25 September 2014
EMA/CHMP/707217/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Budesonide/Formoterol Teva Pharma B.V.

International non-proprietary name: budesonide / formoterol

Procedure No. EMEA/H/C/003953

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Administrative information

Name of the medicinal product:	Budesonide/Formoterol Teva Pharma B.V.
Applicant:	Teva Pharma B.V. Computerweg 10 3542 DR Utrecht The Netherlands
Active substance:	budesonide / formoterol fumarate dihydrate
International Nonproprietary Name/Common Name:	budesonide / formoterol
Pharmaco-therapeutic group (ATC Code):	Glucocorticosteroid/Selective β_2 adrenoceptor agonist fixed-dose combination product. Group: Adrenergics and other drugs for obstructive airway diseases (R03AK07)
Therapeutic indication(s):	BF Teva is indicated in adults 18 years of age and older only Asthma Budesonide/Formoterol Teva Pharma B.V. 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.
Pharmaceutical form:	Inhalation powder
Strengths:	160 µg / 4.5 µg and 320 µg / 9 µg
Route of administration:	Inhalation use
Packaging:	Inhaler
Package sizes:	1 x 120 inhalations, 1 x 60 inhalations

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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 5 March 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Budesonide/Formoterol Teva Pharma B.V., 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 February 2014. 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

Budesonide/Formoterol Teva Pharma B.V. 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.

The legal basis for this application refers to:

Hybrid application (Article 10(3) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data, comparative studies with the reference medicinal product Symbicort Turbuhaler and appropriate clinical data.

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.

This application is submitted as a multiple of DuoResp Spiromax, authorised on 28 April 2014, in accordance with Article 82.1 of Regulation (EC) No 726/2004.

Reference medicinal product

The chosen reference product is:

Medicinal product which is or has been authorised 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 in: Sweden
- 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 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 (160/4,5 mcg)/ 28-12-2001(320/9 mcg)
- Marketing authorisation granted in: Sweden
- Marketing authorisation number: 160/4,5 mcg 16047, 320/9 mcg 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 in:	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 in:	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 in:	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 in:	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 in:	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 in:	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 in:	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 in:	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 in:	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 in:	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 in:	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

Manufacturer(s) responsible for batch release

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

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

Teva Operations Poland Sp. z o.o.
ul. Mogilska 80
31-546 Krakow
Poland

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 5 March 2014.
- The procedure started on 26 March 2014.
- The Rapporteur's initial Assessment Report was circulated to all CHMP members on 24 June 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 18 June 2014.
- During the meeting on 10 July 2014 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.
- During the meeting on 24 July 2014, 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 2014.

- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 August 2014.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 11 September 2014.
- During the meeting on 25 September 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 Budesonide/Formoterol Teva Pharma B.V.

2. Scientific discussion

2.1. Introduction

Budesonide/Formoterol Teva Pharma B.V. 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 of 6 years 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).

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 two 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:

- Budesonide/Formoterol Teva Pharma B.V. 160/4.5 µg per dose, inhalation powder and
- Budesonide/Formoterol Teva Pharma B.V. 320/9 µg per dose, inhalation powder

The proposed indication is in the regular treatment of adults with asthma where the use of the combination of an inhaled corticosteroid and an inhaled long-acting β_2 adrenoceptor agonist is appropriate. 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 indication.

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 Turbuhaler, 160 mikrogram/4,5 mikrogram/inhalation, inhalationspulver and
- Symbicort forte Turbuhaler, 320 mikrogram/9 mikrogram/inhalation, inhalationspulver

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

The development of Budesonide/Formoterol Teva Pharma B.V. 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 have 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

Budesonide/Formoterol Teva Pharma B.V. is a fixed-dose combination product presented as dry powder for oral inhalation containing budesonide and formoterol fumarate dihydrate. Two strengths are proposed: budesonide 160 µg and formoterol (as fumarate dihydrate) 4.5 µg (middle strength) and budesonide 320 µg and formoterol (as fumarate dihydrate) 9 µg (high strength). The only other ingredient is lactose monohydrate. The product is administered *via* a novel inhalation-driven multi-dose

[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.

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.

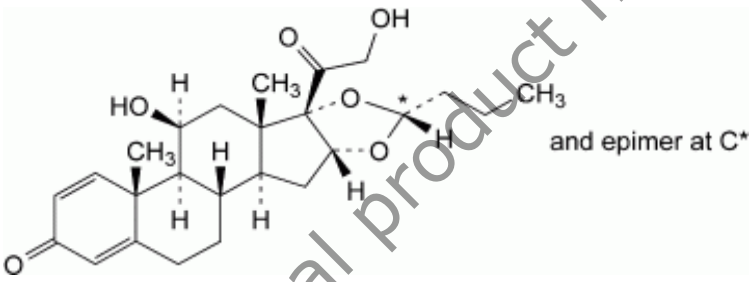
2.2.2. Active substance

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.

Figure 1. The chemical structure of budesonide



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.

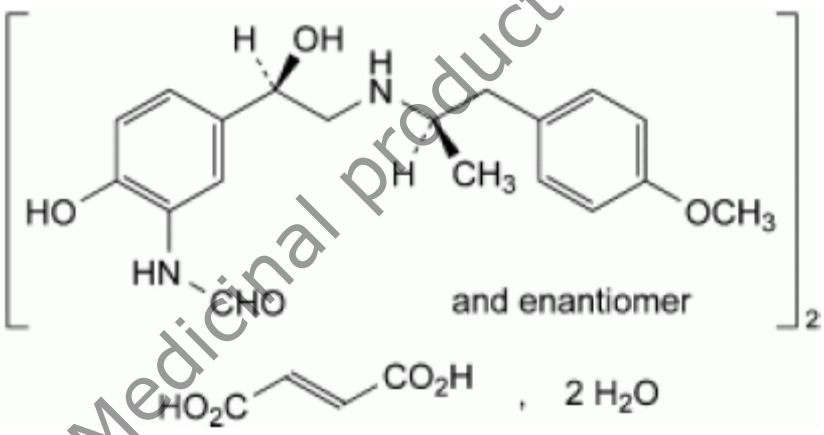
Stability data on 10 pilot and commercial scale batches of budesonide from the proposed manufacturer stored in the intended commercial packaging for up to 60 months under long term conditions (25 ºC / 60% RH) and on 7 pilot and commercial scale batches stored for up to 6 months under accelerated conditions (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.

Figure 2. The chemical structure of formoterol fumarate dihydrate



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

Description of the product and 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. 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 medicinal product, Symbicort Turbohaler. As such, Budesonide/Formoterol Teva Pharma B.V. was 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 Budesonide/Formoterol Teva Pharma B.V. 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.

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.

Manufacture of the product and process controls

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 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 ^{o}C 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.

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.

2.2.4. Discussion on chemical, and pharmaceutical 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

The applicant has presented a pharmacology review based on literature reports of budesonide and formoterol activity alone and in combination. No new pharmacology studies were performed to support this MAA. Budesonide and formoterol are long-established bronchodilators and their pharmacology has been well characterised. Budesonide is a glucocorticoid that has local anti-inflammatory effects in the respiratory tract. Budesonide efficacy in animal models of airway inflammation and hyper-responsiveness was demonstrated over 20 years ago. The exact anti-inflammatory mechanism of action of glucocorticoids is unknown, but effects include inhibition of neutrophil and monocyte-macrophage adherence, phospholipase inhibition of A2 activity, inhibition of eosinophil activation, and inhibition of plasma exudation in the bronchial endothelium.

Formoterol exerts its bronchodilatory action through the β2-adrenoreceptor, leading to cAMP activation and relaxation of bronchial smooth muscle. Formoterol pharmacology has been characterised in a series of studies in isolated animal and human tissue preparations, where it demonstrated effects consistent with β2-receptor agonism. Inhibition of release of mast cell mediators such as histamine and leukotrienes may contribute to efficacy in airway hypersensitivity.

In studies performed during the development of the reference product, Symbicort, combination ICS/LABA treatment was found to inhibit release of inflammatory mediators in human bronchial epithelial cells and lung fibroblasts, inhibit oxidative burst in human eosinophils stimulated by bronchial epithelial cell-derived condition medium, inflammation-induced lung edema, proliferation of airway smooth muscle cells, production of proteoglycans by lung fibroblasts, and the bronchoconstriction response to provocation. Combination ICS/LABA therapies appear to have additive, synergistic, complementary and or compensatory effects in pre-clinical models, which underlie the clinical efficacy seen in asthma patients.

