC_{0-t} (h·pg/mL)	90.0	85.3	95.0	0.214	Yes
	AUC_{0-inf} (h·pg/mL)	91.4	86.8	96.1	0.204	Yes
	C_{max} (pg/mL)	91.6	84.5	99.4	0.327	Yes
	t_{max} (min)[a]	-0.38	-2.3	0.3	NA	Yes
BF Spiromax (80/4.5 mcg) + charcoal vs. Symbicort Turbohaler (100/6 mcg) + charcoal	AUC_{0-t} (h·pg/mL)	91.3	86.5	96.3	0.214	Yes
	AUC_{0-inf} (h·pg/mL)	91.9	87.3	96.7	0.204	Yes
	C_{max} (pg/mL)	97.7	90.0	106.1	0.327	Yes
	t_{max} (min)[a]	-2.6	-4.8	-1.1	NA	Yes

BE = bioequivalence

[a] From Wilcoxon Signed Rank test.

[b] For t_{max}, this represents the estimated treatment difference.

Source: Module 5 Section 5.3.1.2 Study BFS-AS-103 CSR Table 14.2.2.5

Both in the absence of and in the presence of a charcoal blockade bioequivalence was demonstrated for AUC0-t, AUC0-inf and Cmax for budesonide as the 90% CIs for the ratios were all within the accepted range for bioequivalence (0.8, 1.25).

Confidence intervals generated for tmax demonstrated no statistically significant difference

between the products in terms of time to reach peak budesonide concentration in plasma both in the absence and in the presence of a charcoal blockade.

Statistical Comparison of PK Parameters of FOR in Study BSF-AS-103 (ITT population)

Comparison	Parameter	Ratio[b]	90% Confidence Interval		RMS Error	BE (yes/no)
			Lower	Upper		
BF Spiromax (80/4.5 mcg) vs. Symbicort Turbohaler (100/6 mcg)	AUC_{0-t} (h·pg/mL)	102.8	97.3	108.6	0.222	Yes
	AUC_{0-inf} (h·pg/mL)	101.2	96.6	105.9	0.182	Yes
	C_{max} (pg/mL)	119.3	112.6	126.3	0.23	No
	t_{max} (min)[a]	-0.04	-0.24	0.13	NA	Yes
BF Spiromax (80/4.5 mcg) + charcoal vs. Symbicort Turbohaler (100/6 mcg) + charcoal	AUC_{0-t} (h·pg/mL)	110.7	104.8	117.0	0.222	Yes
	AUC_{0-inf} (h·pg/mL)	104.2	99.5	109.2	0.182	Yes
	C_{max} (pg/mL)	137.6	129.9	145.7	0.23	No
	t_{max} (min)[a]	-0.34	-1.25	-0.03	NA	Yes

BE = bioequivalence

[a] From Wilcoxon Signed Rank test

[b] For t_{max}, this represents the estimated treatment difference

Source: **Module 5 Section 5.3.1.2 Study BFS-AS-103 CSR Table 14.2.2.5**

Both in the absence of and in the presence of a charcoal blockade bioequivalence was only demonstrated for AUC0-t and AUC0-inf for formoterol fumarate, the 90% CIs for the ratios were all within the accepted range for bioequivalence (0.8, 1.25).

In the absence of and in the presence of a charcoal blockade, Cmax for formoterol fumarate was higher for BF Spiromax than for Symbicort Turbohaler. The 90% CIs for the ratios were not within the accepted range for bioequivalence. In the absence of a charcoal blockade 90% CIs were 1.13, 1,26, in the presence of a charcoal blockade they were 1.30, 1.46.

Confidence intervals generated for tmax demonstrated no statistically significant difference between the products in terms of time to reach peak formoterol fumarate concentration in plasma both in the absence and in the presence of a charcoal blockade.

The following tables summarise the primary/key pharmacokinetic findings in the one pivotal study with the low strength of this new orally inhaled fixed-dose combination product:

Across Study Comparison of BUD Bioequivalence - Low Strength

Study / Comparison	Parameter	Ratio[b]	90% CI		RMS Error			BE (yes/no)
			Lower	Upper	Overall	BFS	ST	
Study BFS-AS-103 BF Spiromax (80/4.5 µg) vs. Symbicort Turbohaler (100/6 µg	AUC_{0-t} (h·pg/mL)	90.0	85.3	95.0	0.214			Yes
	C_{max} (pg/mL)	91.6	84.5	99.4	0.327			Yes
	t_{max} (min)[a]	-0.38	-2.3	0.3	NA			
BF Spiromax (80/4.5 µg) + charcoal vs. Symbicort	AUC_{0-t} (h·pg/mL)	91.3	86.5	96.3	0.214			Yes
	C_{max} (pg/mL)	97.7	90.0	106.1	0.327			Yes

Turbohaler (100/6 µg) + charcoal	t_{max} (min)[a]	-2.6	-4.8	-1.1	NA			

a From Wilcoxon Signed Rank test
b For t_{max}, this represents the estimated treatment difference.

Across Study Comparison of FOR Bioequivalence - Low Strength

Study / Comparison	Parameter	Ratio[b]	90% Confidence Interval		RMS Error			BE (yes/no)
			Lower	Upper	Overall	BFS	ST	
Study BFS-AS-103 BF Spiromax (80/4.5 µg) vs. Symbicort Turbohaler (100/6 µg)	AUC_{0-t} (h·pg/mL)	102.8	97.3	108.6	0.222			Yes
	C_{max} (pg/mL)	119.3	112.6	126.3	0.23			No
	t_{max} (min)[a]	-0.04	-0.24	0.13	NA			
BF Spiromax (80/4.5 µg) + charcoal vs. Symbicort Turbohaler (100/6 µg) + charcoal	AUC_{0-t} (h·pg/mL)	110.7	104.8	117.0	0.222			Yes
	C_{max} (pg/mL)	137.6	129.9	145.7	0.23			No
	t_{max} (min)[a]	-0.34	-1.25	-0.03	NA			

a From Wilcoxon Signed Rank test
b For t_{max}, this represents the estimated treatment difference.

In the pivotal study, Study BFS-AS-103, BF Spiromax 80/4.5µg and Symbicort Turbohaler 100/6µg were shown to be bioequivalent in respect of budesonide pharmacokinetic parameters, when administered both with and without charcoal blockade.

For formoterol fumarate pharmacokinetic parameters in respect of AUC, bioequivalence was shown when BF Spiromax 80/4.5µg and Symbicort Turbohaler 100/6µg were administered both with and without charcoal blockade. However peak/maximum plasma concentration, Cmax, was slightly higher following administration of BF Spiromax compared with Symbicort turbohaler, both with and without charcoal blockade.

A general overview of the findings in the six bioequivalence studies is presented below:

PK Bioequivalence Summary for BF Spiromax versus Symicort Turbohaler (the three emboldened studies in this table are the three pivotal studies in the pharmacokinetic programme of studies)

Strength/Study	With Charcoal		Without Charcoal	
	AUC_{0-t}	C_{max}	AUC_{0-t}	C_{max}
High Strength (BF Spiromax 320/9µg compared with Symbicort Turbohaler 400/12µg)				
BFS-BE-109 – pivotal study				
budesonide	**Yes**	**Yes**	**Yes**	**Yes**
formoterol	**Yes**	**Yes**	**Yes**	**Yes**
BFS-AS-105				
BUD	Yes	Yes	Yes	No
FOR	Yes	Yes	No	No
BFS-AS-107				
BUD			Yes	Yes
FOR			Yes	No
Middle Strength (BF Spiromax 160/4.5µg compared with Symbicort Turbohaler 200/6µg)				
BFS-BE-108 – pivotal study				
BUD	**Yes**	**Yes**	**Yes**	**Yes**
FOR	**Yes**	**Yes**	**Yes**	**Yes**
BFS-AS-104[a]				
BUD	No	No	No	No
FOR	No	No	No	No
Low Strength (BF Spiromax 80/4.5µg compared with Symbicort Turbohaler 100/6µg)				
BFS-AS-103 – pivotal study				
BUD	**Yes**	**Yes**	**Yes**	**Yes**
FOR	**Yes**	**No***	**Yes**	**No***

[a] this study did not use the final formulation of the Middle Strength product

* PK bioequivalence for formoterol fumarate can be claimed by use of the new formoterol fumarate drug substance and bioequivalence results from the Middle and High Strength products

Pharmacokinetic bioequivalence for budesonide, with and without charcoal blockade was observed for all strengths with the exception of two of the supportive studies:

- the high strength supportive study (study BFS-AS-105) (n=88) – initial pharmacokinetic bioequivalence study – this was considered by the Applicant to be a *spurious result* and out-of-line with other pharmacokinetic studies presented

and

- the middle strength supportive study (study BFS-AS-104) (n=90) – fourth pharmacokinetic bioequivalence study – the findings in this study resulted in a

change in the micronisation process for formoterol fumarate and a change in the grade of lactose, with subsequent modification of both the high strength and the middle strength products by inclusion of coarser formoterol fumarate particles (see study BFS-BE-110).

Data from food-interaction studies

No food effect studies have been submitted. This is acceptable since the clinical pharmacology of budesonide and formoterol fumarate has been investigated extensively in the past, is well known and has been the subject of many publications. The development of these new fixed-dose combination OIP aims to demonstrate therapeutic equivalence of this new products to appropriate reference products and the development is based on the demonstration of pharmacokinetic and/or pharmacodynamic equivalence between each strength of this fixed-dose combination, BF Spiromax and the corresponding strength of the reference product, Symbicort Turbohaler.

There are no known relevant interactions between either of these actives, budesonide and formoterol fumarate and food intake and no adverse effects of food on the rate and/or extent of absorption of either active.

Budesonide undergoes extensive first pass hepatic biotransformation, approximately 90%, to metabolites of low glucocorticoid activity (less that 1% of that of budesonide); formoterol fumarate is inactivated by conjugation.

Distribution

No studies have been submitted, which is acceptable since the clinical pharmacology of budesonide and formoterol fumarate has been investigated extensively in the past, is well known and has been the subject of many publications. The development of these new fixed-dose combination OIPs aims to demonstrate therapeutic equivalence of these new products to appropriate reference products and the development is based on the demonstration of pharmacokinetic and/or pharmacodynamic equivalence between each strength of this fixed-dose combination, BF Spiromax and the corresponding strength of the reference product, Symbicort Turbohaler.

Elimination

There is no discussion and no studies have been submitted. This is acceptable for the same reasons stated above for lack of distribution studies.

Dose proportionality and time dependencies

In vitro performance for formoterol fumarate is the same for the middle and low strength products and dose proportionality for formoterol fumarate between the middle and low strength products compared with the high strength has been established. The specifications of FPD and delivered dose of the middle and low strength products are in line with the high strength product.

However, there is a lack of an *in vitro*/*in vivo* correlation between the low strength product compared with the middle and the high strength products, due to differences in lactose grade and dosing cup size between the three strengths.

Section 2.4.4 ‘Discussion on clinical pharmacology’ contains further details on the Applicant’s justification for bridging the *in vivo* data generated from one strength to another lower

strength and on the modification of the micronisation process for the formoterol fumarate drug substance.

Special populations

No studies in special populations have been submitted, which is acceptable for the same reasons as for the lack of data on distribution and elimination. The adults recruited in the clinical programme presented (a total of nine pharmacokinetic studies and one pharmacodynamic study) were healthy volunteers. No clinical studies have been submitted in adults or adolescents with asthma or in patients with COPD.

The CHMP Guideline on orally inhaled products (CPMP/EWP/4151/00 Rev. 1) states that "*Unless justified otherwise, comparative in vitro data on flow rate dependence should be obtained with a range of flow rates. This range should be justified in relation to the intended patient population. The minimum (e.g. 10th percentile), median and maximum (e.g. 90th percentile) achievable flow rate in this patient population(s) should be investigated.*"

Taking the above into account, the Applicant submitted data on the inhalation characteristics of healthy adult volunteers (aged 18 to 45 years), adults (18 to 45 years), adolescents 12 to 17 years) and children (6 to 11 years) with asthma and adults over 50 years of age with COPD in order to bridge the findings in the clinical pharmacology studies in healthy volunteers to the target patient populations in whom this fixed-dose combination product will be used. This data aimed at showing the appropriateness of the pharmacokinetic findings obtained in healthy volunteers to support equivalence in patients with chronic obstructive pulmonary disease and in other populations with low inspiratory capacity, taking into account the differences in *in vitro* flow rates for all three strengths at low flow rates and differences in peak inspiratory flow rates between healthy volunteers and the different patient populations in whom this fixed-dose combination will be used. It was a study of peak inspiratory flow rates (PIFR) generated from the proposed Spiromax device and the Turbohaler device by various patient groups (pre- and post-enhanced device training). Four patient groups were included in the study as follows (n=50 in each of the four study groups listed):

1. Children and adolescents with asthma aged 6-17 years
2. Adults with asthma aged 18-45 years
3. Adults with COPD aged >50 years
4. Healthy volunteers aged 18-45 years

Overall results obtained from this study were presented as follows:

Peak Inspiratory Flow Rates (PIFR, L/min) Generated by Different Patient Groups Post-training Through (placebo) Spiromax and Turbohaler devices (10th, 50th and 90th Percentiles)

Study Group	Turbohaler			Spiromax		
	10th	50th	90th	10th	50th	90th
Paediatric Asthma (6-11 years; n=23)	50	67	88	58	80	98
Paediatric Asthma (12-17 years; n=27)	57	72	93	65	81	105
Adult Asthma (18-45 years; n=50)	54	82	94	66	88	104
COPD (50+ years; n=50)	38	60	84	45	68	93
Healthy volunteers (18-45 years; n=50)	77	92	102	83	104	105

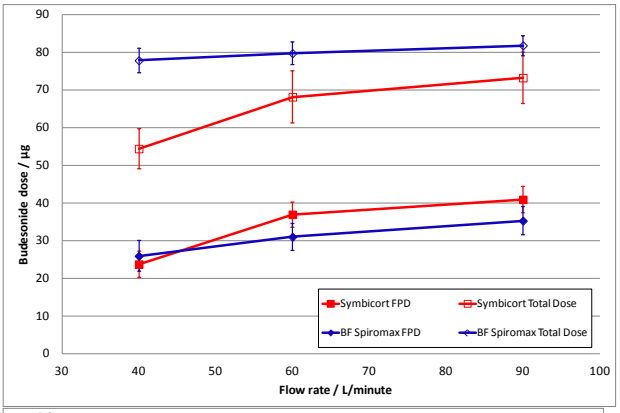
- Healthy volunteers and patients were able to generate a slightly higher inspiratory flow rate from the Spiromax device than from the Turbohaler device.
- In asthma, the 10th percentile was equal to or greater than 50L/min in children, adolescents and adults using both inhalation devices.
- In COPD, the 10th percentile was approx. 40L/min through both devices.
- The PIFR 90th percentile was between 84-105L/min for all patient groups (asthma and COPD).
- The PIFR 50th percentile was between 60-88L/min for all patient groups (asthma and COPD).
- Few subjects had a mean PIFR below 40L/min – with no clustering by age or asthma severity (as defined by the measurement of forced expiratory volume in one second (FEV_1) percent predicted
- There was little difference in PIFR between adolescents and adults with asthma with either device.
- With both devices there was a slight trend towards higher PIFR with increasing age in children with asthma and only one patient had a PIFR below 40 L/min, with no evidence of clustering at the lower ages.