Mechanistic studies in the literature are limited but a number are described by the applicant. A study by Adner et al suggests ICS treatment may enhance LABA action through upregulation of the β2-adrenoreceptor and inhibition of COX-2 mediated receptor desensitization. Similarly, corticosteroids attenuated β2-adrenoreceptor desensitization in rats administered salmeterol for 1 week, and increased β2-adrenoreceptor mRNA in human lung tissue. A study by Holden et al (2011) also suggest a synergistic action through induction of regulator of G-protein signalling 2 (RGS2), which reduces intracellular free calcium flux and the subsequent bronchoconstriction. This is supported by characterization of RGS2-/- mice, which display increased bronchoconstriction in response to spasmogens. Taken together the studies support the well-established clinical efficacy of budesonide and formoterol.

Discussion of secondary pharmacodynamics is limited to a single study of mice with acute lung injury, where pre-treatment with a combination of budesonide and formoterol reduced endothelial and cardiac dysfunction and associated IL-6 expression. This report is described in primary pharmacodynamics but is considered a secondary pharmacodynamic effect. The mechanism of action underlying this observation and its clinical relevance is uncertain. No formal safety pharmacology studies have been performed for this application. As the clinical safety of the reference product, Symbicort® Turbohaler, is well established, nonclinical safety pharmacology studies would not significantly add to the clinical safety of the product; thus the lack of studies is acceptable. As the same racemic mixture of formoterol is used as the reference product, the report by Abraha et al on the potential adverse effects associated with (S,S)-formoterol, is not a concern; the clinical safety profile of formoterol is already well-established. Pharmacodynamic drug interactions are well characterised and are described in the relevant sections of the SmPC. The absence of a non-clinical pharmacodynamic interaction summary is acceptable.

2.3.3. Pharmacokinetics

No new pharmacokinetic studies were performed for this application. The applicant described ADME profiles budesonide and formoterol based on available information from assessments of prior applications, and published literature reports. Budesonide was rapidly absorbed and with high bioavailability following inhalation. T_{max} for [3H]-budesonide administered to rats intratracheally was about 3 minutes, with a plasma AUC of 61% suggesting high bioavailability. Formoterol is reported to be readily absorbed following inhalation.

In the pharmacokinetic modelling system described by Ewing et al (2008), budesonide and formoterol were administered to isolated rat lung by aerosol, with a predicted deposition of ~27 and 37 µg/dose in the lung. Both compounds reached peak local concentration rapidly, with T_{max} of 2.2 and 6.7 minutes, respectively. The study of pulmonary absorption by Tronde et al (2002) in isolated rat lung showed a similar absorption profile with rapid absorption of budesonide and more moderate absorption of formoterol. Given that the absorption and bioavailability of budesonide and formoterol are well-characterised clinically, the applicant's review is acceptable.

Human plasma protein binding of formoterol was 61-64% and 31-38% in two separate assays. The protein binding of formoterol according to the reference product SmPC is ~50%. Plasma protein binding of budesonide is reported to be about 90%. The study by Ewing et al suggests both budesonide and formoterol is retained in lung tissue, but budesonide distribution throughout the body is not discussed. Formoterol is reported to also distribute to kidney, liver, plasma, heart and brain. Following intratracheal administration radioactivity was also detected in stomach, kidney medulla, urine and bile, which correlates with the routes of elimination.

The applicant describes metabolism of formoterol based on assessments of prior applications. Formoterol is mainly metabolised by glucuronide conjugation in humans, and by o-demethylation. Budesonide is reported to undergo extensive first pass metabolism. The major metabolites budesonide are 6-beta-hydroxy-budesonide and 16-alfa-hydroxy-prednisolone, formed from both enantiomers, and the (R;R)-enantiomer, respectively. The metabolites have less than 1% of the pharmacological activity of the parent. Due to the extensive clinical experience with both formoterol and budesonide, the limited review of their metabolism is acceptable.

Formoterol is eliminated primarily through urinary excretion and to a lesser extent by biliary excretion. Budesonide was reported to be eliminated mainly through the faeces in rat and dog, and equally through faeces and urine in rabbit. Human excretion is through both urine and faeces. Given that the pharmacokinetics of both formoterol and budesonide are well characterised clinically, the absence of a detailed discussion on excretion is acceptable.

The applicant has not provided any discussion of pharmacokinetic drug interactions. As relevant pharmacokinetic drug interactions have been established clinically with the reference product, and are described in SmPC section 4.5, a discussion of a nonclinical PK drug interaction would be of limited use and its absence is acceptable. Taken together, as the pharmacokinetics of both active substances are well characterised both alone and in combination, there are no nonclinical issues relating to pharmacokinetics for this MAA. The limited pharmacokinetic overview is considered sufficient for the hybrid MAA.

2.3.4. Toxicology

No new toxicity studies have been performed for this MAA; the nonclinical toxicology summary is largely based on the information available for the Symbicort Turbohaler reference product. No original study reports are available. Considering this is a hybrid application this approach is acceptable.

In single-dose toxicity studies no lethality was seen in rats following administration of inhaled dry powder containing 97 mg/kg budesonide and 3 mg/kg formoterol, with a deposited dose of 7.9 and 0.24 mg/kg respectively. Treatment was well tolerated with effects on body and spleen, thymus and adrenal gland weight decreases attributed budesonide pharmacology. Combination treatment in beagle dogs did not cause lethality up to 737 µg/kg budesonide and 22 µg/kg formoterol, with a deposited dose of 117 and 3.3 µg/kg, respectively. Cardiovascular effects could be attributed to the pharmacological action of formoterol. In rat, mouse, and/or dog studies with oral or parenteral administration of either budesonide or formoterol alone, LD50 values generally offer a large margin of safety from the proposed clinical dose. Major findings for these studies can be attributed to the pharmacological action of each drug.

Combination of budesonide and formoterol in the 13-week repeat dose rat study produced effects including decreased body weight, thymus and spleen effects, which can generally be attributed to the pharmacology of budesonide. In the 13 week dog study, additional tachycardic effects were noted, which is attributable to formoterol pharmacology, and effects on lymph nodes and adrenal gland, which can be attributed to budesonide pharmacology. Neither study identified additive or synergistic toxic effects in the combination treatment compared to studies of either drug alone. There are no new nonclinical studies so there are no concerns of additional systemic toxicities following repeated administration.

Both budesonide and formoterol were negative in a battery of genotoxicity tests. The absence of studies with the combination is acceptable, as neither compound alone is considered a potential genotoxin. In a two year carcinogenicity study in rats, budesonide caused a statistically significant increase in gliomas in male rats at an oral dose of 50 µg/kg. In another two year study these findings were not replicated, however budesonide caused a statistically significant increase in gliomas in hepatocellular tumors at the same dose. In a 2 year study by Ryrfeldt et al, the glucocorticoids budesonide, prednisolone and triamcinolone were associated with increased hepatocellular adenomas/carcinomas, suggestive of a class-related effect.

Formoterol was associated with an increase ovarian and uterine leiomyomas in two 2 year rodent carcinogenicity studies. As these findings are typically associated with long-term treatment of rats with β2-adrenergic drugs, and the clinical relevance is uncertain.

Combination treatment of inhaled budesonide and formoterol was teratogenic in rats from a dose 12 + 0.66 µg/kg/day, with a deposited dose of 1.01 + 0.057 µg/kg/day. Effects included umbilical hernia, aortic arch and fused stemebra. Teratogenicity and embryolethality is associated with subcutaneous administration of budesonide, and with oral doses of formoterol, in rats and rabbits. However in contrast to the combination study, in inhalation studies of each drug alone, neither drug was associated with teratogenic effects. Taken together the combination treatment is considered to have teratogenic potential. Appropriate warnings are included in SmPC section 4.6.

No new studies have been performed to qualify excipients or impurities. The only excipient is lactose monohydrate. At the maximum daily exposure with this product, no toxic effects are expected, and the lack of specific studies to qualify the excipient is acceptable. As all impurities are present at equal or lower levels than in the reference product, or are maintained below the ICH limit of 1.0% (CPMP/ICH/2738/99), the impurities are considered qualified through extensive clinical use of the reference product.