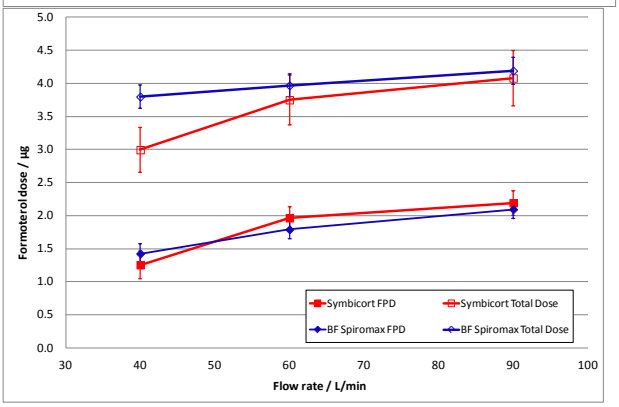
Aerodynamic particle size distribution (APSD) was evaluated over 40, 60 and 90 L/min for all three proposed strengths of the finished product.

API	Parameter	BF Spiromax			Symbicort		
		40 L/min	60 L/min	90 L/min	40 L/min	60 L/min	90 L/min
BUD	TD, % LC	94.78	97.08	99.94	70.73	85.52	93.94
	IP+PS, % LC	59.25	53.81	50.02	37.16	35.47	37.73
	FPD, % LC	31.07	38.39	44.21	29.19	45.23	51.47
	MMAD, µm	2.41	2.20	2.09	2.58	2.25	2.01
	GSD	1.86	1.94	1.98	1.78	1.83	1.95
FOR	TD, % LC	88.04	91.15	96.76	69.90	84.53	93.86
	IP+PS, % LC	57.27	51.85	49.29	37.43	35.38	38.61
	FPD, % LC	27.54	35.51	42.44	27.93	43.95	50.19
	MMAD, µm	2.39	2.18	2.11	2.63	2.30	2.08
	GSD	1.86	1.90	2.01	1.78	1.84	1.94

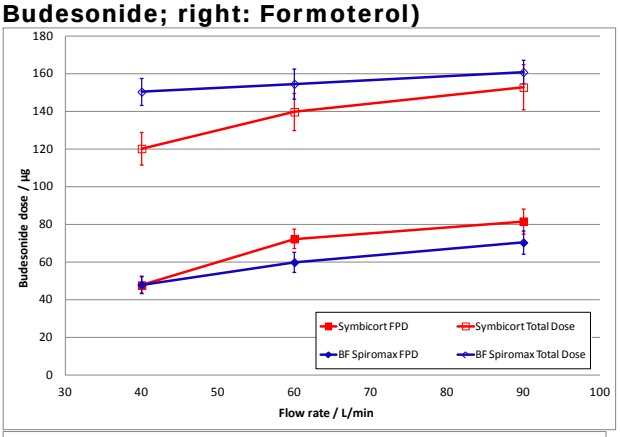
Flow rate dependency for all three proposed product strengths compared with the equivalent strength for the reference product at the aforementioned flow rates have been evaluated and graphically represented as follows:

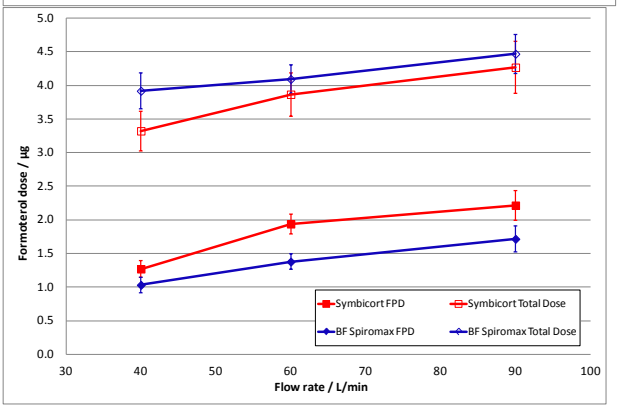
Low Strength Flow Rate Dependency of Total Dose (NGI) and FPD (left: Budesonide; right: Formoterol)



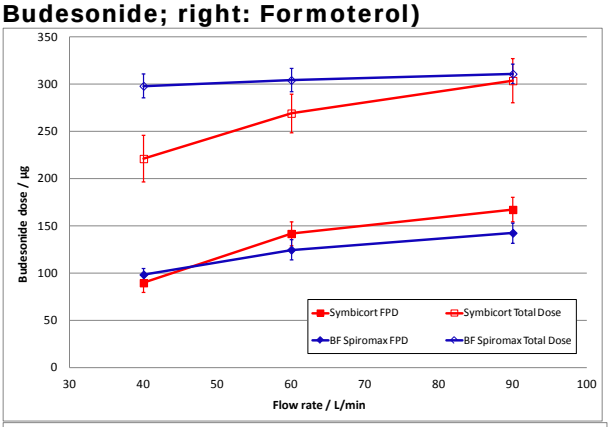


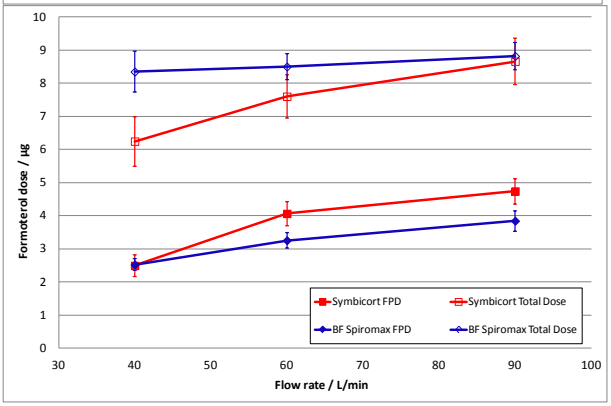
Middle Strength Flow Rate Dependency of Total Dose (NGI) and FPD (left: Budesonide; right: Formoterol)





High Strength Flow Rate Dependency of Total Dose (NGI) and FPD (left: Budesonide; right: Formoterol)





Pharmacokinetic interaction studies

No *in vitro*/*in vivo* studies have been submitted for the same reason as above. Interactions with other medicinal products are well known and well documented.

There are no known indications of any relevant metabolic interactions or any displacement reactions between either of these actives, budesonide and formoterol fumarate, neither *in vitro* nor *in vivo*.

Budesonide undergoes extensive first pass hepatic biotransformation, approximately 90%, to metabolites of low glucocorticoid activity (less that 1% of that of budesonide); formoterol fumarate is inactivated by conjugation.

2.4.3. Pharmacodynamics

Mechanism of action

Budesonide is an orally inhaled glucocorticosteroid with high local anti-inflammatory activity and a lower incidence of adverse effects than is seen with oral corticosteroids. Budesonide has been shown to decrease airways reactivity to histamine and methacholine in patients with hyperreactive airways. Inhaled budesonide is recommended for use in the management of patients with asthma.

Formoterol fumarate dihydrate is a selective long-acting β2 adrenergic agonist and exerts a preferential effect on β2 adrenergic receptors on bronchial smooth muscle to produce relaxation and bronchodilatation. Formoterol is used via the orally inhaled route in the management of patients with reversible airways obstruction. Formoterol produces bronchodilation within 1-3 minutes following inhalation, which lasts for 12 hours following a single dose. Formoterol is particularly useful in patients with reversible airways obstruction who continue to experience symptoms despite treatment with an anti-inflammatory agent such as an inhaled corticosteroid. Guidelines for the management of reversible airways obstruction and particularly asthma recommend the addition of a long-acting β2 agonist to the treatment regimen in these patients and studies have shown that the addition of a long-acting β2 agonist provides better control of asthma than increasing the dose of inhaled corticosteroid.

The mechanisms of action of the two drugs, budesonide and formoterol fumarate dihydrate are different but complementary. Budesonide and formoterol fumarate demonstrate additive effects.

Primary and Secondary pharmacology

The CHMP Guideline on orally inhaled products (CHMP/EWP/4151/00 Rev. 1) describes the development of an OIP for use in the management of asthma and COPD, including the development of a new OIP where demonstration of therapeutic equivalence to a well-known and established reference product is required, as a cascade of development from *in vitro* characterisation through pharmacokinetic studies to pharmacodynamic and/or clinical studies, as required.

As small differences were detected in Cmax for formoterol fumarate between the low strengths of BF Spiromax and Symbicort Turbohaler, the low strength was included in a single pharmacodynamic study (study BFS-AS-106) conducted to evaluate whether the pharmacokinetic differences seen in Cmax were associated with greater extrapulmonary effects of formoterol fumarate from BF Spiromax when compared with Symbicort Turbohaler.

Study BFS-AS-106: A randomised, double-blind, double-dummy, cumulative dose, four-period crossover study to evaluate the pharmacodynamic effects of Budesonide/Formoterol Spiromax Inhalation Powder and Symbicort Turbohaler administered in healthy volunteers (n=56 randomised)

This was a phase I single centre, cumulative dose study carried out in the UK.

- Primary Objective: The primary objective was to compare the pharmacodynamic (extrapulmonary) effects of BF Spiromax and Symbicort Turbohaler following cumulative delivered doses of 36µg and 72µg of formoterol administered as 1+1+2+4 inhalations of budesonide/formoterol fumarate 80/4.5µg (delivered dose) per inhalation and 1+1+2+4 inhalations of budesonide/formoterol fumarate 320/9µg (delivered dose) per inhalation, in healthy volunteers aged 18 to 45 years.

- Secondary Objective: The secondary objective was to evaluate the safety of BF Spiromax and Symbicort Turbohaler following cumulative delivered doses of formoterol fumarate of 36µg and 72µg.

All subjects had to complete a training period over two consecutive days, prior to entering the treatment phase of the study. The study assessed when they learnt how to use the BF Spiromax and Symbicort Turbohaler devices, as well as the tolerability to the two drug substances, budesonide and formoterol fumarate.

A 5- to 8-day wash-out period followed training prior to the commencement of the treatment phase and each of the four treatment days was separated from the next by a similar 5- 8-day wash-out. There were six clinic visits, including the screening and training days/visits and the total study duration for each subject was between 6 and 8 weeks.

The study saw recruitment of male and female healthy volunteers, aged 18 to 45 years, inclusive and in good general health.

Criteria for evaluation:

- Primary pharmacodynamic endpoint: Change from baseline in corrected QT interval using the Fridericia correction formula (QTcF) (msec) at 5 minutes after each of the four cumulative doses.

- Secondary pharmacodynamic endpoints:

- Change from baseline in QTcF interval (msec) at 15 minutes after each of the four cumulative doses.
- Change from baseline in corrected QT interval using the Bazzett correction formula (QTcB) (msec) at 5 minutes after each of the four cumulative doses.
- Change from baseline in QTcB interval (msec) at 15 minutes after each of the four cumulative doses.
- Baseline corrected QTcF AUC0-4hr following the administration of the last cumulative dose.
- Baseline corrected QTcB AUC0-4hr following the administration of the last cumulativedose.

- Change from baseline in the following additional parameters at 5 and 15 minutes after each of the four cumulative doses, as well as over 4 hours following the last cumulative dose:
    - Heart rate (HR) taken from vital signs
    - Systolic blood pressure (SBP)
    - Diastolic blood pressure (DBP)
    - Potassium
    - Glucose
    - HR taken from the ECG
    - QT interval (uncorrected)

- Safety and tolerability endpoints:

- The frequency of treatment-emergent adverse events (TEAEs) during and between on-site treatment-evaluation visits;
- The nature, incidence, severity and causality of spontaneously reported and elicited adverse events;
- Comparison of pre- and post-study vital signs (blood pressure and HR);
- Comparison of pre- and post-study safety laboratory assessments (i.e., routine clinical laboratory parameters);
- Comparison of pre- and post-study ECGs;
- Comparison of pre- and post-study physical examinations.

- Other study endpoints: Inspiratory flow rate

Study treatments

Treatment A: BF Spiromax 80/4.5µg and placebo Symbicort Turbohaler

Treatment B: Symbicort Turbohaler 100/6µg and placebo BF Spiromax

Treatment C: BF Spiromax 320/9µg and placebo Symbicort Turbohaler

Treatment D: Symbicort Turbohaler 400/12µg and placebo BF Spiromax

Dose of test and reference study treatments:

Test:

- BF Spiromax 80/4.5µg (budesonide 80µg and formoterol fumarate dihydrate 4.5µg inhalation powder per delivered dose); cumulative delivered dose of 36µg of formoterol administered as 1+1+2+4 inhalations with 29, 28, and 26 minutes between each set following the first inhalation set;

- BF Spiromax 320/9µg (budesonide 320µg and formoterol fumarate dihydrate 9µg inhalation

powder per delivered dose); cumulative delivered dose of 72µg of formoterol fumarate administered as 1+1+2+4 inhalations with 29, 28, and 26 minutes between each set following the first inhalation set

Reference:

- Symbicort Turbohaler 100/6µg (budesonide 100µg and formoterol fumarate dihydrate 6µg

inhalation powder per metered dose); cumulative metered dose of 48µg of formoterol fumarate administered as 1+1+2+4 inhalations with 29, 28, and 26 minutes between each set following the first inhalation set;

- Symbicort Turbohaler 400/12µg (budesonide 400µg and formoterol fumarate dihydrate 12µg inhalation powder per metered dose); cumulative metered dose of 96µg of formoterol administered as 1+1+2+4 inhalations with 29, 28, and 26 minutes between each set following the first inhalation set

Number of subjects:

Planned: Randomise 56 (14 per sequence) to ensure 52 (13 per sequence) evaluable

Analysed: Screened 124, randomised: 56, completed 52

All 56 subjects were included in the safety, ITT and PP analyses.

Treatment phase:

The randomly assigned treatment was administered by cumulative dosing of 1+1+2+4 inhalations from each device on each of the four study treatment days and on each study day serial pharmacodynamic assessments (ECG, vital signs, glucose and potassium) were measured prior to and following dosing which was then followed by a 5- to 8-day washout period between treatments.

Statistical methods:

The primary pharmacodynamic analysis was based upon a comparison of BF Spiromax and Symbicort Turbohaler with respect to the primary pharmacodynamic endpoint. The following treatments were compared:

Low strength: Treatment A (BF Spiromax 80/4.5µg) versus Treatment B (Symbicort Turbohaler 100/6µg)

High strength: Treatment C (BF Spiromax 320/9µg) versus Treatment D (Symbicort Turbohaler 400/12µg)

The following null and alternative hypotheses were used:

H_0: |µSpiromax - µSymbicort| >10msec, for at least one of the cumulative doses at either the low or high strength

versus

H_1: |Spiromax - _Symbicort| ≤10msec, for all cumulative doses at both the low and high strengths

where µSpiromax and µSymbicort represent the mean change from baseline in QTcF interval at 5 minutes after a given cumulative dose at a given strength.