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 stated that the proposed budesonide/formoterol Spiromax 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

This product is developed to be an equivalent version of the reference product containing the same active ingredients, marketed as Symbicort Turbohaler across the EU. As this is a "hybrid" application, the absence of new nonclinical studies with this product is acceptable. The pharmacology, pharmacokinetics, and toxicology of the combination have been characterised for the reference product, and there are no new studies in the published literature that would indicate additional concerns. The nonclinical overview is considered sufficient for an application of this type.

Pharmacodynamic and pharmacokinetic drug interactions are well characterised based on previously available data and are described in the relevant sections of the SmPC. Appropriate warnings on the teratogenic potential of the combination treatment are included in the SmPC.

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 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 indication.

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.

There are no objections to authorisation of this medicinal product from a non-clinical perspective.

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 and the corresponding strength of the reference product, Symbicort Turbohaler.

The applicant applied for the following indication:

> Asthma
>
> Budesonide/Formoterol Teva Pharma B.V. 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.

The therapeutic indication stated are covered by the therapeutic indications of the reference fixed-dose combination products containing the same active substances and formulated as an inhalation powders in the EU Member states (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.

Further to pharmacokinetic studies, one pharmacodynamic study has been carried out. No Phase 3 clinical efficacy or safety studies have been conducted comparing the test and reference products.

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.

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.

Clinical studies

Table 1. 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
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

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
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

The studies BFC-AS-102 and BFC-AS-103 are not discussed in detail since the strength 80/4.5 µg was not applied for in this application of the medicinal product Budesonide/Formoterol Teva Pharma B.V..

2.4.2. Pharmacokinetics

Analytical methods

Blood for analysis of budesonide and formoterol was collected into tubes. Within 30 minutes of collection, samples were centrifuged. Plasma was harvested from each centrifuge tube and aliquoted equally into two tubes. The plasma aliquots were immediately frozen at -20°C and maintained frozen state until analysis.

Budesonide

An LC-MS/MS instrument with positive electro-spray ionization (ESI) multiple-reaction monitoring (MRM) mode was used to quantify the analyte. All reported analytical data met the data acceptance criteria The validated calibration curve ranged from 10.0 pg/mL to 2000 pg/mL. The lower limit of quantitation (LLOQ) was 10.0 pg/mL.

Formoterol

An LC-MS/MS instrument with positive ESI MRM mode was used to quantify the analyte. All reported analytical data met the data acceptance criteria The validated calibration curve ranged from 0.4 pg/mL to 100 pg/mL . The LLOQ was 0.4 pg/mL. Extraction recovery data from human plasma indicated 97.50% and 102.11% of formoterol was recovered at the low and high levels, respectively. Data for long-term stability under frozen conditions indicated stability for approximately 258 days at -70°C and 117 days at -20°C.

Pharmacokinetic data analysis

Based on a simulation study with 1,000 runs, it was estimated that a sample size of 80 would provide a power of at least 90% to demonstrate bioequivalence, defined as the 90% confidence intervals for both the geometric mean AUC0-t ratio and the geometric mean C_{max} ratio being contained within (0.8, 1.25), for the two treatment comparisons (A vs. B and C vs. D) with respect to both budesonide and formoterol. This assumed that as a conservative power calculation, budesonide and formoterol are statistically independent, that AUC0-t and C_{max} are weakly correlated with a correlation coefficient set at 0.5, that the true geometric mean AUC0-t and C_{max} ratios between treatment groups are within the range of 0.95 to 1.05 for both budesonide and formoterol, and that the intra-subject standard deviation of the logarithmically transformed data on AUC_{0-t} and C_{max} are 0.25 and 0.30, respectively, for both budesonide and formoterol. The intra-subject variability assumptions are based on the results from three completed PK studies (BFS-AS-103, BFS-AS-105 and BFS-AS-107). Estimating a drop-out rate of 10%, approximately 90 subjects were randomised to most studies.

Statistical analysis

The primary pharmacokinetic endpoints in the bioequivalence studies 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 (C_{max}).

Pharmacokinetic parameters for budesonide and formoterol fumarate were calculated by non-compartmental analysis methods from the concentration-time data. The AUC_{0-t} was calculated using

the trapezoidal rule. The AUC_{0-t} and C_{max} data were natural log-transformed prior to analysis. Comparisons between BF Spiromax and Symbicort Turbohaler were carried out using a parametric analysis of variance (ANOVA) model with terms for sequence, period, treatment group and a random effect of subject within sequence. The treatment difference and the associated 90% confidence interval (CI) were back-transformed to obtain the estimated ratio of geometric means between treatment groups and the 90% CI for this ratio.

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

Pilot, supportive and pivotal bioequivalence studies 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. Only the 160/4.5, 320/9 µg strengths are considered in this application.

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 30 kg/m^2 and a body weight ≥50 kg. 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, AUC_{0-t} and AUC_{0-inf}, C_{max}, t_{max} and $t_{½}$ were calculated for both budesonide and formoterol fumarate in each study.

The primary endpoints were AUC_{0-t} (calculated using the trapezoidal rule) and C_{max}. 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 C_{max} in the ANOVA crossover model exceeded 0.30, indicating high intra-subject variability, the acceptance criteria for C_{max} 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 t_{max} 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 5 g 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 (C_{max})

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.

High Strength – Budesonide/Formoterol Teva Pharma B.V. 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.

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 320/9 µg, each with a different fine particle dose (FPD), with Symbicort Turbohaler 400/12 µg. 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 AUC_{last} were contained within the acceptance limits of 0.8, 1.25. For the secondary endpoints AUC_{0-inf} and C_{max}, the 90% CIs for the ratios were also contained within these acceptance limits (0.8, 1.25) but with the exception of C_{max} 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 C_{max} 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 320/9 µg 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.

Table 2. 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 t_{max}, this represents the estimated treatment difference.

In the absence of charcoal blockade, bioequivalence was demonstrated for AUC_{0-t} and AUC_{0-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 C_{max} for budesonide was slightly higher for BF Spiromax 320/9 µg than for Symbicort Turbohaler 400/12 µg and the 90% CIs for the ratio were not contained within (0.8, 1.25).

In the presence of charcoal blockade equivalence for AUC_{0-t}, AUC_{0-inf} and C_{max} 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.

Table 3. 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 AUC_{0-t}, AUC_{0-inf} or C_{max} 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.

Table 4. 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 C_{max} 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 AUC_{0-t} was essentially unchanged, C_{max} 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 C_{max} which is almost entirely due to pulmonary absorption of OIPs. There is no physiological reason why C_{max} 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.

Table 5. 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.

Table 6. 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

Table 7. 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.

Table 8. 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	103.55	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 Pharmacodynamics section below).

<u>Pivotal pharmacokinetic study</u> BFS-BE-109 (n=90) – third pharmacokinetic bioequivalence study (a pivotal study at the high strength)

Based on the findings in respect of C_{max} for formoterol fumarate across studies 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 C_{max}, 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.

Study BFS-BE-109 was an open, single-dose, randomised, five-way crossover comparison of the pharmacokinetic and safety profiles following two inhalations of BF Spiromax 320/9 mcg Inhalation Powder and Symbicort Turbohaler 400/12 mcg, with and without charcoal block in healthy volunteers.

The study was conducted between June and August 2012 at a single investigative centre in Paris, France.

Methods

The primary objective of the study was to assess the pharmacokinetic profiles of budesonide and formoterol administered as two inhalations from BF Spiromax 320/9 mcg Inhalation Powder and two inhalations from Symbicort Turbohaler 400/12 mcg, with and without charcoal block. The secondary objectives were to evaluate the safety and tolerability of BF Spiromax and Symbicort Turbohaler, and to evaluate the intra-subject variability of Symbicort Turbohaler (without charcoal block).

Eligible subjects were men and women, aged 18–45 years, in good general health with; body mass index (BMI) 19 -30 kg/m^2, body weight ≥50 kg; not pregnant, breast feeding, or attempting to become pregnant; agreement by women of childbearing potential to use appropriate contraception; non-smokers for at least one year prior to screening visit and a maximum smoking history of five pack-pack years; willing and able to give informed written consent.

Eligible subjects attended a one day training period where they were trained on device use and tolerability to drug substance was assessed. Following successful completion of the training period, subjects entered a 7 (±2)-day washout period. During Treatment Periods 1-5, all subjects took two inhalations from the DPI device to which they were randomised for each treatment period. Each treatment was followed by a 7 (±2)-day washout period except for the last treatment period. At the end of the washout period after Treatment Periods 1 to 4, the subject was exposed to the next treatment. Safety was monitored by clinical laboratory examinations, 12-lead ECGs, physical examination, vital sign measurements, and adverse events. For the treatments when subjects were randomised to receive co-administration of activated charcoal, a suspension of 5 g activated charcoal in water was administered 2 min before and 2, 62, 122, and 242 min after dose inhalation.

The primary pharmacokinetic endpoints were AUC_t and C_{max} for budesonide and formoterol, t_{max} was a secondary endpoint, additional endpoints were $AUC_{0-\infty}$ and apparent elimination half-life ($t_{½}$).

The following treatments were administered (treatment B was administered twice in each of ten possible dosing schedules, giving five treatment periods):

- Treatment A BF Spiromax 320/9 mcg – 2 inhalations
- Treatment B Symbicort Turbohaler 400/12 mcg – 2 inhalations
- Treatment C BF Spiromax 320/9 mcg with 5 g activated charcoal suspended in 25 mL water – 2 inhalations
- Treatment D Symbicort Turbohaler 400/12 mcg with 5 g activated charcoal suspended in 25 mL water– 2 inhalations

Results

One hundred and forty-five subjects were screened and 90 recruited to the study three of whom withdrew during the treatment periods and 87 completed the study. Subjects' mean age was 29.4 years (s.d. 6.63) and BMI was 23.7 kg/m^2 (s.d. 2.8) forty-eight were male.

Table 9. Pharmacokinetics of budesonide (geometrical mean and cv% for AUC and C_{max}; median and range for t_{max} and $t_{1/2}$)

	BF Spiromax 320/9	Symbicort 400/12	BF Spiromax 320/9 + charcoal	Symbicort 400/12 + charcoal
AUC_{0-t} (h.pg/mL)	4125 (24)	4074 (27)	3644 (26)	3614 (28)
AUC_{0-inf}(h.pg/mL)	4242 (24)	4177 (26)	3792 (26)	3710 (28)
C_{max} (pg.mL)*	2039 (39)	1945 (44)	1844 (37)	1767 (37)
t_{max} (h)	0.17 (0.03-0.52)	0.17 (0.03-1.00)	0.17 (0.33-0.75)	0.17 (0.08-0.75)
$t_{½}$ (h)	4.5 (2.19-8.91)	4.6 (2.19-9.66)	4.37 (2.36-8.89)	4.44 (2.04-12.87)

PP population n varies by pharmacokinetic parameter from n = 88 for AUC_{0-t} to n = 84 for t½

Table 10. Pharmacokinetics of formoterol (geometrical mean and cv% for AUC and C_{max}; median and range for t_{max} and $t_{1/2}$)

	BF Spiromax 320/9	Symbicort 400/12	BF Spiromax 320/9 + charcoal	Symbicort 400/12 + charcoal
AUC_{0-t} (h.pg/mL)	112.67 (28.35)	115.31 (28.04)	90.97 (28.41)	94.53 (29.76)
AUC_{0-inf}(h.pg/mL)	130.29 (28.63)	132.80 (28.91)	104.01 (29.51)	109.36 (29.09)
C_{max} (pg.mL)*	44.0 (31.9)	44.3 (35.8)	42.9 (32.2)	41.8 (35.5)
t_{max} (h)	0.08 (0.03-1.50)	0.08 (0.03-0.17)	0.08 (0.03-0.17)	0.08 (0.06-0.12)
$t_{½}$ (h)	8.99 (6.46-15.96)	9.17 (5.26-18.42)	9.15 (4.42-20.40)	9.16 (5.63-19.87)

PP population n varies by pharmacokinetic parameter from n = 90 for AUC_{0-t} to n = 75 for t½

Analysis of bioequivalence

For budesonide in the absence of charcoal the test/reference ratio for AUC_{0-t} was 1.014 with 90% CI 0.979, 1.050 and an RMS error of <0.3. For AUC_{0-inf} the ratio was 1.017 with 90% CI 0.981, 1.054 and an RMS error <0.3. For C_{max} the ratio was 1.046 with 90% CI 0.982, 1.113 the RMS error was 0.332.

For budesonide in the presence of charcoal the test/reference ratio for AUC_{0-t} was 1.005 with 90% CI 0.957, 1.056 and an RMS error of <0.3. For AUC_{0-inf} the ratio was 1.012 with 90% CI 0.962, 1.064 and an RMS error <0.3. For C_{max} the ratio was 0.994 with 90% CI 0.949, 1.042 the RMS error was <0.03.

For formoterol in the absence of charcoal the test/reference ratio for AUC_{0-t} was 0.978 with 90% CI 0.940, 1.018 and an RMS error of <0.3. For AUC_{0-inf} the ratio was 0.989 with 90% CI 0.945, 1.035 and RMS error <0.03. For C_{max} the ratio was 0.973 with 90% CI 0.922, 1.026 the RMS error was <0.3.

For formoterol in the presence of charcoal the test/reference ratio for AUC_{0-t} was 0.959 with 90% CI 0.909, 1.012 and an RMS error of <0.3. For AUC_{0-inf} the ratio was 0.952 with 90% CI 0.895, 1.013 and RMS error <0.3. For C_{max} the ratio was 1.020 with 90% CI 0.960, 1.083 the RMS error was <0.3.

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 320/9 µg and Symbicort Turbohaler 400/12 µg were shown to be bioequivalent in respect of both budesonide and formoterol fumarate pharmacokinetic parameters, when administered both with and without charcoal blockade.

Middle Strength – Budesonide/Formoterol Teva Pharma B.V. 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).

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 160/4.5 µg with Symbicort Turbohaler 200/6 µg 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 07.00 hours and 09.00 hours.

The primary pharmacokinetic endpoints were AUC_{0-t} and C_{max} 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)[2] for the comparison of BF Spiromax with Symbicort Turbohaler.

Table 11. 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
a From Wilcoxon Signed Rank test.
b For t_{max} and $t_{1/2}$ this represents the estimated treatment difference.
c RMS for Symbicort Turbohaler is shown.
d For BF Spiromax – Symbicort Turbohaler C_{max} acceptance criteria were widened to (0.698-1.432), for all other comparisons the acceptance criteria were (0.80-1.25)

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

Table 12. 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 t_{max}, this represents the estimated treatment difference.
c RMS for Symbicort Turbohaler is shown.
d For BF Spiromax – Symbicort Turbohaler C_{max} 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 AUC_{0-t}, AUC_{0-inf} or C_{max} either in the presence or absence of charcoal for budesonide or formoterol fumarate. The CIs generated for t_{max} 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, BF 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:

Table 13. 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 08.00 hours and 10.00 hours. 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 160/4.5 µg and Symbicort Turbohaler 200/6 µg.

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 C_{max}, 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 $t_{½}$ and t_{max}.

A higher formoterol C_{max} was observed for BF Spiromax compared with Symbicort Turbohaler. As explained above, 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 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 C_{max} and that a larger, coarser particle size produced a lower C_{max}.

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 C_{max} for the high and middle strength products. Therefore, the applicant stated their intention to use this new fomoterol fumarate formulation (with larger, coarser particles).

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).

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

Study BFS-BE-108 was an open-label, single-dose, randomised, five-way crossover comparison of the pharmacokinetic and safety profiles following two inhalations of BF Spiromax 160/4.5 mcg Inhalation Powder and Symbicort Turbohaler 200/6 mcg, with and without charcoal block in healthy volunteers.

The study was conducted from July to September 2012 at a single investigative centre in France.

Methods

The primary objective of the study was to assess the pharmacokinetic (PK) profiles of budesonide and formoterol administered as two inhalations from BF Spiromax 160/4.5 mcg Inhalation Powder and two inhalations from Symbicort Turbohaler 200/6 mcg, with and without charcoal block, in healthy volunteers. The secondary objectives were to evaluate the safety and tolerability of BF Spiromax and

Symbicort Turbohaler, and to evaluate the intra-subject variability of Symbicort Turbohaler (without charcoal block).