The alternative hypothesis that the absolute difference in means is less than 10msec was concluded only if each of the individual null hypotheses was rejected. Each of the individual hypotheses was tested by rejecting the null hypothesis if the 90% CI for the difference in device means was contained within the equivalence bounds ±10msec controlling alpha at 0.05 for each test.

Therefore BF Spiromax and Symbicort Turbohaler were declared equivalent for each strength if the 90% CIs for the difference in treatment means for the change from baseline in QTcF interval at 5 minutes after each cumulative dose were all within the limits ±10msec.

The primary analysis for the hypotheses described above was conducted using a mixed-effect ANCOVA model with baseline (pre-dose) QTcF interval as covariate, fixed effects of sequence, period, treatment (i.e., device), cumulative dose within treatment and random effects for subject within sequence and period by subject within sequence.

The secondary pharmacodynamic endpoints were analysed using the same method as the one described above for the primary pharmacodynamic endpoint.

Safety

Each adverse event was classified using Medical Dictionary for Regulatory Activities (MedDRA). The overall incidence of adverse events, as well the incidence of TEAEs, serious adverse events (SAEs), drug-related adverse events and adverse events leading to withdrawal, were summarised by treatment group, body system and preferred MedDRA term. Prior and concomitant medication were coded according to the World Health Organisation-Drug Dictionary (WHO-DD) and the Anatomical Therapeutic Chemical (ATC) classification system. Changes in the physical examinations, clinical laboratory findings, ECGs, and vital signs (blood pressure and HR from pre- to post-study were also summarised.

Other (Inspiratory flow rate):

A listing of inspiratory flow rate was provided by subject and study time point and includes changes from baseline. Absolute values as well as changes from baseline were also summarised descriptively.

Findings:

Low Strength Comparison

The differences in mean change from baseline in QTcF, QTcB, and the uncorrected QT intervals were comparable between the two low strength products following each dosing administration for both the 5 and 15 minute post-dose assessments (see table below).

The 90% CIs for the difference in mean change from baseline in QTcB, QTcF and uncorrected QT intervals for the BF Spiromax 80/4µg compared with Symbicort Turbohaler 100/6µg at 5 minutes and 15 minutes after each of the four cumulative doses are contained within the pre-specified equivalence bounds ±10msec. In most instances, the 90% CI for the comparisons between these two low strength products included the value of zero indicating that differences were not statistically significant.

The 90% CIs for the difference in maximum change from baseline after the last cumulative dose and standardized area under the curve between 0 and 4 hours (AUC_{0-4}) for QTcB, QTcF

and uncorrected QT intervals for BF Spiromax 80/4.5µg and Symbicort Turbohaler 100/6µg, are also contained within the equivalence bounds ±10msec.

For the secondary pharmacodynamic variables, HR (measured both from vital signs and ECG), SBP, DBP, blood glucose and serum potassium, all observed differences were small and in the opinion of the Applicant, not clinically meaningful. In most instances, the 90% CI for the comparisons between the test and reference products included the value of zero and were not statistically significant.

Comparison of QT Intervals After the Low Doses in Study BFS-AS-106 (PP population)

Comparison	Parameter	Dose	Treatment difference[a]	90% Confidence Interval		Equivalent ±10 msec (yes/no)
				Lower	Upper	
BF Spiromax (80/4.5 mcg) vs. Symbicort Turbohaler (100/6 mcg) (PP=56)	QTcF 5 mins (msec)	1	2.031	-1.112	5.175	Yes
		2	0.711	-2.392	3.814	Yes
		3	0.265	-2.838	3.367	Yes
		4	-0.631	-3.747	2.484	Yes
	QTcF 15 mins (msec)	1	-1.298	-4.352	1.756	Yes
		2	1.002	-2.065	4.069	Yes
		3	3.034	-0.020	6.087	Yes
		4	3.355	0.301	6.408	Yes
	Maximum change in QTcF		2.951	0.049	5.853	Yes
	QTcF AUC_{0-4}		2.101	-0.257	4.459	Yes
	QTcB 5 mins (msec)	1	3.235	-0.839	7.309	Yes
		2	1.872	-2.149	5.894	Yes
		3	0.690	-3.332	4.712	Yes
		4	1.145	-2.894	5.183	Yes
	QTcB 15 mins (msec)	1	-1.555	-5.551	2.442	Yes
		2	1.670	-2.344	5.684	Yes
		3	4.141	0.144	8.137	Yes
		4	5.152	1.156	9.149	Yes
	Maximum change in QTcB		3.666	-0.366	7.699	Yes
	QTcB AUC_{0-4}		3.212	0.375	6.049	Yes
	Uncorrected QT 5mins (msec)	1	0.156	-3.442	3.754	Yes
		2	-0.959	-4.512	2.595	Yes
		3	0.327	-3.227	3.880	Yes
		4	-3.167	-6.735	0.401	Yes
	Uncorrected QT 15 mins (msec)	1	0.286	-3.343	3.916	Yes
		2	0.922	-2.723	4.567	Yes
		3	2.034	-1.595	5.663	Yes
		4	1.113	-2.517	4.742	Yes
	Maximum change in Uncorrected QT		0.809	-2.386	4.005	Yes
	Uncorrected QT AUC_{0-4}		0.247	-2.507	3.001	Yes

[a] From ANCOVA.

Source: **Module 5 Section 5.3.4.1 Study BFS-AS-106 CSR Table 14.2.2.14**

High Strength Comparison

The 90% CI for the difference in mean change from baseline in QTcB and QTcF intervals for the high strength treatments at 5 minutes and 15 minutes after each of the four cumulative doses are contained within the pre-specified equivalence bounds ±10msec (see table below). In most instances, the 90% CI for the comparisons between BF Spiromax 320/9µg and Symbicort Turbohaler 400/12µg included the value of zero indicating that differences were not statistically significant.

The 90% CIs for the difference in mean change from baseline in the uncorrected QT interval for the high strength treatments were (-12.788, -5.605) at 5 minutes after the last cumulative dose, (-10.928, -3.581) at 15 minutes after the third cumulative dose, and (-12.262, -4.920) at 15 minutes after the last cumulative dose. All other 90% CIs at 5 minutes and 15 minutes were contained within the equivalence bounds ±10msec.

The 90% CIs for the difference in maximum change from baseline after the last cumulative dose and standardised AUC_{0-4} for QTcB, QTcF and uncorrected QT intervals for BF Spiromax 320/9µg and Symbicort Turbohaler 400/12µg are contained within the equivalence bounds ±10msec.

For the secondary pharmacodynamic variable of HR the observed differences between the two high strength treatments at 5 minutes and 15 minutes after each of the four cumulative doses were small (approximately 3 beats per minute (bpm) or less) at the therapeutic doses of formoterol fumarate (i.e., a delivered dose of ≤18µg of formoterol) and in the opinion of the Applicant were not thought to be clinically meaningful. At supra-therapeutic doses of formoterol fumarate (i.e., a delivered dose of ≥36µg of formoterol), the observed differences in heart rate, as well as in maximum change from baseline and standardized AUC_{0-4}, were again small (approximately 6 bpm or less for heart rate from vital signs and approximately 4 bpm or less for heart rate from the ECG). The difference between treatments for heart rate from the ECG did not reach the clinically meaningful threshold of 5 bpm even at supra-therapeutic formoterol doses.

For the secondary pharmacodynamic variable of blood glucose the observed differences in glucose measurements between BF Spiromax 320/9µg and Symbicort Turbohaler 400/12µg were small (approximately 0.1 mmol/L or below) at therapeutic doses of formoterol fumararte (i.e., a delivered dose of formoterol of ≤18µg) and not clinically meaningful. At therapeutic doses, the 90% CI for the comparisons between BF Spiromax 320/9µg and Symbicort Turbohaler 400/12µg included zero and the differences were not statistically significant. While greater effects with BF Spiromax 320/9µg were observed at supra-therapeutic doses of formoterol (i.e., a delivered dose of formoterol of ≥36µg), the observed differences in glucose measurements, as well as in the maximum change from baseline and standardised AUC_{0-4}, did not exceed approximately 0.3-0.4 mmol/L.

For the secondary pharmacodynamic variables, SBP and DBP (and in most instances, the 90% CI for the comparisons between the test and reference products included zero and were not statistically significant) and serum potassium, all observed differences were small and in the opinion of the Applicant, not clinically meaningful.

Comparison of QT Intervals After the High Doses in Study BFS-AS-106 (PP population)

Comparison	Parameter	Dose	Treatment difference[a]	90% Confidence Interval		Equivalent ±10 msec (yes/no)
				Lower	Upper	
BF Spiromax (320/9 mcg) vs. Symbicort Turbohaler (400/12 mcg) (PP=56)	QTcF 5 mins	1	-0.342	-3.470	2.785	Yes
		2	0.285	-2.843	3.414	Yes
		3	-2.022	-5.178	1.134	Yes
		4	-3.448	-6.603	-0.293	Yes
	QTcF 15 mins	1	1.325	-1.754	4.403	Yes
		2	1.032	-2.048	4.111	Yes
		3	-2.171	-5.278	0.936	Yes
		4	-3.500	-6.606	-0.394	Yes
	Maximum change in QTcF		-1.180	-4.146	1.786	Yes
	QTcF AUC_{0-4}		-1.275	-3.688	1.139	Yes
	QTcB 5 mins	1	0.845	-3.208	4.897	Yes
		2	2.777	-1.278	6.832	Yes
		3	0.431	-3.659	4.520	Yes
		4	-0.014	-4.102	4.074	Yes
	QTcB 15 mins	1	1.985	-2.040	6.012	Yes
		2	4.168	0.138	8.197	Yes
		3	0.506	-3.560	4.571	Yes
		4	-0.899	-4.963	3.164	Yes
	Maximum change in QTcB		2.016	-2.103	6.135	Yes
	QTcB AUC_{0-4}		2.109	-0.796	5.014	Yes
	Uncorrected QT 5 mins	1	-2.567	-6.128	0.994	Yes
		2	-4.150	-7.712	-0.589	Yes
		3	-6.198	-9.792	-2.605	Yes
		4	-9.196	-12.788	-5.605	No
	Uncorrected QT 15 mins	1	-0.264	-3.835	3.394	Yes
		2	-5.453	-9.093	-1.814	Yes
		3	-7.255	-10.928	-3.581	No
		4	-8.591	-12.262	-4.920	No
	Maximum change in Uncorrected QT		-5.011	-8.241	-1.781	Yes
	Uncorrected QT AUC_{0-4}		-6.795	-9.574	-4.016	Yes

[a] From ANCOVA

Source: **Module 5 Section 5.3.4.1 Study BFS-AS-106 CSR Table 14.2.2.14**

According to the Applicant, based on the results of this pharmacodynamic study, low strength BF Spiromax and Symbicort Turbohaler showed to be equivalent as defined in the protocol. Therefore the small pharmacokinetic differences in Cmax for formoterol fumarate observed in the pivotal pharmacokinetic study (study BFS-AS-103) were not associated with clinically meaningful pharmacodynamic differences.

A higher formoterol Cmax was observed with all three strengths for BF Spiromax (low, middle and high) compared with Symbicort Turbohaler. As explained in section 2.4.2 'Pharmacodynamics', subsequent further *in vitro* evaluation of BF Spiromax aiming at

achieving pharmacokinetic bioequivalence for formoterol fumarate C_{max} suggested that a change in the micronisation process for the formoterol fumarate drug substance, such that a larger particle would be produced, might help achieve bioequivalence for all formoterol fumarate comparisons. This hypothesis was tested and validated in the pilot pharmacokinetic study carried out with the middle strengths of BF Spiromax and Symbicort Turbohaler (see study BFS-BE-110).

2.4.4. Discussion on clinical pharmacology

The clinical pharmacology of budesonide and formoterol fumarate has been investigated extensively in the past, is well known and has been the subject of many publications. The development of these new fixed-dose combination OIPs aims to demonstrate therapeutic equivalence of these new products to appropriate reference products and the development is based on the demonstration of pharmacokinetic and/or pharmacodynamic equivalence between each strength of this fixed-dose combination, BF Spiromax and the corresponding strength of the reference product, Symbicort Turbohaler.

The Applicant initially requested indications for use in adults and adolescents with asthma and in adults with COPD. The clinical dossier comprises nine pharmacokinetic studies and one pharmacodynamic study, all carried out in male and female healthy volunteers, aged between 18 and 45 years and one pharmacodynamic study in children with asthma, aged 6 to 11 years.

The study design with recruitment of healthy adult male and female volunteers, the sampling schedules, pharmacokinetic endpoints and analyses for comparison of all pharmacokinetic profiles are acceptable for studies of this type.

The CHMP Guideline on orally inhaled products (CPMP/EWP/4151/00 Rev. 1) does state that pharmacokinetic studies should be carried out in the intended patient population. However, it is considered that healthy adult volunteers without the bronchoconstriction of asthma and who are less variable are more discriminative than patients with asthma, as bronchoconstriction of the airways in the patient with asthma may result in greater central pulmonary deposition and two inhaled products then appearing to be more similar that they actually are. Furthermore although the expiratory capacity in patients with asthma is compromised, the inspiratory capacity is much less so and generally similar to that of healthy volunteers. Therefore, the CHMP concluded that the recruitment of healthy volunteers in the bioequivalence studies described is acceptable.

The Applicant submitted additional data on the inhalation characteristics of healthy adult volunteers, adults, adolescents and children with asthma and adults over 50 years of age with COPD in order to bridge the findings in the clinical pharmacology studies in healthy volunteers to the target patient populations in whom this fixed-dose combination product will be used. Although the elderly were not studied *per se*, the inhalation characteristics in patients with COPD and over 50 years of age were and this is acceptable in the lack of a specific study of the elderly over 65 years of age.

The CHMP concluded the following:

- Regarding the use in COPD, it would appear that regardless of age and underlying disease severity, children, adolescents and adults with asthma, as well as patients with COPD can achieve inspiratory flow rates through both the Spiromax device and Turbohaler device.

- While flow through both devices was lower in patients with asthma or COPD relative to healthy volunteers, the mean PIFR achieved by asthma and COPD patients was over 60 L/min, flow rates at which the Spiromax device and the Turbohaler device are known to deliver comparable amounts of drug to the lungs (pharmacokinetic studies with the high strength and middle strength products, Study BFS-BE-109 (pivotal study) and Study BFS-BE-108 (pivotal study), respectively) and at which optimal drug deposition in the lung is achieved with the Turbohaler device.
- Very few patients had PIFRs below 40 L/min. When PIFRs were less than 40 L/min there appeared to be no clustering by age or disease severity.