Eligible subjects were men and women, aged 18–45 years, in good general health with; body mass index (BMI) 19 -30 kg/m^2, body weight ≥50 kg; not pregnant, breast feeding, or attempting to become pregnant; agreement by women of childbearing potential to use appropriate contraception; non-smokers for at least one year prior to screening visit and a maximum smoking history of five pack-pack years; willing and able to give informed written consent.

Eligible subjects attended a one day training period where they were trained on device use and tolerability to drug substance was assessed. Following successful completion of the training period, subjects entered a 7 (±2)-day washout period. During Treatment Periods 1-5, all subjects took two inhalations from the DPI device to which they were randomised for each treatment period. Each treatment was followed by a 7 (±2)-day washout period except for the last treatment period. At the end of the washout period after Treatment Periods 1 to 4, the subject was exposed to the next treatment. Safety was monitored by clinical laboratory examinations, 12-lead ECGs, physical examination, vital sign measurements, and adverse events. For the treatments when subjects were randomised to receive co-administration of activated charcoal, a suspension of 5 g activated charcoal in water was administered 2 min before and 2, 62, 122, and 242 min after dose inhalation.

The primary pharmacokinetic endpoints were AUC_t and C_{max} for budesonide and formoterol, t_{max} was a secondary endpoint, additional endpoints were $AUC_{0-\infty}$ and apparent elimination half-life ($t_{1/2}$).

The following treatments were administered: (treatment B was administered twice in each of ten possible treatment sequences):

- Treatment A BF Spiromax 160/4.5 mcg – 2 inhalations
- Treatment B Symbicort Turbohaler 200/6 mcg – 2 inhalations
- Treatment C BF Spiromax 160/4.5 mcg with 5 g activated charcoal suspended in 25 mL water – 2 inhalations
- Treatment D Symbicort Turbohaler 200/6 mcg with 5 g activated charcoal suspended in 25 mL water – 2 inhalations

Results

One hundred and fifty-seven subjects were screened and 90 recruited to the study, two of whom did not receive study medication and are excluded from analysis; eighty six subjects completed the study. Subjects' mean age was 27.7 years (s.d. 7.34) and BMI was 23.5 kg/m2 (s.d. 2.7) fifty-one were male.

Table 14. Pharmacokinetics of budesonide (geometrical mean and cv% for AUC and C_{max}; median and range for t_{max} and $t_{1/2}$)

	BF Spiromax 160/4.5	Symbicort 200/6	BF Spiromax + charcoal 160/4.5	Symbicort + charcoal 200/6
PP population n =	86	86	84	84
AUC_{0-t} (h.pg/mL)	2205 (24)	2438 (27)	1914 (22)	2229 (24)
AUC_{0-inf}(h.pg/mL)	2323 (23)	2534 (26)	2001 (22)	2327 (24)
Cmax (pg.mL)*	1080 (43)	1161 (44)	985 (45)	1071 (41)
tmax (h)	0.08 (0.03-0.5)	0.17 (0.03-1.07)	0.17 (0.03-0.75)	0.17 (0.08-0.75)
t½ (h)	3.9 (2.1-7.7)	4.0 (1.7-9.3)	3.4 (2.2)	3.4 (2.2-5.7)

Table 15. Pharmacokinetics of formoterol (geometrical mean and cv% for AUC and C_{max}; median and range for t_{max} and $t_{1/2}$)

	BF Spiromax 160/4.5	Symbicort 200/6	BF Spiromax + charcoal 160/4.5	Symbicort + charcoal 200/6
AUC_{0-t} (h.pg/mL)	59.07 (25.99)	61.30 (29.97)	45.68 (27.24)	52.08 (29.96)
AUC_{0-inf}(h.pg/mL)	69.34 (23.41)	71.50 (31.11)	52.93 (24.82)	62.92 (26.87)
Cmax (pg.mL)*	21.7 (32.7)	22.3 (32.3)	20.3 (28.9)	21.6 (28.6)
tmax (h)	0.08 (0.03-0.17)	0.08 (0.03-0.25)	0.08 (0.08-0.17)	0.08 (0.03-0.17)
t½ (h)	9.2 (5.4-17.2)	9.3 (4.5-36.1)	8.3 (4.7-25.7)	9.3 (4.1-14.5)

PP population n varies by pharmacokinetic parameter from n = 86 for AUC_{0-t} to n = 67 for t½

Analysis of bioequivalence

For budesonide in the absence of charcoal the test/reference ratio for AUC_{0-t} was 0.9050 with 90% CI 0.874, 0.938 and an RMS error of <0.3. For AUC_{0-inf} the ratio was 0.912 with 90% CI 0.881, 0.944 and an RMS error <0.3. For C_{max} the ratio was 0.931with 90% CI 0.873, 0.993 the RMS error was <0.3.

For budesonide in the presence of charcoal the test/reference ratio for AUC_{0-t} was 0.856 with 90% CI 0.819, 0.895 and an RMS error of <0.3. For AUC_{0-inf} the ratio was 0.857 with 90% CI 0.822, 0.894 and an RMS error <0.3. For C_{max} the ratio was 0.915 with 90% CI 0.851, 0.984 the RMS error was <0.03.

For formoterol in the absence of charcoal the test/reference ratio for AUC_{0-t} was 0.963 with 90% CI 0.928, 0.100 and an RMS error of <0.3. For AUC_{0-inf} the ratio was 0.952 with 90% CI 0.913, 0.993 and RMS error <0.03. For C_{max} the ratio was 0.973 with 90% CI 0.922, 1.026 the RMS error was <0.3.

For formoterol in the presence of charcoal the test/reference ratio for AUC_{0-t} was 0.876 with 90% CI 0.831, 0.923 and an RMS error of <0.3. For AUC_{0-inf} the ratio was 0.855 with 90% CI 0.806, 0.986 and RMS error <0.3. For C_{max} the ratio was 0.935 with 90% CI 0.884, 0.989 the RMS error was <0.3.

Overview of bioequivalence findings

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

Table 16. PK Bioequivalence Summary for BF Spiromax versus Symicort Turbohaler (the two emboldened studies in this table are the two 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

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

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
- 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, investigating 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 dose proportionality for formoterol fumarate between the middle strength products compared with the high strength has been established. The specifications of FPD and delivered dose of the middle strength products are in line with the high strength product.

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.

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 different patient populations, including those where this fixed-dose combination product will be used. The indication proposal from the applicant does not include COPD and children and adolescents with asthma; therefore data in these populations is to be regarded only as supportive for overall inhalation characteristics. This study aimed at showing the appropriateness of the pharmacokinetic findings obtained in healthy volunteers to support equivalence in patients and in other populations with low inspiratory capacity, taking into account the differences in *in vitro* flow rates 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):

- Children and adolescents with asthma aged 6-17 years
- Adults with asthma aged 18-45 years
- Adults with COPD aged >50 years (indication in this population is not applied for in this application)
- Healthy volunteers aged 18-45 years

Overall results obtained from this study are presented below. Results in children and adolescents are not discussed in detail as this age group is not included in the claimed indication for this product.

Table 17. Peak Inspiratory Flow Rates (PIFR, L/min) Generated by Different Patient Groups Post-training Through (placebo) Spiromax and Turbohaler devices (10^{th}, 50^{th} and 90^{th} Percentiles)

Study Group	Turbohaler			Spiromax		
	10^{th}	50^{th}	90^{th}	10^{th}	50^{th}	90^{th}
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 10^{th} percentile was equal to or greater than 50L/min in children, adolescents and adults using both inhalation devices.

The PIFR 90^{th} percentile was between 84-105L/min for all patient groups.

The PIFR 50^{th} percentile was between 60-88L/min for all patient groups.

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

Table 18. Aerodynamic particle size distribution (APSD) over 40, 60 and 90 L/min for 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 proposed product strengths compared with the equivalent strength for the reference product at the aforementioned flow rates have been evaluated and graphically represented below.