In the lack of appropriate clinical data in children, the requirement of Section 9 of the CHMP Guideline on orally inhaled products (CHMP/EWP/4151/00 Rev. 1) in respect of the interpolation from data generated in adults in the light of specific studies in children having been carried out, which states: "*For adolescents aged between 12 and 17 years, interpolation from data generated in studies in adults may be possible if specific studies have been carried out in children less than 12 years of age. If this is not possible a sufficient number of adolescents should be recruited to the adult studies such that the entire age range of intended use (12 years through to the elderly) has been studied. Stratification into a 12 to 17 years age group and 18 years and above is not necessarily required; however data generated (both efficacy and safety data) from the two age groups should be documented and analysed separately, if possible. If studies have not been carried out in children (less than 12 years of age) authorisation in adolescents may require the generation of clinical data in the adolescent as a specific sub-population…"* cannot be met. Therefore at this stage in the development of this fixed-dose combination product, as neither children nor adolescents have been studied appropriately in the development programme submitted with these applications, the CHMP recommended that the this product should not be authorised for use in adolescents at this time and that the lower limit of the age range for use of this fixed-dose combination should be 18 years. As the reference product, containing the same drug substances, is authorised for use in adolescents there is a sizeable risk, as there is with children 12 years of age and younger, that this new product will also be used "off-licence" in adolescents. In order to mitigate this risk, sections 4.1 and 4.2 of the Summary of Product Characteristics (SmPC) state that DuoResp Spiromax is indicated in adults 18 years and above only and in addition section 4.2 states that DuoResp Spiromax is not indicated for use in children, 12 years of age and younger or adolescents, 13 to 17 years of age. The package leaflet has been updated accordingly.

The CHMP recommended that further development of this new fixed-dose combination product in children and adolescents should be considered particularly in the light of this combination containing an inhaled corticosteroid. In addition, the CHMP recommended that demonstration of therapeutic equivalence in respect of both efficacy and safety and an appropriate benefit/risk balance in this age group should be demonstrated should the Applicant seek approval of the lower strength fixed-dose combination in the future.

Although the original middle strength study, Study BFS-AS-104, ultimately designated a supportive study, failed to demonstrate pharmacokinetic bioequivalence in any of the pharmacokinetic comparisons, the relative difference between BF Spiromax and Symbicort Turbohaler was disproportionally greater for formoterol fumarate Cmax and this was seen for all three strengths. This consistency was seen across strengths.

The Applicant claimed the low strength product (80/4.5µg) using the proposed modified micronisation process to the larger, coarser particle size, without conducting a further

pharmacokinetic study. The Applicant based this decision on the *in vitro* performance of the three strengths, extrapolation from the high and middle strength pivotal studies (studies BFS-BE-109 and BFS-BE-108, respectively), and the consistency seen across the three strengths in respect of the device, formulation and manufacturing process (except for the differences in lactose grade and dosing cup size between the three strengths).

In vitro performance for formoterol fumarate was the same for the middle and low strength products and dose proportionality for formoterol fumarate between the middle and low strength products compared with the high strength has been established. The specifications of FPD and delivered dose of middle and low strength products were in line with the high strength product.

However, there was a lack of an *in vitro*/*in vivo* correlation between the low strength product compared with the middle and the high strength products, due to differences in lactose grade and dosing cup size between the three strengths. The lack of a pharmacokinetic study with the low strength product is not considered acceptable by the CHMP.

The Applicant stated that the approach of bridging the *in vivo* data generated from one strength to another lower strength based only on the *in vitro* data was already accepted in the approval of a fixed-dose combination inhalation powder containing fluticasone propionate and salmeterol xinafoate (inhalation powder, pre-dispensed, 50/250 µg and 50/500 µg) and approved at national level. The approval of this product was based on the *in vivo* data generated from a pharmacokinetic study with charcoal blockade using the 50/500µg product and on the *in vitro* quality data in the absence of a pharmacokinetic study without charcoal blockade for the 50/500µg product (and without a pharmacokinetic study data for the 50/250µg strength product).

The CHMP considered that reference to another previously authorised product was not an acceptable justification for the Applicant's proposed approach to bridge *in vivo* data generated from one strength to another lower strength based only on the *in vitro* data.

The CHMP noted that the modification of the micronisation process for formoterol fumarate drug substance, such that a larger particle is produced, resulted in a lowering of the CIs not only for formoterol fumarate but also for budesonide and for the middle strength product, with the exception of Cmax without charcoal for formoterol fumarate. The CIs did not include unity. The pharmacokinetic data generated were consistently lower for BF Spiromax than for the reference product, Symbicort Turbohaler, particularly for budesonide.

The *in vitro* performance of the BF Spiromax batch was inferior to the Symbicort Turbohaler batch with regards to FPD. If batches of the two products which were more similar *in vitro* characteristics had been used, unity might have been included in the confidence intervals.

The CHMP therefore concluded that:

- The two pivotal pharmacokinetic studies in the high strength (320/9 µg per dose) and the middle strength (160/4.5 µg per dose), carried out with the proposed modified micronisation process to the larger, coarser particle size, demonstrated equivalence between BF Spiromax and Symbicort Turbohaler for all comparisons both with and without a charcoal blockade. The change in the micronisation process resulted in some slight lowering of $C_{max,}$ in the absence of charcoal blockade, for both formoterol fumarate (as required from earlier study results) and budesonide in BF Spiromax such that equivalence for all comparisons was shown.

- With regard to the low strength product, 80/4.5 µg per dose, the Applicant claimed this strength using the proposed modified micronisation process to the larger, coarser particle size, but without any further pharmacokinetic study. Instead the Applicant presents a pharmacodynamic systemic safety study to address the findings in the low strength pivotal pharmacokinetic study (Study BFS-AS-106). However, there is a lack of an *in vitro/in vivo* correlation between the low strength product compared with the middle and the high strength products, due to differences in lactose grade and dosing cup size between the three strengths. Therefore, the lack of a pharmacokinetic/pharmacodynamic study or other appropriate *in vivo* study with the low strength product (80/4.5 µg per dose) with the formulation micronised by an alternative micronisation process resulting in larger and coarser particles, which was proposed as the final formulation for this low strength, was not considered acceptable by the CHMP.

Given the lack of a pharmacokinetic study/other clinical study to conclusively demonstrate the equivalence of the low strength (80/4.5) of DuoResp Spiromax with the low strength of the reference product, the Applicant withdrew the lower strength of this fixed-dose combination.

As small differences were detected in Cmax for formoterol fumarate between the low strengths of BF Spiromax and Symbicort Turbohaler in the pharmacokinetic study (study BFS-AS-103), the low strength was included in a single pharmacodynamic study (BFS-AS-106) conducted to evaluate whether the pharmacokinetic differences seen in Cmax were associated with greater extrapulmonary effects of formoterol fumarate from BF Spiromax when compared with Symbicort Turbohaler. This progression through pharmacokinetics to a pharmacodynamic study(ies) is appropriate and in line with the CHMP Guideline on orally inhaled products (CHMP/EWP/4151/00 Rev. 1).

The study design, objectives and endpoints of Study BFS-AS-106 are acceptable and the findings correlate with the pharmacokinetic profile for formoterol fumarate seen in the pharmacokinetic studies presented in respect of the low strength (study BFS-AS-103). For the majority of the pharmacodynamic endpoints assessed in Study BFS-AS-106, greater changes were observed in the measured parameters at 5 minutes post-dose than at 15 minutes post-dose which fits with the rapid rise and fall seen in formoterol fumarate Cmax. This pattern of change occurred following successively higher doses up to the administration of the last cumulative dose, indicating that the changes in pharmacodynamic measures were driven by administration of the next higher dose rather than by carryover effects from the earlier, lower dose in the cumulative dosing.

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology of budesonide and formoterol fumarate has been investigated extensively in the past, is well known and has been the subject of many publications.

The study design with recruitment of healthy adult male and female volunteers, the sampling schedules, pharmacokinetic endpoints and analyses for comparison of all pharmacokinetic profiles are acceptable for studies of this type.

Although the elderly were not studied per se, the inhalation characteristics in patients with COPD and over 50 years of age were and this is acceptable in the lack of a specific study of the elderly over 65 years of age.

At this stage in the development of this fixed-dose combination product, as neither children nor adolescents have been studied appropriately in the development programme submitted with this application, the CHMP recommended that the this product should not be authorised for use in adolescents at this time and that the lower limit of the age range for use of these fixed-dose combinations should be 18 years. The applicant agreed to update the product information accordingly.

The CHMP recommended that further development of this new fixed-dose combination product in children and adolescents should be considered particularly in the light of this combination containing an inhaled corticosteroid. In addition, the CHMP recommended that demonstration of therapeutic equivalence in respect of both efficacy and safety and an appropriate benefit/risk balance in this age group should be demonstrated should the Applicant seek approval of the lower strength fixed-dose combination in the future.

The two pivotal pharmacokinetic studies in the high strength (320/9 µg per dose) and the middle strength (160/4.5 µg per dose), carried out with the proposed modified micronisation process to the larger, coarser particle size, demonstrated equivalence between BF Spiromax and Symbicort Turbohaler for all comparisons both with and without a charcoal blockade. The change in the micronisation process resulted in some slight lowering of Cmax, in the absence of charcoal blockade, for both formoterol fumarate (as required from earlier study results) and budesonide in BF Spiromax such that equivalence for all comparisons was shown.

The lack of an *in vitro*/*in vivo* correlation between the low strength product (80/4.5 µg per dose) compared with the middle and the high strength products, due to differences in lactose grade and dosing cup size between the three strengths is of concern. Therefore, the lack of a pharmacokinetic/pharmacodynamic study or other appropriate *in vivo* studies with the low strength product with the formulation micronised by an alternative micronisation process resulting in larger and coarser particles, which was proposed as the final formulation for this low strength, was not considered acceptable by the CHMP.

Given the lack of a pharmacokinetic study/other clinical study to conclusively demonstrate the equivalence of the low strength (80/4.5) of DuoResp Spiromax with the low strength of the reference product, the Applicant withdrew the lower strength of this fixed-dose combination and stated in writing that they will provide further data in support of the re-formulated low strength in due course.

2.5. Clinical efficacy

The development of DuoResp Spiromax is based on the demonstration of pharmacokinetic equivalence between each strength of this fixed-dose combination, BF Spiromax and the corresponding strength of the reference product, Symbicort Turbohaler. Nine pharmacokinetic studies and one pharmacodynamic study have been carried out in adults or adolescents.

The clinical efficacy of budesonide and formoterol fumarate dihydrate has been investigated extensively, is well known and has been the subject of many publications.

2.5.1. Discussion on clinical efficacy

The clinical development was performed in line with the CHMP Guideline on orally inhaled products (CHMP/EWP/4151/00 Rev. 1). The clinical development of BF Spiromax aims to

demonstrate therapeutic equivalence of this new product to the reference product authorised in a Member State or in the Community on the basis of a complete dossier. The development is based on the demonstration of pharmacokinetic equivalence between each strength of this fixed-dose combination, BF Spiromax4 and the corresponding strength of the reference product, Symbicort Turbohaler.

2.5.2. Conclusions on the clinical efficacy

The presence of clinical efficacy studies comparing the test and reference products in adults or adolescents is not required since the clinical efficacy of budesonide and formoterol fumarate dihydrate has been investigated extensively, is well known and has been the subject of many publications. Moreover, this is in line with the CHMP Guideline on orally inhaled products (CHMP/EWP/4151/00 Rev. 1) since equivalence has been demonstrated for the high strength (320/9 µg per dose) and the middle strength (160/4.5 µg per dose).

The two pivotal pharmacokinetic studies in the high strength (320/9 µg per dose) and the middle strength (160/4.5 µg per dose) demonstrated equivalence between BF Spiromax and Symbicort Turbohaler for all comparisons both with and without a charcoal blockade

However the pharmacokinetic studies and other clinical studies presented were not sufficient to conclusively demonstrate the equivalence of the low strength (80/4.5) of DuoResp Spiromax with the low strength of the reference product. Therefore, the Applicant withdrew the lower strength of this fixed-dose combination.

There is no conclusive data on the equivalence of DuoResp Spiromax with the reference product in children and adolescents and therefore there is a lack of demonstration of a positive benefit/risk balance in this population. Therefore, the applicant agreed to limit the use of DuoResp Spiromax to adults aged 18 and older.

The CHMP recommended that further development of this new fixed-dose combination product in children and adolescents should be considered should the Applicant seek approval of the lower strength fixed-dose combination. In addition, the CHMP recommended that demonstration of therapeutic equivalence in respect of both efficacy and safety and an appropriate benefit/risk balance in this age group should be demonstrated should the Applicant seek approval of the lower strength fixed-dose combination in the future.

2.6. Clinical safety

The clinical safety of budesonide and formoterol fumarate dihydrate has been investigated extensively, is well known and has been the subject of many publications.

The Applicant has assessed and presented the safety data generated in the clinical pharmacology studies presented in support of these applications. No Phase III safety studies in adults, including long-term safety studies, have been included in the submitted dossier.

Systemic effects of the inhaled corticosteroid, budesonide, have been assessed in children aged 6 to 11 years in study BFS-AS-305 (see below). Systemic effects of the long-acting β2 agonist, formoterol fumarate have been assessed in Study BFS-AS-106 (see section 2.4.3 ‘Pharmacodynamics’).

Patient exposure

Overall, 628 healthy adult volunteers and 77 children with persistent asthma received at least one dose of a study treatment in the clinical development programme presented for BF Spiromax.

In the single dose pharmacokinetic studies 268 subjects received the high strength product (320/9µg per actuation), 198 received the middle strength product (160/4.5µg per actuation) and 106 received the low strength product (80/4.5µg per actuation).

A total of 56 subjects received cumulative doses of high and low strength products in the pharmacodynamic study.

A total of 77 children aged 6 to 11 years received 2-weeks treatment with the low strength product in the Phase III safety study on this young age group.

Adverse events

The pharmacokinetic studies were all single dose crossover studies and provided very limited safety data. The nature and intensity of AEs for BF Spiromax was very similar to that for Symbicort Turbohaler. Headache was amongst the most common AEs in each of the pharnacokinetic studies.

Study BFS-AS-106 involved cumulative doses of 36µg and 72µg of formoterol fumarate administered as 1+1+2+4 inhalations from BF Spiromax 80/4.5µg per inhalation (delivered dose) and Symbicort Turbohaler 100/6µg per inhalation (metered dose) and 1+1+2+4 inhalations from BF Spiromax 320/9µg per inhalation (delivered dose) and Symbicort Turbohaler 400/12µg per inhalation (metered dose).

The AE profile in this study showed that nature and intensity of AEs for both strengths of BF Spiromax was similar to that of the corresponding strengths of Symbicort Turbohaler. Given the cumulative dose design of this study, it was expected that there would be pharmacologically predictable AEs (e.g., tremor, palpitations) with both BF Spiromax and Symbicort Turbohaler, especially at the highest cumulative administered doses. However pharmacologically predictable AEs occurred infrequently with both strengths of BF Spiromax and Symbicort Turbohaler. The most common pharmacologically predictable AEs were tremor of the hand and dizziness. These occurred at similar frequencies with BF Spiromax relative to Symbicort Turbohaler with the exception of tremor of the hand, which occurred slightly more frequently with BF Spiromax 80/4.5µg (4 subjects) than with Symbicort Turbohaler 100/6µg (1 subject) but at a similar incidence with BF Spiromax 320/9µg (6 subjects) and Symbicort Turbohaler 400/12µg (5 subjects). Of note, the pharmacologically predictable AEs with BF Spiromax 320/9µg and Symbicort Turbohaler 400/12µg were primarily reported following supra-therapeutic doses of formoterol (i.e., a delivered dose of formoterol of ≥ 36µg).