Figure 3. Middle Strength Flow Rate Dependency of Total Dose (NGI) and FPD (left: Budesonide; right: Formoterol)

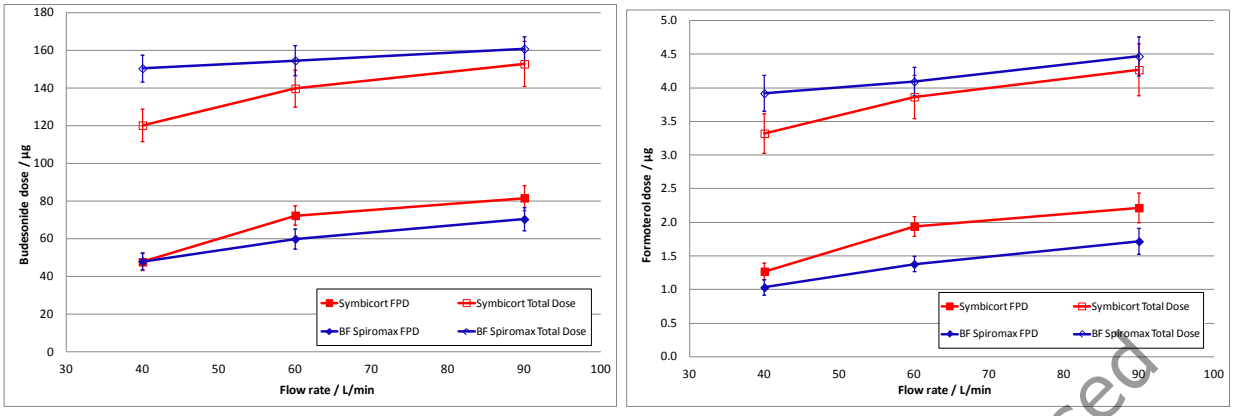
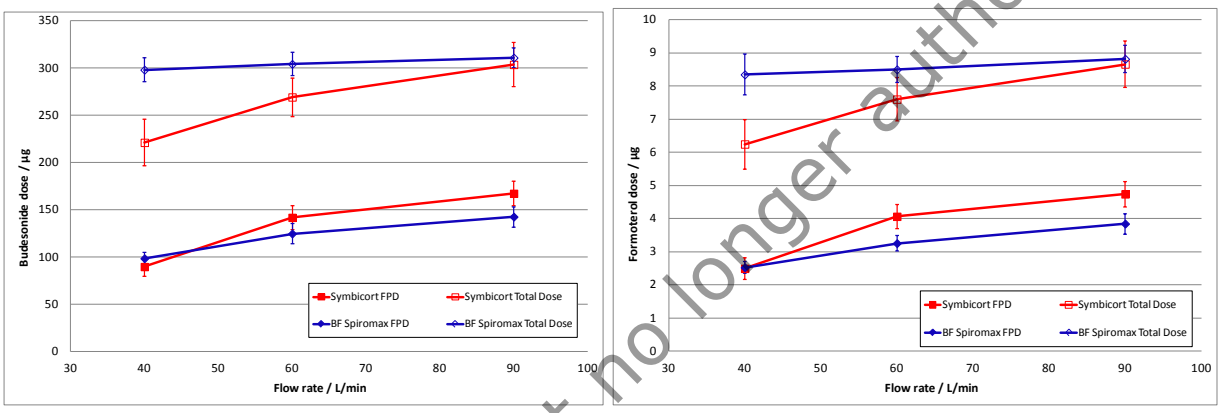


Figure 4. High Strength Flow Rate Dependency of Total Dose (NGI) and FPD (left: Budesonide; right: Formoterol)



Pharmacokinetic interaction studies

No *in vitro*/*in vivo* studies have been submitted. 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 pharmacology

The applicant has not generated any new data relating to the primary pharmacology of the active substances, which is acceptable for this hybrid application.

Secondary pharmacology

The applicant has conducted two studies of the secondary pharmacodynamic action of the combination budesonide/formoterol. Study BFS-AS-106 addressed the effects of the combination primarily on the cardiovascular system in healthy adults thus evaluating the LABA component. Study BFS-AS305 examined the effect of the combination on growth and cortisol excretion in asthmatic children thus evaluating the ICS component. However, as a paediatric indication is not sought the latter study is not represented in this assessment report.

Study BFS-AS-106

This was a randomised, double-blind, double-dummy, cumulative dose, four period crossover study to evaluate the pharmacodynamic effects of BF Spiromax and Symbicort Turbohaler in healthy volunteers. The study was conducted at a single UK centre from October to December 2010.

Methods

The primary objective of the study was to compare the pharmacodynamic, extra-pulmonary, effects of BF Spiromax and Symbicort Turbohaler after cumulative delivered doses of formoterol, administered as 1+1+2+4 inhalations of BF Spiromax low dose compared to Symbicort low dose and BF Spiromax high dose compared to Symbicort high dose in healthy volunteers aged 18 to 45 years. The secondary objective was to evaluate the safety of BF Spiromax and Symbicort after cumulative delivered doses of formoterol.

Eligible subjects were healthy men and women 18 to 45 years of age at screening visit. If female, currently not pregnant, breast feeding, or attempting to become pregnant and was of non-childbearing potential, or using a consistent and acceptable method of birth control. They had a body mass index of 19 to 30 kg/m^2 and a body weight ≥50 kg, resting sitting HR of ≥50 to ≤90 beats per minute; blood pressure of ≤140/90 mmHg; non-smokers for at least 1 year and had a maximum smoking history of five-pack years. Each subject participated in the study for approximately 6 to 8 weeks.

The primary endpoint was change from baseline in corrected QT interval using the Fridericia correction formula (QTcF) at 5 minutes after each of the four cumulative doses; a treatment difference of 10 msec or less was set as the non-inferiority margin.

Secondary endpoints were change from baseline in QTcF at 15 minutes after each of the four cumulative doses; change from baseline in QTcB (Bazett's correction) at 5 and 15 minutes after each of the four cumulative doses; baseline corrected QTcF area under the curve from time 0 to 4 hours (AUC_{0-4hr}) following the administration of the last cumulative dose; baseline corrected QTcB AUC_{0-4hr} following the administration of the last cumulative dose. Heart rate, systolic and diastolic blood pressure measured manually and relevant biochemistry.

Treatments were as shown below, figures in parenthesis are the cumulative dose of formoterol:

- Treatment A: BF Spiromax 80/4.5 mcg and placebo Symbicort Turbohaler (4.5/9/18/36)
- Treatment B: Symbicort Turbohaler 100/6 mcg and placebo BF Spiromax (6/12/24/48)
- Treatment C: BF Spiromax 320/9 mcg and placebo Symbicort Turbohaler (9/18/36/72)
- Treatment D: Symbicort Turbohaler 400/12 mcg and placebo BF Spiromax (12/24/48/96)

Cumulative delivered dose of 36 mcg of formoterol administered as 1+1+2+4 inhalations with 29, 28, and 26 minutes between each set following the first inhalation set. The cumulative dose of formoterol was administered in a double-blinded manner using matched inhalations of BF Spiromax and placebo Symbicort Turbohaler. Each inhalation within a set was to be completed within 30 seconds.

Results

One hundred and twenty-four subjects were screened and fifty-six randomised; fifty-two subjects completed all phases of the study. Subjects' mean age was 28.7 years (s.d. 6.66) and BMI was 24.26 kg/m^2 (s.d. 2.8) thirty-eight were male.

Data for the primary variable QTcF for the low strength (not applied for in this application) comparison are shown in the table and figure below; equivalent data, as well as changes in non-corrected QT interval for the high strength comparison are also presented.

For the lower strength heart rate rose by a maximum of approximately 10 bpm (after the third dose) 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 BF Spiromax and 11.9 mm Hg for Symbicort. Changes in serum potassium over time for the low and high strength comparisons and changes in blood glucose are shown below.