Study BFS-AS-305 was the only repeat dose study presented. Prepubescent children with asthma received BF Spiromax 80/4.5µg (delivered dose), Symbicort Turbohaler 100/6µg (metered dose) or placebo in a randomised, double blind study. Each treatment was administered as two inhalations in the morning and evening for 14 days.

The AE profile confirmed a similar safety profile for BF Spiromax 80/4.5µg and Symbicort Turbohaler 100/6µg with 8 (10.8%) subjects experiencing at least one AE on BF Spiromax compared with 6 subjects (8.0%) on Symbicort Turbohaler and 11 subjects (14.7%) on placebo. Cough was the most common treatment-emergent AE, reported for 1 subject (1.4%) after BF Spiromax, 2 subjects (2.7%) after Symbicort Turbohaler and 6 subjects (8.0%) after placebo. All other AEs were isolated occurrences in only one subject. None of

the treatment-emergent AEs reported during the study were considered treatment related. In addition there were no abnormal findings during the oropharyngeal examination at any visit in any treatment group.

Serious adverse event / deaths / other significant events

No deaths were reported. Two serious adverse events (SAEs) were reported in Study BFS-AS-305:

- One subject (Subject 0009) experienced gastroenteritis during BF Spiromax 80/4.5µg treatment; this SAE resolved after 2 days and was considered unrelated to study treatment.
- The second subject (Subject 0042) experienced an asthma exacerbation during placebo treatment. This SAE caused the subject to discontinue and was ongoing at the final visit.

One SAE was reported in Study BFS-BE-110:

- One subject (Subject 1012) had an SAE of cranial traumatism with loss of consciousness and amnesia following a motor accident. This resolved within 11 days and was considered unrelated to study treatment.

Safety in special populations

A Phase III single centre study in prepubescent children with persistent asthma, aged 6 to 11 years (study BFS-AS-305) was carried out to evaluate the systemic effects of BF Spiromax and Symbicort Turbohaler in this young age group (see details below). No safety studies have been presented in adolescents.

Study BFS-AS-305: A *double blind, double dummy, randomised, placebo- and active-controlled, three-way crossover study to evaluate the effect of Budesonide / Formoterol Spiromax 80 / 4.5µg Inhalation Powder and Symbicort Turbohaler 100 / 6µg on the short-term lower leg growth rate in prepubescent children with persistent asthma* (n=77 randomised)

This was a randomised, double-blind, placebo-controlled, two-week, crossover study to evaluate the short-term effect of the inhaled corticosteroid, budesonide on lower leg growth rate (LLGR) through knemometry and to evaluate the effects of budesonide on the hypothalamic pituitary adrenocortical (HPA) axis. BF Spiromax 80/4.5µg, Symbicort Turbohaler 100/6µg and placebo were administered in a dose of two inhalations twice daily.

- Primary Objective: To demonstrate non inferiority of BF Spiromax 80/4.5µg relative to Symbicort Turbohaler 100/6µg on short-term growth rate of the right lower leg as measured by knemometry in prepubescent children with persistent asthma.

- Secondary Objectives: Assess the safety and tolerability of BF Spiromax and Symbicort Turbohaler; assess 24-hour urinary cortisol excretion during treatment with BF Spiromax relative to Symbicort Turbohaler; assess short-term right LLGR and 24-hour urinary cortisol excretion with BF Spiromax relative to Symbicort Turbohaler.

Criteria for evaluation:

Primary efficacy endpoint:

- growth rate of the right lower leg as measured by knemometry after 2 weeks of study treatment.

Other endpoints:

- inspiratory flow rates measured at each visit
- morning and evening peak expiratory flow (PEF) over the 2-week treatment period
- *rescue-free* days over the 2-week treatment period

Safety:

- 24-hour urinary cortisol excretion at the end of each treatment period
- blood pressure and HR at the beginning and end of each treatment period
- physical examinations before and at the end of the study
- oropharyngeal examinations at all visits for evidence of oral candidiasis
- the incidence of AEs throughout the study

Study treatments:

Children were randomised to one of six treatment sequences containing the following treatment arms:

- Treatment A: BF Spiromax 80/4.5µg and placebo Symbicort Turbohaler – two inhalations of each in the morning and two inhalations of each in the evening (twice daily dosing)
- Treatment B: Symbicort Turbohaler 100/6µg and placebo BF Spiromax – two inhalations of each in the morning and two inhalations of each in the evening (twice daily dosing)
- Treatment C: Placebo BF Spiromax and placebo Symbicort Turbohaler – two inhalations of each in the morning and two inhalations of each in the evening (twice daily dosing)

Treatment Periods: The study treatment periods were preceded by a 14-day run-in period; each treatment period was 14 days duration with a 14-day washout between each treatment period.

Number of subjects:

Planned: approximately 78 (13 per sequence group) children were enrolled to ensure that a minimum of 72 (12 per sequence group) children completed all dosing periods and all critical assessments.

Randomised/safety population: 77 (100%)

ITT population: 76 (98.7%)

PP population (efficacy assessments): 75 (97.4%)

Urinary cortisol population: 19 (24.7%)

Modified urinary cortisol population: 73 (98.4%)

Completed all three treatment periods: 73 (98.4%)

Statistical methods:

Sample Size: A sample size of 72 (12 per sequence group) evaluable subjects was required to assure a power of 90% to detect a difference in growth rate of no more than 0.20 mm/week, which was considered to be the non-inferiority margin for the difference between BF Spiromax and Symbicort Turbohaler, with a within-subject standard deviation of 0.275 mm/week and a one-sided significance level of 2.5%. This assumed that the true mean difference between BF Spiromax and Symbicort Turbohaler in the short-term LLGR was 0.05 mm/week. Estimating a drop-out rate of about 5-10%, approximately 78 (13 per sequence group) prepubescent children with persistent asthma were to be enrolled in this study. Any subject who withdrew after randomisation was not replaced.

Primary endpoint – Systemic safety: The short-term LLGR as measured by knemometry of the right lower leg [mm/week] was compared between BF Spiromax and Symbicort Turbohaler via a 97.5% one-sided confidence interval derived for treatment difference from a crossover ANOVA model allowing for fixed effects due to treatment, sequence and period and a random effect of subject within sequence. A non-inferiority analysis was performed to demonstrate that BF Spiromax is not inferior to Symbicort Turbohaler in short-term LLGR. Non-inferiority was demonstrated if the lower limit of the 97.5% one-sided confidence interval for the treatment difference in the short-term LLGR (BF Spiromax minus Symbicort Turbohaler) was greater than -0.20 mm/week. The PP population was the primary population for this analysis and the ITT population was the secondary population.

Secondary endpoint – Systemic safety: The urinary cortisol (UC) population was the primary population for analyses of 24-hour urinary cortisol excretion and cortisol/creatinine ratio, the ITT Population was the secondary. However, the number of subjects who met the criteria for inclusion in the UC population was <25% (n=19) of the overall population, thus making it difficult to draw meaningful conclusions. As a result, a modified urine cortisol (MUC) population was defined in which the only individual values excluded were those associated with an inadequate collection (based on examination of both the urine volume and urine creatinine relative to published normal and laboratory standards) or for which there was an obvious mismatch between the urine volume and urine creatinine (e.g., very high urine volume with very low urine creatinine). All decisions for inclusion in the MUC population were made while the data were still blinded and without knowledge of the urine cortisol excretion results.

Other endpoints including inspiratory flow rates, morning and evening PEF and the percentage of *rescue-free* days were summarised by treatment group. Changes from period-specific baseline were also summarised by treatment group. Further details of the statistical models used in the analysis of these endpoints can be found in the main body of the clinical study report (CSR).

All the other safety assessments were conducted using the Safety Population.

Data were summarised by incidence, means, changes, and shifts depending on the measure. The statistical model for 24-hour urinary cortisol excretion and cortisol/creatinine ratio is detailed in the main body of the CSR.

Results

Systemic safety:

- **primary endpoint – growth rate of the right lower leg as measured by knemometry**

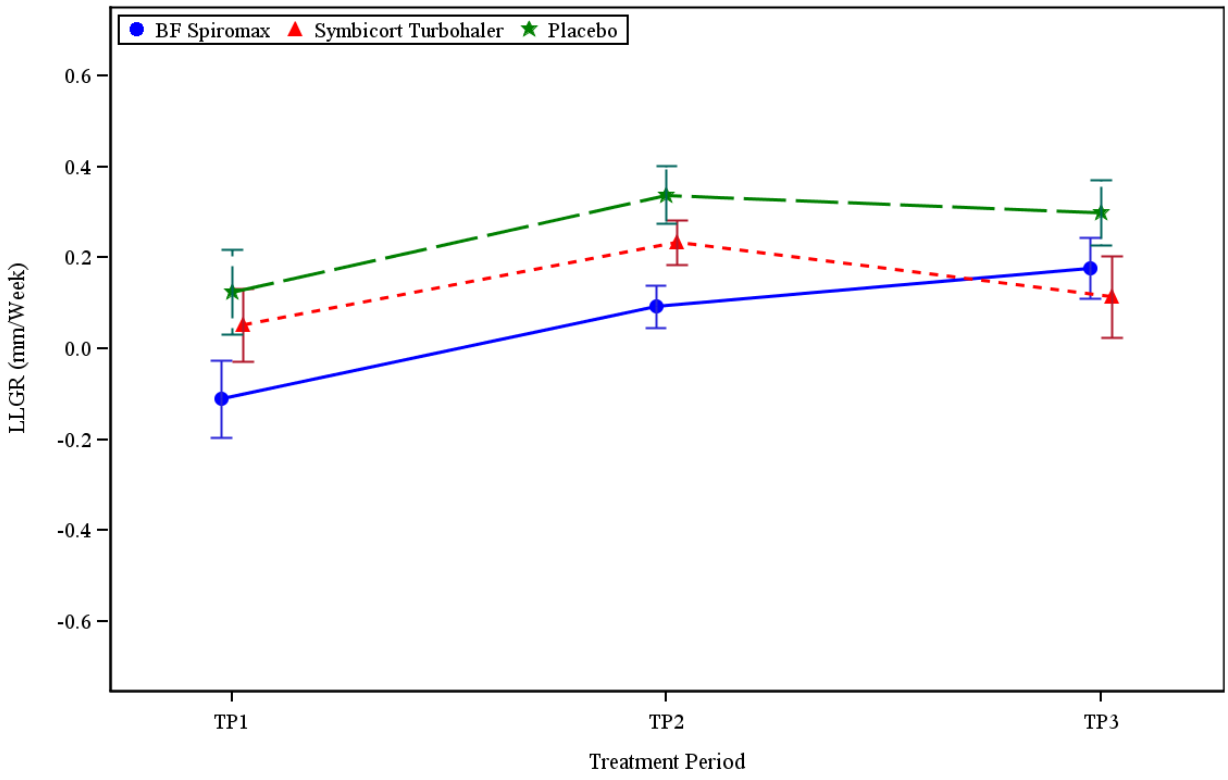
Analysis of Lower Leg Growth Rate by Knemometry (PP Population) in Study BFS-AS-305

Lower leg growth rate (mm/week)	LS mean	Treatment difference (95% CI)	
		BF Spiromax - Symbicort Turbohaler	Active - placebo
BF Spiromax	0.0484	-0.0858 (-0.2033, 0.0317)	-0.2042 (-0.3221, -0.0863)
Symbicort Turbohaler	0.1342		-0.1184 (-0.2362, -0.0006)
Placebo	0.2526		

Lower Leg Growth Rate by Knemometry in Each Period (PP Population) in Study BFS-AS-305

Mean (SD) Lower leg growth rate (mm/week)	Treatment period			
	1	2	3	All combined
BF Spiromax	-0.111 (0.4045)	0.092 (0.2327)	0.176 (0.3140)	0.052 (0.3396)
Symbicort Turbohaler	0.052 (0.3933)	0.234 (0.2388)	0.114 (0.4192)	0.134 (0.3605)
Placebo	0.124 (0.4671)	0.338 (0.2746)	0.299 (0.3632)	0.247 (0.3901)

Mean Plot of Lower Leg Growth Rate by Treatment Period (PP Population)



Non-inferiority was not demonstrated as the lower limits of the 95% confidence interval was just below the -0.2 mm/week non-inferiority margin. Similar results were shown with the ITT population where the LS mean treatment difference (BF Spiromax minus Symbicort Turbohaler) was -0.096 mm/week (95% CI: -0.211,0.018).

- **Secondary endpoint – 24-hour urinary cortisol excretion at the end of each treatment period**

Analysis of Cortisol and Cortisol/Creatinine Ratio (Modified UC Population)[1] in Study BFS-AS-305

Variable / Treatment	LS means	Geometric mean ratio (95% CI)	
		BF Spiromax/Symbicort Turbohaler	Active/placebo
Cortisol			
BF Spiromax	32.39	0.989 (0.818, 1.195)	0.859 (0.712, 1.036)
Symbicort Turbohaler	32.75		0.868 (0.720, 1.047)
Placebo	37.72		
Cortisol:Creatinine Ratio			
BF Spiromax	6.85	1.059 (0.848, 1.323)	0.978 (0.783, 1.221)
Symbicort Turbohaler	6.47		0.923 (0.740, 1.152)
Placebo	7.01		

[1] Subjects 0005 and 0028 in Treatment Period 3 were excluded due to cortisol values considered to be outliers (over 1000 nmol/L)

A urine cortisol population was defined but the number of subjects who met the criteria for inclusion was < 25% (n=19) of the overall study population and therefore conclusions from the data collected were difficult to draw. Prior to unblinding the study a modified urine cortisol (UC) population was defined in which the only individual values excluded were those associated with an inadequate collection or for which there was an obvious mismatch between the urine volume and urine creatinine.

There appeared to be no real differences in 24-hour urine cortisol excretion between BF Spiromax 80/4.5µg, Symbicort Turbohaler 100/6µg and placebo.

Efficacy

The assessment of efficacy is based on the other (secondary) endpoints, listed above.

Morning and Evening Peak Expiratory Flow

Analysis of Change from Period-specific Baseline in Morning and Evening Peak Expiratory Flow in Study BFS-AS-305 (PP population)

Variable / Treatment	LS mean change from period-specific baseline	Treatment difference (95% CI)	
		BF Spiromax – Symbicort Turbohaler	Active vs Placebo
AM PEF			
BF Spiromax	19.18 (2.11)	2.795 (-3.064, 8.655)	18.761 (12.882, 24.640)
Symbicort Turbohaler	16.38 (2.09)		15.966 (10.117, 21.814)
Placebo	0.42 (2.10)		
PM PEF			

BF Spiromax	16.64 (2.21)	0.419 (-5.644, 6.482)	15.441 (9.337, 21.544)
Symbicort Turbohaler	16.22 (2.20)		15.022 (8.945, 21.098)
Placebo	1.20 (2.22)		

The overall effects of BF Spiromax 80/4.5µg and Symbicort Turbohaler 100/6µg were similar, the ANCOVA showed no significant differences between BF Spiromax and Symbicort Turbohaler for morning or evening PEF. For the PP population the overall least squares (LS) mean treatment difference (BF Spiromax minus Symbicort Turbohaler) was 2.8 L/min; 95% CI (-3.1, 8.7); p=0.3470 for morning PEF and 0.4 L/min; 95% CI (-5.6, 6.5) p=0.8915 for evening PEF.