Table 19. QTcF (msec) five minutes post cumulative doses (low strength inhaler) PP population data are mean (s.d)

Dose	**BF Spiromax 80/4.5 mcg**	**Symbicort 100/6 mcg**
1st	4.4 (7.85)	3.3 (10.74)
Difference (90% CI)	2.03 (-1.12, 5.175)	
2nd	5.9 (11.78)	4.9 (12.74)
Difference (90% CI)	0.711 (-2.392, 3.814)	
3rd	7.1 (10.90)	6.6 (13.47)
Difference (90% CI)	0.265 (-2.838, 3.367)	
4th	8.7 (11.71)	9.1 (14.87)
Difference (90% CI)	-0.631 (-3.747, 2.484)	

Figure 5. Mean change from baseline for QTcF intervals over time PP population BF Spiromax 80/4.5 mcg vs. Symbicort 100/60 mcg

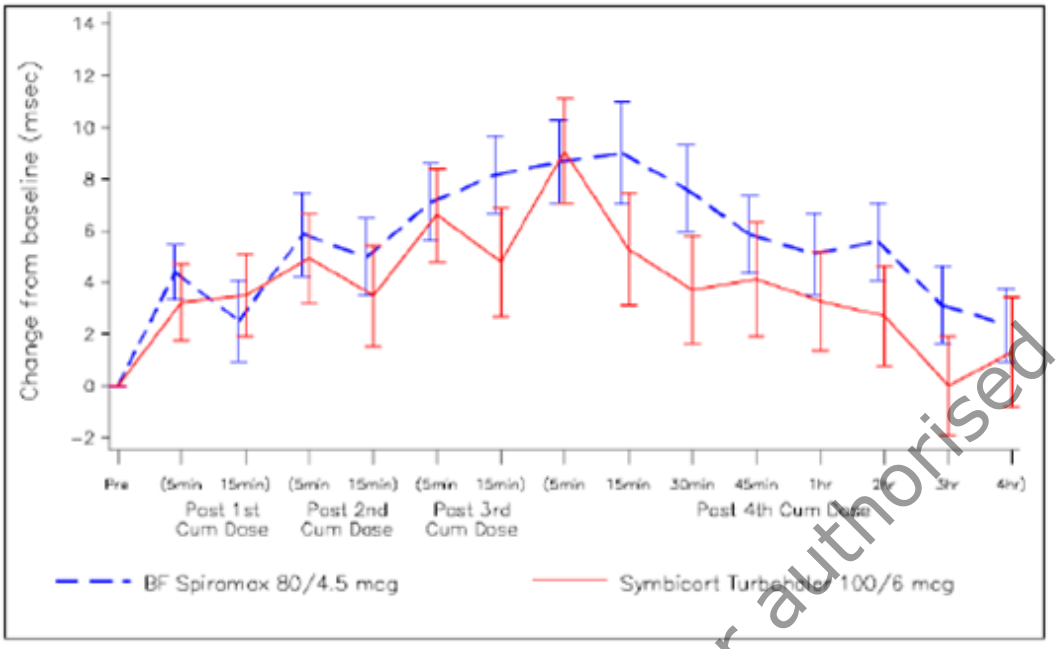


Table 20. QTcF (msec) five minutes post cumulative doses (high strength inhaler) PP population data are mean (s.d)

Dose	BF Spiromax 320/9 mcg	Symbicort 400/12 mcg
1st	3.8 (8.15)	6.5 (8.14)
Difference (90% CI)	-0.342 (-3.470, 2.785)	
2nd	6.1 (10.27)	8.2 (11.55)
Difference (90% CI)	0.285 (-2.843, 3.414)	
3rd	7.2 (11.81)	11.3 (12.30)
Difference (90% CI)	-2.022 (-5.178, 1.134)	
4th	2.7 (21.30)	8.5 (13.77)
Difference (90% CI)	-3.448 (-6.603, -0.293)	

Figure 6. Mean change from baseline for QTcF intervals over time PP population BF Spiromax 320/9 mcg vs. Symbicort 400/12 mcg

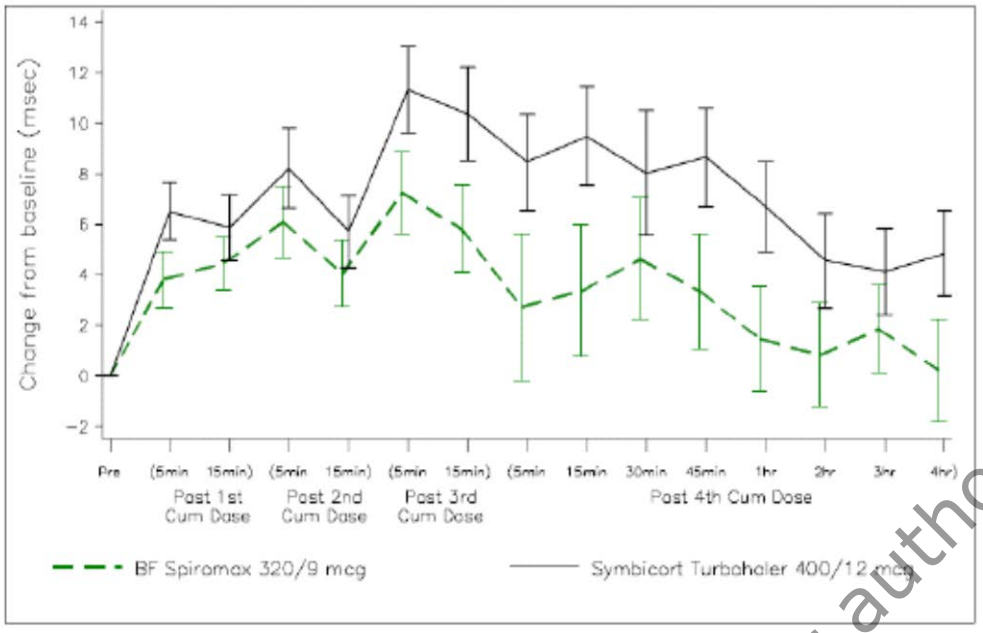


Figure 7. Mean change from baseline for uncorrected QT intervals over time PP population BF Spiromax 320/9 mcg vs. Symbicort 400/12 mcg

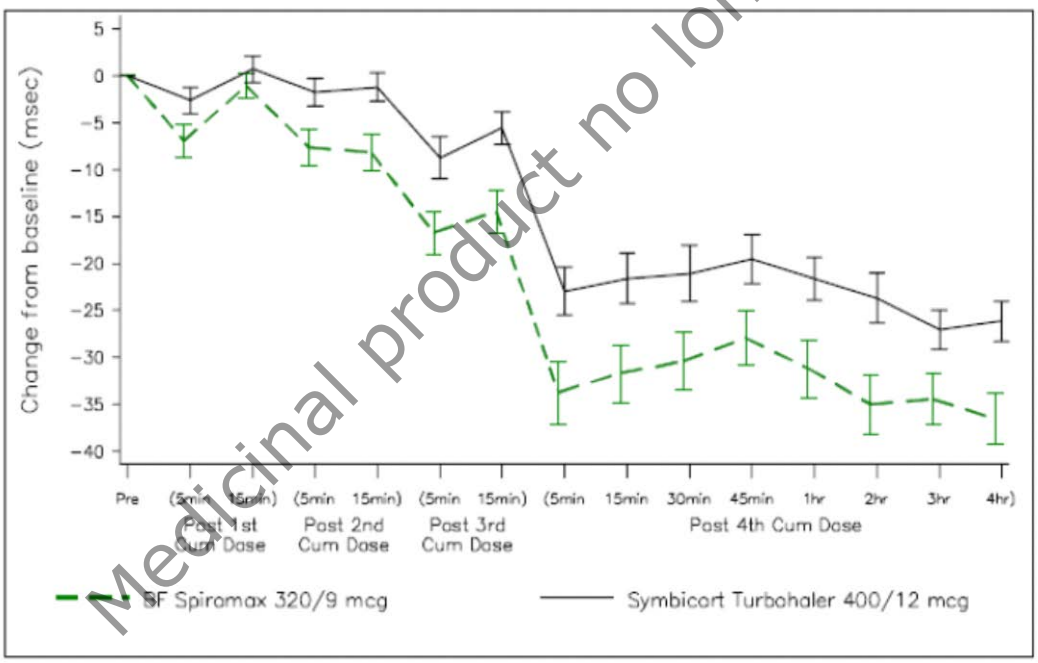


Figure 8. Mean change from baseline for potassium over time PP population BF Spiromax 80/4.5 mcg vs. Symbicort 100/60 mcg