Following both BF Spiromax 80/4.5µg and Symbicort Turbohaler 100/6µg, statistically and clinically significant increases were seen in both morning and evening PEF compared with placebo. Both treatments resulted in improvements relative to placebo exceeding 15 L/min for both morning and evening PEF. It can be noted that15 L/min is a commonly used superiority margin in efficacy studies in asthma in children.

The overall LS mean treatment difference for BF Spiromax relative to placebo was 18.8 L/min; 95% CI (12.9, 24.6); p<0.0001 for morning PEF and 15.4 L/min; 95% CI (9.3, 21.5); p<0.0001 for evening PEF.

The overall LS mean treatment difference for Symbicort Turbohalerrelative to placebo was 16.0 L/min; 95% CI (10.1, 21.8); p<0.0001 for morning PEF and 15.0 L/min; 95% CI: (8.9, 21.1); p<0.0001 for evening PEF.

***Rescue-free* Days**

There were no significant differences among any of the treatment groups for the percentage of *rescue-free* days; baseline values ranged from 72-88% across the treatment groups leaving minimal room for any improvement.

Laboratory findings

Regarding study BFS-AS-106, heart rate rose by a maximum of approximately 10 bpm (after the third dose) in the lower strength for both products and systolic blood pressure by approximately 3 mm Hg. For the high strength comparison the maximum change in heart rate was 21.6 bpm for BF Spiromax at four hours and 14.0 for Symbicort at four hours. The maximum change from baseline in systolic blood pressure was 15.5 mm Hg for Spiromax and 11.9 mm Hg for Symbicort. Additionally, there were changes in serum potassium over time for the low and high strength as well as changes in blood glucose.

Safety related to drug-drug interactions and other interactions

No studies were performed on drug interactions with regard to safety.

Discontinuation due to adverse events

In Study BFS-AS-105**,** four subjects were withdrawn due to non-serious AEs:

- Subject 10003 was withdrawn on Day 1 of treatment period 4 (Symbicort Turbohaler 400/12 mcg + charcoal) due to an episode of moderate cataplexy which lasted for approximately 5 hours. The event was not considered related to study medication.

- Subject 10053 was withdrawn on Day 7 of treatment period 1 (Symbicort Turbohaler 400/12 mcg) due to a moderate tooth infection. The event was not considered related to study medication.

- Subject 10056 was withdrawn on Day 7 of treatment period 3 (BF Spiromax 320/9 mcg + charcoal) due to a moderate tooth infection. The event was not considered related to study medication.

- Subject 10087 was withdrawn on Day 8 of treatment period 3 (BF Spiromax 320/9 mcg + charcoal) due to moderate gastroenteritis. The event was not considered related to study medication.

In Study BFS-AS-107, Subject 17047 withdrew due to moderate gingival abscess after receiving BF Spiromax 320/9 mcg in treatment period 3. This event was considered unrelated to treatment.

In Study BFS-BE-109 Subject 2016 presented during the end of study visit, with a positive pregnancy test result. The pregnancy was reported according to protocol requirements.

In Study BFS-BE-110 Subject 1020 presented a mild cough during the wash-out period after period 2 (Symbicort Turbohaler 200/6 mcg) and was withdrawn from the study. This AE resolved spontaneously without any corrective treatment and was considered not related to study treatment.

In Study BFS-BE-108 Subject 3040 withdrew after the wash-out period after period 2 (Symbicort Turbohaler 200/6 mcg) due to mild gastroenteritis. This AE resolved spontaneously without any corrective treatment and was considered not related to study treatment.

Post-marketing experience

This new fixed-dose combination of budesonide and formoterol fumarate is not marketed in any country worldwide.

2.6.1. Discussion on clinical safety

The clinical safety of budesonide and formoterol fumarate dihydrate has been investigated extensively, is well known and has been the subject of many publications.

The lack of the submission of a full clinical safety programme is acceptable in this type of application and is in line with the CHMP Guideline on orally inhaled products (CHMP/EWP/4151/00 Rev. 1) since equivalence has been demonstrated for the high strength (320/9 µg per dose) and the middle strength (160/4.5 µg per dose).

The Applicant has assessed and presented the safety data generated in the clinical pharmacology studies presented in support of these applications. No Phase III safety studies in adults, including long-term safety studies, have been included in the submitted dossier.

The systemic safety of inhaled budesonide and inhaled formoterol fumarate on the short-term lower leg growth rate in prepubescent children with persistent asthma has been presented in study BFS-AS-305 (children aged 6 to 11 years) and in study BFS-AS-106 (healthy volunteers). Both of these studies were carried out with the original formulation of this fixed-dose combination, a formulation which will not progress to authorisation or the market. A new formulation was subsequently proposed with an alternative micronisation process resulting in larger and more course particles, which is proposed as the final formulation for all

three strengths of this new fixed-dose combination. Section 9 of the CHMP Guideline on orally inhaled products (CHMP/EWP/4151/00 Rev. 1) also addresses the requirements for authorisation of orally inhaled products in adolescents aged 13 to 17 years. In the light of these requirements, the systemic safety study (study BFS-AS-305) in children with asthma aged 6 to 11 years, has been included in these submissions not only to ensure that all clinical studies carried out with this new fixed-dose combination of budesonide and formoterol fumarate are presented but also to bridge between adults and children, primarily in respect of efficacy, in order that adolescents (aged 13 to 17 years) can be included in the indicated patients with asthma in whom this new FDC can be used.

Considering the findings in Study BFS-AS-305 described above and the use of the low strength product micronised to the original specifications, this study was not accepted by the CHMP as a 'bridging study' for authorisation of this new fixed-dose combination in adolescents. The study should have been designed to use the proposed final formulation for this low strength product, formulated with the modified micronisation process and appropriately designed and powered to assess therapeutic equivalence in respect of both efficacy and safety.

This study has used the low strength product, BF spiromax 80/4.5µg, micronised to the original specifications and a formulation not proposed for authorisation or the market.

Although both the test and the reference products were shown to be superior to placebo, the primary objective of the study was the assessment of the systemic effects of the inhaled corticosteroid component of this fixed-dose combination in children less than 12 years of age. The study was not designed to show equivalent efficacy in terms of pulmonary function (the efficacy assessments were secondary objectives).

In respect of efficacy the study did have assay sensitivity. However the study should have included other dose regimens in further treatment arms to enable differentiation between doses of budesonide and formoterol fumarate between the test and reference products and confirm equivalence of the test and the reference product or superiority of the test product over the reference product.

Furthermore, in respect of the primary systemic safety endpoint (growth rate of the right lower leg as measured by knemometry), there is some evidence to suggest that BF Spiromax suppresses lower leg growth rate by a greater amount than Symbicort Turbohaler, indicating a possible greater systemic effect.

In the light of the findings in this study and the use of the low strength product micronised to the original specifications, this study cannot be accepted as a 'bridging study' for authorisation of this new fixed-dose combination in adolescents (aged 13 to 18 years). The study should have used the proposed final formulation for this low strength product, formulated with the modified micronisation process and appropriately designed and powered to assess therapeutic equivalence in respect of both efficacy and safety.

The CHMP recommended that the further development of this new fixed-dose combination product in adolescents should be considered particularly in the light of this combination containing an inhaled corticosteroid.

In conclusion, adolescents (and children) have not been studied appropriately in the development programme submitted with this application. Therefore, the CHMP concluded that this product should not be authorised for use in adolescents at this time and that the lower limit of the age range for use of these fixed-dose combinations should be 18 years.

2.6.2. Conclusions on the clinical safety

The clinical safety of budesonide and formoterol fumarate dihydrate has been investigated extensively, is well known and has been the subject of many publications.

The presence of a full clinical safety programme is not considered necessary in this type of application and is in line with the CHMP Guideline on orally inhaled products (CHMP/EWP/4151/00 Rev. 1) since equivalence has been demonstrated for the high strength (320/9 µg per dose) and the middle strength (160/4.5 µg per dose). The high dose and the medium dose of DuoResp Spiromax have been shown to be equivalent to the reference product. Hence their unfavourable effects are expected to be similar to the well-known safety profile of the reference product (Symbicort Turbohaler) when used in line with the approved indications and posology of the reference product. As the low-dose formulation has not been conclusively shown to be equivalent to the reference product, there is uncertainty about its safety profile at the proposed dose and indications.

The CHMP aslo concluded that Study BFS-AS-305 cannot be accepted as a 'bridging study' for authorisation of this new fixed-dose combination in adolescents and recommended that the proposed final formulation for this low strength product, formulated with the modified micronisation process and appropriately designed and powered to assess therapeutic equivalence in respect of both efficacy and safety should be used by the applicant.

This was agreed by the Applicant and the indication in adolescents was withdrawn.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 1.3, the PRAC considered by consensus that the risk management system for Budesonide/Formoterol fumarate dihydrate (Duoresp Spiromax) in the treatment of asthma and COPD could be acceptable with minor revisions to be provided before the CHMP Opinion. This advice is based on the following content of the Risk Management Plan:

- **Safety concerns**

Table 1. Summary of safety concerns

IMPORTANT IDENTIFIED RISKS	• **Systemic glucocorticosteroid effects** • **Cardiac effects of long-acting adrenergic beta$_2$ receptor agonists (LABA)**

	• **Life-threatening and fatal asthma events with long-acting adrenergic beta$_2$ receptor agonists** • **Paradoxical bronchospasm** • **Hypokalaemia**
IMPORTANT POTENTIAL RISKS	• **Off label use in children and adolescents under 18 years** • **Potential for off-label use of Budesonide/Formoterol Spiromax® inhalation powder, 320/9.0 µg delivered dose corresponding to 400/12 µg metered dose, per actuation, in the "maintenance and reliever therapy regimen"** • **Drug interactions (with beta-adrenergic blockers and strong inhibitors of CYP3A4)**
MISSING INFORMATION	• **Use in pregnant or breast feeding women** • **Use in renal impairment** • **Use in hepatic impairment** • **Use in children and adolescents**

- **Pharmacovigilance plans**

The PRAC, having considered the data submitted, was of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

- **Risk minimisation measures**

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
IMPORTANT IDENTIFIED RISKS		
Systemic glucocorticosteroid effects	*Section 4.4, special warnings and precautions for use, SmPC:* Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur with inhalation treatment than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	aggression (particularly in children) (see section 4.8). It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be re-evaluated with the aim of reducing the dose of inhaled corticosteroid to the lowest dose at which effective control of asthma is maintained, if possible. The benefits of the corticosteroid therapy and the possible risks of growth suppression must be carefully weighed. In addition consideration should be given to referring the patient to a paediatric respiratory specialist. Limited data from long-term studies suggest that most children and adolescents treated with inhaled budesonide will ultimately achieve their adult target height. However, an initial small but transient reduction in growth (approximately 1 cm) has been observed. This generally occurs within the first year of treatment. Potential effects on bone density should be considered, particularly in patients on high doses for prolonged periods that have co-existing risk factors for osteoporosis. Long-term studies with inhaled budesonide in children at mean daily doses of 400 micrograms (metered dose) or in adults at daily doses of 800 micrograms (metered dose) have not shown any significant effects on bone mineral density. No information regarding the effect of a budesonide/formorterol fumarate dihydrate fixed-dose combination at higher doses is available If there is any reason to suppose that adrenal function is impaired from previous systemic steroid therapy, care should be taken when transferring patients to a budesonide/formoterol fumarate fixed dose combination therapy. The benefits of inhaled budesonide therapy would normally minimise the need for oral steroids, but patients transferring from oral steroids may remain at risk of impaired adrenal reserve for a considerable time. Recovery may take a considerable amount of time after cessation of oral steroid therapy and hence oral steroid-dependent patients transferred to inhaled budesonide may remain at risk from impaired adrenal	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	function for some considerable time. In such circumstances hypothalamic pituitary adrenocortical (HPA) axis function should be monitored regularly. Prolonged treatment with high doses of inhaled corticosteroids, particularly higher than recommended doses, may also result in clinically significant adrenal suppression. Therefore additional systemic corticosteroid cover should be considered during periods of stress such as severe infections or elective surgery. Rapid reduction in the dose of steroids can induce acute adrenal crisis. Symptoms and signs which might be seen in acute adrenal crisis may be somewhat vague but may include anorexia, abdominal pain, weight loss, tiredness, headache, nausea, vomiting, decreased level of consciousness, seizures, hypotension and hypoglycaemia. Treatment with supplementary systematic steroids or inhaled budesonide should not be stopped abruptly. During transfer from oral therapy toa budesonide/formoterol fumarate fixed dose combination therapy, a generally lower systemic steroid action will be experienced which may result in the appearance of allergic or arthritic symptoms such as rhinitis, eczema and muscle and joint pain. Specific treatment should be initiated for these conditions. A general insufficient glucocorticosteroid effect should be suspected if, in rare cases, symptoms such as tiredness, headache, nausea and vomiting should occur. In these cases a temporary increase in the dose of oral glucocorticosteroids is sometimes necessary. *Section 4.8, undesirable effects, SmPC:* Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for long periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include Cushing´s syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma. Increased susceptibility to infections and impairment of the ability to adapt to stress may also occur. Effects are probably dependent on dose, exposure time, concomitant and previous steroid exposure and individual sensitivity.	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Prescription-only medicine	
Cardiac effects of long-acting adrenergic beta$_2$ receptor agonists (LABA)	*Section 4.4, special warnings and precautions for use, SmPC:* A fixed-dose combination of budesonide and formoterol fumarate dihydrate should be administered with caution in patients with thyrotoxicosis, phaeochromocytoma, diabetes mellitus, untreated hypokalaemia, hypertrophic obstructive cardiomyopathy, idiopathic subvalvular aortic stenosis, severe hypertension, aneurysm or other severe cardiovascular disorders, such as ischaemic heart disease, tachyarrhythmias or severe heart failure. Caution should be observed when treating patients with prolongation of the QTc-interval. Formoterol itself may induce prolongation of the QTc-interval. Potentially serious hypokalaemia may result from high doses of beta$_2$-adrenoceptor agonists. Concomitant treatment of beta$_2$-adrenoceptor agonists with drugs which can induce hypokalaemia or potentiate a hypokalaemic effect, e.g. xanthine-derivatives, steroids and diuretics, may add to a possible hypokalaemic effect of the beta$_2$-adrenoceptor agonist. Particular caution is recommended in unstable asthma with variable use of rescue bronchodilators, in acute severe asthma as the associated risk may be augmented by hypoxia and in other conditions when the likelihood for hypokalaemia is increased. It is recommended that serum potassium levels are monitored during these circumstances. *Section 4.5, interactions with other medicinal products and other forms of interactions, SmPC:* Concomitant treatment with quinidine, disopyramide, procainamide, phenothiazines, antihistamines (terfenadine), monoamine oxidase inhibitors and tricyclic antidepressants can prolong the QTc-interval and increase the risk of ventricular arrhythmias. In addition L-Dopa, L-thyroxine, oxytocin and alcohol can impair cardiac tolerance towards beta$_2$-sympathomimetics. There is an elevated risk of arrhythmias in patients receiving concomitant anaesthesia with halogenated hydrocarbons.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Hypokalaemia may increase the disposition towards arrhythmias in patients who are treated with digitalis glycosides. Prescription-only medicine	
Life-threatening and fatal asthma events with long-acting adrenergic beta$_2$ receptor agonists	*Section 4.4, special warnings and precautions for use, SmPC:* If patients find the treatment ineffective, or exceed the highest recommended dose of Budesonide/Formoterol Spiromax®, medical attention must be sought (see section 4.2). Sudden and progressive deterioration in control of asthma or COPD is potentially life threatening and the patient should undergo urgent medical assessment. In this situation, consideration should be given to the need for increased therapy with corticosteroids, e.g. a course of oral corticosteroids, or antibiotic treatment if an infection is present. Patients should not be initiated on Budesonide/Formoterol Spiromax® during an exacerbation, or if they have significantly worsening or acutely deteriorating asthma. Serious asthma-related adverse events and exacerbations may occur during treatment with Budesonide/Formoterol Spiromax®. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation with Budesonide/Formoterol Spiromax®. Prescription-only medicine	None
Paradoxical bronchospasm	*Section 4.4, special warnings and precautions for use, SmPC:* Paradoxical bronchospasm may occur, with an immediate increase in wheezing and shortness of breath after dosing. If the patient experiences paradoxical bronchopasm Budesonide/Formoterol Spiromax® should be discontinued immediately, the patient should be assessed and an alternative therapy instituted, if necessary. Paradoxical bronchopasm responds to a rapid-acting inhaled bronchodilator and should be treated straightaway	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Section 4.8, undesirable effects, SmPC: 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 bronchopasm responds to a rapid-acting inhaled bronchodilator and shoud be treated straightaway. Budesonide/Formoterol Spiromax should be discontinued immediately, the patient should be assessed and an alternative therapy is instituted if necessary Prescription-only medicine	
Hypokalaemia	*Section 4.4, special warnings and precautions for use, SmPC:* A fixed-dose combination of budesonide and formoterol fumarate dihydrate should be administered with caution in patients with untreated hypokalaemia. Potentially serious hypokalaemia may result from high doses of beta2-adrenoceptor agonists. Concomitant treatment of beta2-adrenoceptor agonists with medicinal products which can induce hypokalaemia or potentiate a hypokalaemic effect, e.g. xanthine-derivatives, steroids and diuretics, may add to a possible hypokalaemic effect of the beta2-adrenoceptor agonist. Particular caution is recommended in unstable asthma with variable use of rescue bronchodilators, in acute severe asthma as the associated risk may be augmented by hypoxia and in other conditions when the likelihood for hypokalaemia is increased. It is recommended that serum potassium levels are monitored during these circumstances. *Section 4.5, Interaction with other medicinal products and other forms of*	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	interaction, SmPC: Hypokalaemia may increase the disposition towards arrhythmias in patients who are treated with digitalis glycosides. *Section 4.8, undesirable effects, SmPC:* Rare: Hypokalaemia Prescription-only medicine	
IMPORTANT POTENTIAL RISKS		
Off label use in children and adolescents under 18 years	Section 4.1, Therapeutic indications, SmPC Budesonide/Formoterol Spiromax is indicated in adults 18 years and above, only Not for use in children or adolescents under the age of 18 years of age. Section 4.2, Posology and method of administration, SmPC Paediatric population The safety and efficacy of DuoResp Spiromax in children, 12 years and younger and adolescents, 13 to 17 years of age has not yet been established. No data are available.Prescription-only medicine	Communication and Educational Program (CEP) directed to prescribing physicians, pharmacists, and patients that emphasizes the risk of Budesonide/Formoterol Spiromax use in children and adolescent
Potential for off-label use of Budesonide/Formoterol Spiromax® inhalation powder, 320/9.0 µg delivered dose corresponding to 400/12 µg metered dose, per actuation, in the “maintenance and reliever therapy regimen”	Section 4.2, Posology and method of administration, SmPC Budesonide/Formoterol Spiromax 320 micrograms/9.0 micrograms should be used as maintenance therapy only. The lower strengths of Budesonide/Formoterol Spiromax are available for the maintenance and reliever therapy regimen. *Recommended doses:* 1 inhalation twice daily. Some patients may require up to a maximum of 2 inhalations twice daily Prescription-only medicine	Communication and Educational Program (CEP) directed to prescribing physicians, pharmacists, and patients that emphasizes that Budesonide/Formoterol Spiromax®, 320/9.0 µg delivered dose corresponding to 400/12 µg metered dose strength is not appropriate for use as maintenance and reliever therapy
Drug interactions (with beta-adrenergic	Section 4.4, special warnings and	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
blockers and strong inhibitors of CYP3A4)	precautions for use, SmPC Interaction with other medicinal products Concomitant treatment with itraconazole, ritonavir or other potent CYP3A4 inhibitors should be avoided (see section 4.5). If this is not possible the time interval between administrations of the interacting medicinal products should be as long as possible. In patients using potent CYP3A4 inhibitors, a budesonide/formoterol fumarate fixed dose combination is not recommended. Section 4.5 Interaction with other medicinal products and other forms of interaction Pharmacokinetic interactions Potent inhibitors of CYP3A4 (eg. ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, nefazodone and HIV protease inhibitors) are likely to markedly increase plasma levels of budesonide and concomitant use should be avoided. If this is not possible the time interval between administration of the inhibitor and budesonide should be as long as possible (see section 4.4). In patients using potent CYP3A4 inhibitors, a fixed-dose combination of budesonide and formoterol fumarate dihydrate maintenance and reliever therapy is not recommended. The potent CYP3A4 inhibitor ketoconazole, 200 mg once daily, increased plasma levels of concomitantly orally administered budesonide (single dose 3 mg) on average six-fold. When ketoconazole was administered 12 hours after budesonide the concentration was on average increased only three-fold showing that separation of the administration times can reduce the increase in plasma levels. Limited data about this interaction for high-dose inhaled budesonide indicates that marked increases in plasma levels	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	(on average four fold) may occur if itraconazole, 200 mg once daily, is administered concomitantly with inhaled budesonide (single dose of 1000 micrograms). Pharmacodynamic interactions β -adrenergic blockers can weaken or inhibit the effect of formoterol. A fixed-dose combination of budesonide and formoterol fumarate dehydrate should therefore not be given together with β -adrenergic blockers (including eye drops) unless there are compelling reasons.	
MISSING INFORMATION		
Use in pregnant or breast feeding women	<u>*Pregnancy*</u> For a fixed-dose combination of budesonide and formoterol fumarate dihydrate or the concomitant treatment with formoterol and budesonide, no clinical data on exposed pregnancies are available. Data from an embryo-fetal development study in the rat, showed no evidence of any additional effect from the combination. There are no adequate data from use of formoterol in pregnant women. In animal studies formoterol has caused adverse reactions in reproduction studies at very high systemic exposure levels (see section 5.3). Data on approximately 2000 exposed pregnancies indicate no increased teratogenic risk associated with the use of inhaled budesonide. In animal studies glucocorticosteroids have been shown to induce malformations (see section 5.3). This is not likely to be relevant for humans given recommended doses. Animal studies have also identified an involvement of excess prenatal glucocorticoids in increased risks for intrauterine growth retardation, adult cardiovascular disease and permanent	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	changes in glucocorticoid receptor density, neurotransmitter turnover and behaviour at exposures below the teratogenic dose range. During pregnancy, a fixed-dose combination of budesonide and formoterol fumarate dihydrate should only be used when the benefits outweigh the potential risks. The lowest effective dose of budesonide needed to maintain adequate asthma control should be used. *Breast-feeding* Budesonide is excreted in breast milk. However, at therapeutic doses no effects on the suckling child are anticipated. It is not known whether formoterol passes into human breast milk. In rats, small amounts of formoterol have been detected in maternal milk. Administration of a fixed-dose combination of budesonide and formoterol fumarate dihydrate to women who are breast-feeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child. Prescription-only medicine	
Use in renal impairment	*Section 4.2, Posology and method of administration, SmPC* There are no data available for use of a fixed-dose combination of budesonide and formoterol fumarate dihydrate in patients with renal impairment Prescription-only medicine	None
Use in hepatic impairment	*Section 4.2, Posology and method of administration, SmPC* There are no data available for use of a fixed-dose combination of budesonide and formoterol fumarate dihydrate in patients with hepatic impairment. As budesonide and formoterol are primarily eliminated	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	via hepatic metabolism, an increased exposure can be expected in patients with severe liver cirrhosis Prescription-only medicine	
Use in children and adolescents	*Section 4.1, Therapeutic indications, SmPC* Budesonide/Formoterol Spiromax is indicated in adults 18 years of age and above only. Not for use in children or adolescents under the age of 18 years of age. *Section 4.2, Posology and method of administration, SmPC* *Paediatric population* The safety and efficacy of Budesonide/Formoterol Spiromax in children, 12 years and younger and adolescents, 13 to 17 years of age has not yet been established. No data are available. Prescription-only medicine	None

In order to address the issues raised by the PRAC the Applicant submitted an updated RMP with the following information:

- **Safety concerns**

Table 2. Summary of safety concerns

IMPORTANT IDENTIFIED RISKS	• **Systemic glucocorticosteroid effects** • **Cardiac effects of long-acting adrenergic beta$_2$ receptor agonists (LABA)** • **Life-threatening and fatal asthma events with long-acting adrenergic beta$_2$ receptor agonists** • **Paradoxical bronchospasm** • **Hypokalaemia**
IMPORTANT POTENTIAL RISKS	• **Off label use in children and adolescents under 18 years** • **Potential for off-label use of Budesonide/Formoterol Spiromax®**

	inhalation powder, 320/9.0 µg delivered dose corresponding to 400/12 µg metered dose, per actuation, in the "maintenance and reliever therapy regimen" • **Drug interactions (with beta-adrenergic blockers and strong inhibitors of CYP3A4)**
MISSING INFORMATION	• **Use in pregnant or breast feeding women** • **Use in renal impairment** • **Use in hepatic impairment** • **Use in children and adolescents**

- **Pharmacovigilance plans**

The PRAC, having considered the data submitted, was of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

- **Risk minimisation measures**

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
IMPORTANT IDENTIFIED RISKS		
Systemic glucocorticosteroid effects	*Section 4.4, special warnings and precautions for use, SmPC:* Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur with inhalation treatment than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children) (see section 4.8). It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth is slowed, therapy should be re-evaluated with the aim of reducing the dose of inhaled corticosteroid to the lowest dose at which effective control of asthma is maintained, if possible. The benefits of the corticosteroid therapy and the possible risks of growth suppression must be carefully weighed. In addition consideration should be given to referring the patient to a paediatric respiratory specialist.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Limited data from long-term studies suggest that most children and adolescents treated with inhaled budesonide will ultimately achieve their adult target height. However, an initial small but transient reduction in growth (approximately 1 cm) has been observed. This generally occurs within the first year of treatment. Potential effects on bone density should be considered, particularly in patients on high doses for prolonged periods that have co-existing risk factors for osteoporosis. Long-term studies with inhaled budesonide in children at mean daily doses of 400 micrograms (metered dose) or in adults at daily doses of 800 micrograms (metered dose) have not shown any significant effects on bone mineral density. No information regarding the effect of a budesonide/formorterol fumarate dihydrate fixed-dose combination at higher doses is available If there is any reason to suppose that adrenal function is impaired from previous systemic steroid therapy, care should be taken when transferring patients to a budesonide/formoterol fumarate fixed dose combination therapy. The benefits of inhaled budesonide therapy would normally minimise the need for oral steroids, but patients transferring from oral steroids may remain at risk of impaired adrenal reserve for a considerable time. Recovery may take a considerable amount of time after cessation of oral steroid therapy and hence oral steroid-dependent patients transferred to inhaled budesonide may remain at risk from impaired adrenal function for some considerable time. In such circumstances hypothalamic pituitary adrenocortical (HPA) axis function should be monitored regularly. Prolonged treatment with high doses of inhaled corticosteroids, particularly higher than recommended doses, may also result in clinically significant adrenal suppression. Therefore additional systemic corticosteroid cover should be considered during periods of stress such as severe infections or elective surgery. Rapid reduction in the dose of steroids can induce acute adrenal crisis. Symptoms and signs which might be seen in acute adrenal crisis may be somewhat vague but may include anorexia, abdominal pain, weight loss, tiredness, headache, nausea, vomiting, decreased level of consciousness, seizures, hypotension and hypoglycaemia. Treatment with supplementary systematic steroids or inhaled budesonide should not be stopped abruptly. During transfer from oral therapy toa budesonide/formoterol fumarate fixed dose	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	combination therapy, a generally lower systemic steroid action will be experienced which may result in the appearance of allergic or arthritic symptoms such as rhinitis, eczema and muscle and joint pain. Specific treatment should be initiated for these conditions. A general insufficient glucocorticosteroid effect should be suspected if, in rare cases, symptoms such as tiredness, headache, nausea and vomiting should occur. In these cases a temporary increase in the dose of oral glucocorticosteroids is sometimes necessary. *Section 4.8, undesirable effects, SmPC:* Systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for long periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include Cushing´s syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma. Increased susceptibility to infections and impairment of the ability to adapt to stress may also occur. Effects are probably dependent on dose, exposure time, concomitant and previous steroid exposure and individual sensitivity. Prescription-only medicine	
Cardiac effects of long-acting adrenergic beta$_2$ receptor agonists (LABA)	*Section 4.4, special warnings and precautions for use, SmPC:* A fixed-dose combination of budesonide and formoterol fumarate dihydrate should be administered with caution in patients with thyrotoxicosis, phaeochromocytoma, diabetes mellitus, untreated hypokalaemia, hypertrophic obstructive cardiomyopathy, idiopathic subvalvular aortic stenosis, severe hypertension, aneurysm or other severe cardiovascular disorders, such as ischaemic heart disease, tachyarrhythmias or severe heart failure. Caution should be observed when treating patients with prolongation of the QTc-interval. Formoterol itself may induce prolongation of the QTc-interval. Potentially serious hypokalaemia may result from high doses of beta$_2$-adrenoceptor agonists. Concomitant treatment of beta$_2$-adrenoceptor agonists with drugs which can induce hypokalaemia or potentiate a hypokalaemic effect, e.g. xanthine-derivatives, steroids and diuretics, may add to a possible hypokalaemic effect of the beta$_2$-adrenoceptor agonist. Particular caution is recommended in unstable asthma with variable use of rescue bronchodilators, in acute severe asthma as the associated risk may be augmented by hypoxia	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	and in other conditions when the likelihood for hypokalaemia is increased. It is recommended that serum potassium levels are monitored during these circumstances. *Section 4.5, interactions with other medicinal products and other forms of interactions, SmPC:* Concomitant treatment with quinidine, disopyramide, procainamide, phenothiazines, antihistamines (terfenadine), monoamine oxidase inhibitors and tricyclic antidepressants can prolong the QTc-interval and increase the risk of ventricular arrhythmias. In addition L-Dopa, L-thyroxine, oxytocin and alcohol can impair cardiac tolerance towards $beta_2$-sympathomimetics. There is an elevated risk of arrhythmias in patients receiving concomitant anaesthesia with halogenated hydrocarbons. Hypokalaemia may increase the disposition towards arrhythmias in patients who are treated with digitalis glycosides. Prescription-only medicine	
Life-threatening and fatal asthma events with long-acting adrenergic $beta_2$ receptor agonists	*Section 4.4, special warnings and precautions for use, SmPC:* If patients find the treatment ineffective, or exceed the highest recommended dose of Budesonide/Formoterol Spiromax®, medical attention must be sought (see section 4.2). Sudden and progressive deterioration in control of asthma or COPD is potentially life threatening and the patient should undergo urgent medical assessment. In this situation, consideration should be given to the need for increased therapy with corticosteroids, e.g. a course of oral corticosteroids, or antibiotic treatment if an infection is present. Patients should not be initiated on Budesonide/Formoterol Spiromax® during an exacerbation, or if they have significantly worsening or acutely deteriorating asthma. Serious asthma-related adverse events and exacerbations may occur during treatment with Budesonide/Formoterol Spiromax®. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation with Budesonide/Formoterol Spiromax®. Prescription-only medicine	None
Paradoxical bronchospasm	*Section 4.4, special warnings and precautions for use, SmPC:* Paradoxical bronchospasm may occur, with an	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	immediate increase in wheezing and shortness of breath after dosing. If the patient experiences paradoxical bronchopasm Budesonide/Formoterol Spiromax® should be discontinued immediately, the patient should be assessed and an alternative therapy instituted, if necessary. Paradoxical bronchopasm responds to a rapid-acting inhaled bronchodilator and should be treated straightaway *Section 4.8, undesirable effects, SmPC:* 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 bronchopasm responds to a rapid-acting inhaled bronchodilator and shoud be treated straightaway. Budesonide/Formoterol Spiromax should be discontinued immediately, the patient should be assessed and an alternative therapy is instituted if necessary Prescription-only medicine	
Hypokalaemia	*Section 4.4, special warnings and precautions for use, SmPC:* A fixed-dose combination of budesonide and formoterol fumarate dihydrate should be administered with caution in patients with untreated hypokalaemia. Potentially serious hypokalaemia may result from high doses of beta2-adrenoceptor agonists. Concomitant treatment of beta2-adrenoceptor agonists with medicinal products which can induce hypokalaemia or potentiate a hypokalaemic effect, e.g. xanthine-derivatives, steroids and diuretics, may add to a possible hypokalaemic effect of the beta2-adrenoceptor agonist. Particular caution is recommended in unstable asthma with variable use of rescue bronchodilators, in acute severe asthma as the associated risk may be augmented by hypoxia and in other conditions when the likelihood for hypokalaemia is increased. It is recommended	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	that serum potassium levels are monitored during these circumstances. *Section 4.5, Interaction with other medicinal products and other forms of interaction, SmPC*: Hypokalaemia may increase the disposition towards arrhythmias in patients who are treated with digitalis glycosides. *Section 4.8, undesirable effects, SmPC:* Rare: Hypokalaemia Prescription-only medicine	
IMPORTANT POTENTIAL RISKS		
Off label use in children and adolescents under 18 years	Section 4.1, Therapeutic indications, SmPC Budesonide/Formoterol Spiromax is indicated in adults 18 years of age and older only. Section 4.2, Posology and method of administration, SmPC Budesonide/Formoterol Spiromax is indicated in adults 18 years of age and older only. Budesonide/Formoterol Spiromax is not indicated for use in children, 12 years of age and younger or adolescents, 13 to 17 years of age. Paediatric population The safety and efficacy of DuoResp Spiromax in children, 12 years and younger and adolescents, 13 to 17 years of age has not yet been established. No data are available.Prescription-only medicine This medicinal product is not recommended for use in children and adolescents under the age of 18 years.	None
Potential for off-label use of Budesonide/Formoterol Spiromax® inhalation powder, 320/9.0 µg delivered dose corresponding to 400/12 µg metered dose, per actuation, in	Section 4.2, Posology and method of administration, SmPC Budesonide/Formoterol Spiromax 320 micrograms/9.0 micrograms should be used as maintenance therapy only. The lower strengths of Budesonide/Formoterol Spiromax are available for the maintenance and reliever therapy regimen.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
the "maintenance and reliever therapy regimen"	*Recommended doses:* 1 inhalation twice daily. Some patients may require up to a maximum of 2 inhalations twice daily Prescription-only medicine	
Drug interactions (with beta-adrenergic blockers and strong inhibitors of CYP3A4)	Section 4.4, special warnings and precautions for use, SmPC Interaction with other medicinal products Concomitant treatment with itraconazole, ritonavir or other potent CYP3A4 inhibitors should be avoided (see section 4.5). If this is not possible the time interval between administrations of the interacting medicinal products should be as long as possible. In patients using potent CYP3A4 inhibitors, a budesonide/formoterol fumarate fixed dose combination is not recommended. Section 4.5 Interaction with other medicinal products and other forms of interaction Pharmacokinetic interactions Potent inhibitors of CYP3A4 (eg. ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, nefazodone and HIV protease inhibitors) are likely to markedly increase plasma levels of budesonide and concomitant use should be avoided. If this is not possible the time interval between administration of the inhibitor and budesonide should be as long as possible (see section 4.4). In patients using potent CYP3A4 inhibitors, a fixed-dose combination of budesonide and formoterol fumarate dihydrate maintenance and reliever therapy is not recommended. The potent CYP3A4 inhibitor ketoconazole, 200 mg once daily, increased plasma levels of concomitantly orally administered budesonide (single dose 3 mg) on average six-fold. When ketoconazole was administered 12 hours after budesonide the concentration was on average increased only three-fold showing that separation of the administration times can reduce the increase in plasma levels. Limited data about this	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	interaction for high-dose inhaled budesonide indicates that marked increases in plasma levels (on average four fold) may occur if itraconazole, 200 mg once daily, is administered concomitantly with inhaled budesonide (single dose of 1000 micrograms). Pharmacodynamic interactions β -adrenergic blockers can weaken or inhibit the effect of formoterol. A fixed-dose combination of budesonide and formoterol fumarate dehydrate should therefore not be given together with β -adrenergic blockers (including eye drops) unless there are compelling reasons.	
MISSING INFORMATION		
Use in pregnant or breast feeding women	<u>*Pregnancy*</u> For a fixed-dose combination of budesonide and formoterol fumarate dihydrate or the concomitant treatment with formoterol and budesonide, no clinical data on exposed pregnancies are available. Data from an embryo-fetal development study in the rat, showed no evidence of any additional effect from the combination. There are no adequate data from use of formoterol in pregnant women. In animal studies formoterol has caused adverse reactions in reproduction studies at very high systemic exposure levels (see section 5.3). Data on approximately 2000 exposed pregnancies indicate no increased teratogenic risk associated with the use of inhaled budesonide. In animal studies glucocorticosteroids have been shown to induce malformations (see section 5.3). This is not likely to be relevant for humans given recommended doses. Animal studies have also identified an involvement of excess prenatal glucocorticoids in increased risks for intrauterine growth retardation, adult cardiovascular disease and permanent changes in glucocorticoid receptor density, neurotransmitter turnover and behaviour at exposures below the teratogenic dose range.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	During pregnancy, a fixed-dose combination of budesonide and formoterol fumarate dihydrate should only be used when the benefits outweigh the potential risks. The lowest effective dose of budesonide needed to maintain adequate asthma control should be used. *Breast-feeding* Budesonide is excreted in breast milk. However, at therapeutic doses no effects on the suckling child are anticipated. It is not known whether formoterol passes into human breast milk. In rats, small amounts of formoterol have been detected in maternal milk. Administration of a fixed-dose combination of budesonide and formoterol fumarate dihydrate to women who are breast-feeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child. Prescription-only medicine	
Use in renal impairment	*Section 4.2, Posology and method of administration, SmPC* There are no data available for use of a fixed-dose combination of budesonide and formoterol fumarate dihydrate in patients with renal impairment Prescription-only medicine	None
Use in hepatic impairment	*Section 4.2, Posology and method of administration, SmPC* There are no data available for use of a fixed-dose combination of budesonide and formoterol fumarate dihydrate in patients with hepatic impairment. As budesonide and formoterol are primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe liver cirrhosis Prescription-only medicine	None
Use in children and adolescents	*Section 4.1, Therapeutic indications, SmPC* Budesonide/Formoterol Spiromax is indicated in	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	adults 18 years of age and older only. *Section 4.2, Posology and method of administration, SmPC* Budesonide/Formoterol Spiromax is indicated in adults 18 years of age and older only. Budesonide/Formoterol Spiromax is not indicated for use in children, 12 years of age and younger or adolescents, 13 to 17 years of age. *Paediatric population* The safety and efficacy of Budesonide/Formoterol Spiromax in children, 12 years and younger and adolescents, 13 to 17 years of age has not yet been established. No data are available. This medicinal product is not recommended for use in children and adolescents under the age of 18 years. Prescription-only medicine	

The CHMP endorsed this RMP without any further changes.

2.9. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Clinical studies in adults have shown that the addition of formoterol to budesonide improved asthma symptoms and lung function, and reduced exacerbations. Budesonide/formoterol provided statistically significant and clinically meaningful reductions in severe exacerbations as well as rapid and effective relief of bronchoconstriction similar to salbutamol and formoterol.

The two pivotal pharmacokinetic studies in the high strength (320/9 µg per dose) and the middle strength (160/4.5 µg per dose) demonstrated equivalence between BF Spiromax and

Symbicort Turbohaler for all comparisons both with and without a charcoal blockade. This fixed-dose combination product is expected to have the same benefits as the reference product (Symbicort Turbohaler) in improving lung function and relieving symptoms in patients with asthma and COPD when used in line with the approved indications and posology of the reference product.

Uncertainty in the knowledge about the beneficial effects

The pharmacokinetic equivalence of the high-dose and the medium-dose has been conclusively shown. However the pharmacokinetic equivalence of the low dose remains to be conclusively demonstrated given the lack of a pharmacokinetic study or any other clinical study to conclusively demonstrate the equivalence of the low strength (80/4.5) of DuoResp Spiromax with the low strength of the reference product. Therefore, the Applicant withdrew the low dose DuoResp Spiromax.

There is no conclusive data on the equivalence of DuoResp Spiromax with the reference product in children and adolescents and therefore there is a lack of demonstration of a positive benefit/risk balance in this population. Therefore, the applicant agreed to limit the use of DuoResp Spiromax to adults aged 18 and older.

Risks

Unfavourable effects

The high dose and the medium dose of DuoResp Spiromax have been shown to be equivalent to the reference product. Hence their unfavourable effects are expected to be similar to the well-known safety profile of the reference product (Symbicort Turbohaler) when used in line with the approved indications and posology of the reference product.

Uncertainty in the knowledge about the unfavourable effects

As the low-dose formulation has not been conclusively shown to be equivalent to the reference product, there is uncertainty about its safety profile at the proposed dose and indications. Since it cannot be accepted that this will be similar to the reference at present, the Applicant decided to withdraw the low strength of DuoResp Spiromax Due to the lack of adequate and conclusive evidence of the equivalence of DuoResp Spiromax in adolescents and children, there is uncertainty about the safety profile in this population. At present, it cannot be accepted that the profile of DuoResp Spiromax will be similar to that of the reference product in this population and hence the above-mentioned withdrawal of the low dose product.

Benefit-risk balance

Importance of favourable and unfavourable effects

Conclusive demonstration of equivalence of DuoResp Spiromax with the reference product has not been done for the low-dose strength and hence this introduces a large risk of undetermined efficacy/safety for this strength. Moreover the downward titration of dose in patients where required cannot be done with confidence.

Furthermore, due to the lack of adequate and conclusive data in adolescents and children, it cannot be concluded with confidence that the efficacy/safety profile of DuoResp Spiromax will be the same as the reference product. Therefore the use of DuoResp Spiromax in children

and adolescents cannot be allowed at present. A restriction in indication only in adults brings with it the practical risk of “off-label” use in children, which is a safety concern.

Benefit-risk balance

DuoResp Spiromax will be an alternative to high dose and medium dose Symbicort Turbohaler available for doctors and patients. However the low dose alternate cannot be allowed due to lack of conclusive evidence of equivalence. This brings in the risk of lack of alternative for down-ward titration of dose when required. The lack of conclusive evidence of equivalence in adolescents and children precludes the use of DuoResp Spiromax in this population. The risk of “off-label” use in this population has been addressed by the inclusion of the statements in sections 4.1 and 4.2 of the SmPC regarding the use of the product by adults 18 years old and older only.

Discussion on the benefit-risk balance

The high dose and medium dose of DuoResp Spiromax have been conclusively shown to be equivalent in adults to the reference Symbicort. The low-dose DuoResp Spiromax has not been conclusively shown to be equivalent and hence cannot be authorised at present.

The benefit of development of an alternative to the reference product which increases treatment options for patients and doctors is outweighed by the potential risks due to the unknowns described above. The CHMP acknowledges that there is a lack of significant safety concerns. However the principles of authorising generics/hybrids rest on the pivotal point of demonstrating equivalence. When this is not adequately demonstrated, as is the case here for the low dose, the posology, safety and efficacy data of the reference cannot be considered to be reflective of the performance of the generic/hybrid product.

Regarding the high strength (320/9 µg per dose) and the middle strength (160/4.5 µg per dose), equivalence between BF Spiromax and Symbicort Turbohaler has been demonstrated and therefore the benefit/risk balance for these strengths is considered positive.

The doses and dose regimens stated for this orally inhaled fixed-dose combination product for use in adults are acceptable. However, neither adolescents nor children have not been studied appropriately in the development programme submitted with this application. Therefore, the CHMP concluded that DuoResp Spiromax should not be authorised for use in adolescents and children at this time and that the lower limit of the age range for use of these fixed-dose combinations should be 18 years.

The proposal not to seek an indication in children is in line with the current data. The risk of “off-label” use in this population has been addressed by the inclusion of the statements in sections 4.1 and 4.2 of the SmPC regarding the use of the product by adults 18 years old and older.

The CHMP recommends that further development of this new fixed-dose combination product in children and adolescents should be considered particularly in the light of this combination containing an inhaled corticosteroid. In addition, the CHMP recommends that demonstration of therapeutic equivalence in respect of both efficacy and safety and an appropriate benefit/risk balance in this age group should be demonstrated should the Applicant seek approval of the lower strength fixed-dose combination in the future.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of DuoResp Spiromax in the regular treatment of asthma, where use of a combination (inhaled corticosteroid and long-acting β2 adrenoceptor agonist) is appropriate (in patients not adequately controlled with inhaled corticosteroids and "as needed" inhaled short-acting β2 adrenoceptor agonists, or in patients already adequately controlled on both inhaled corticosteroids and long-acting β2 adrenoceptor agonists), and in the symptomatic treatment of patients with severe COPD (FEV1 < 50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators, is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreeed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.