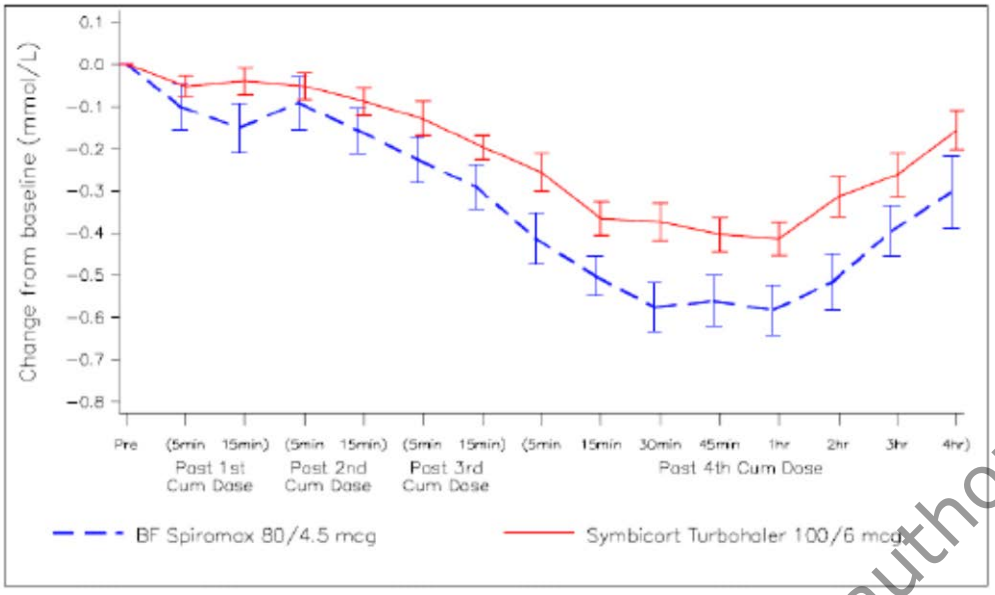


Figure 9. Mean change from baseline for potassium over time PP population BF Spiromax 320/9 mcg vs. Symbicort 400/12 mcg

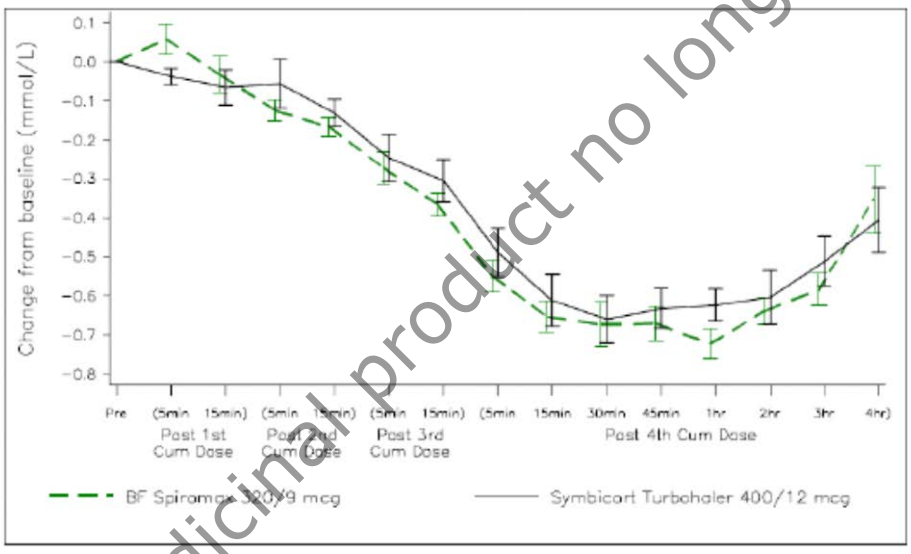


Figure 10. Mean change from baseline for glucose over time PP population BF Spiromax 80/4.5 mcg vs. Symbicort 100/60 mcg

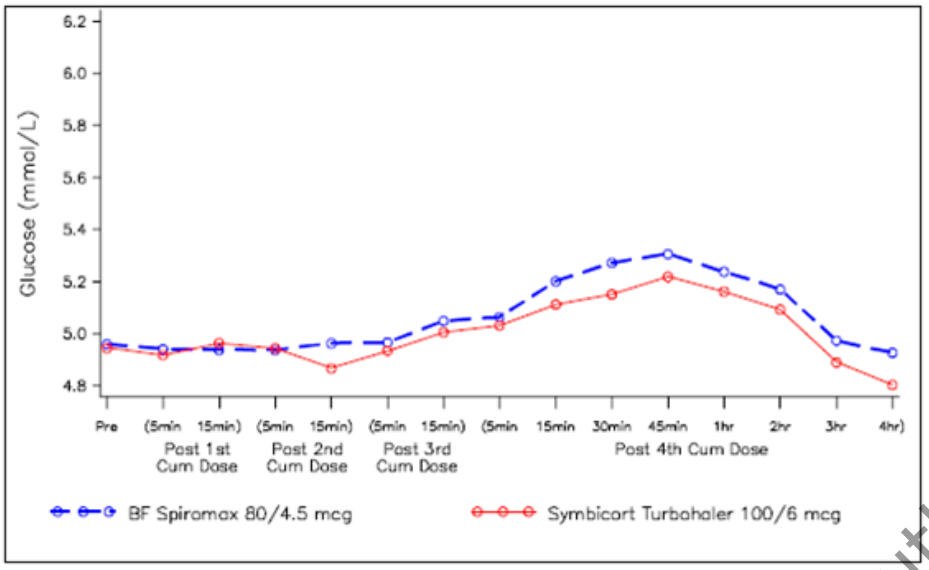
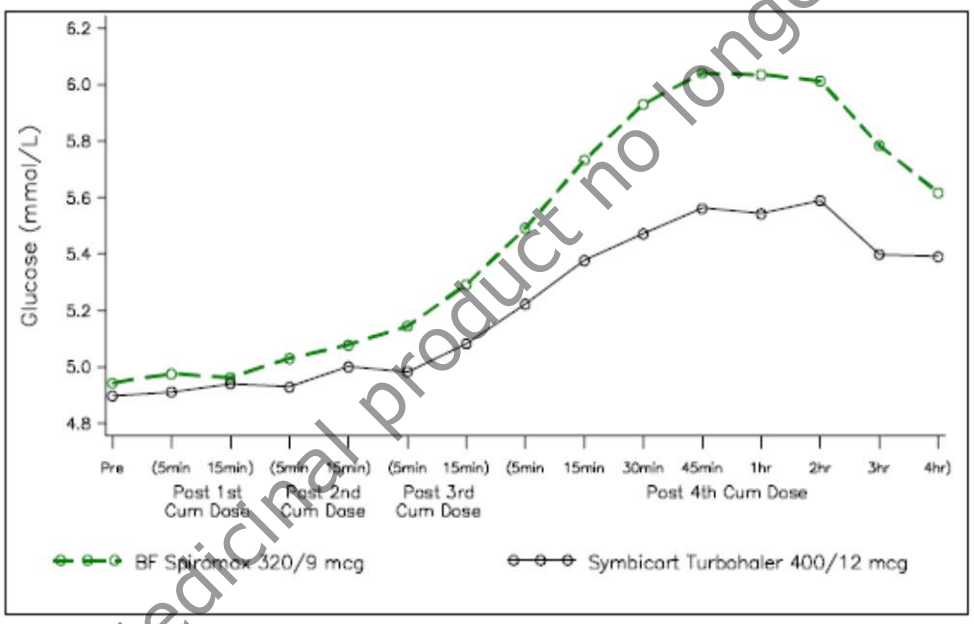


Figure 11. Mean change from baseline for glucose over time PP population BF Spiromax 320/9 mcg vs. Symbicort 400/12 mcg



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 primarily 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 has conducted a well-designed and executed programme of clinical studies to demonstrate the bioequivalence of the BF Spiromax (test) range of products with the reference Symbicort. The difficulty of demonstrating bioequivalence of orally inhaled products is widely acknowledged and this is particularly so for a fixed dose combination for inhalation. The programme involved several clinical trials from pilot, though supportive to pivotal and required reformulation of the test active pharmaceutical ingredient (API) formoterol component. For the high and intermediate strengths bioequivalence for budesonide and formoterol were demonstrated. For a lower strength 80/4.5 mcg bioequivalence of C_{max} for formoterol was not demonstrated, and the applicant does not seek approval for that strength. The applicant proposes to confine the therapeutic indication to use in adults 18 years of age and older only.

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 presented is acceptable.

The applicant submitted additional data on the inhalation characteristics of healthy adult volunteers, adults, adolescents and children with asthma 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:

- 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 relative to healthy volunteers, the mean PIFR achieved by asthma 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 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 Budesonide/Formoterol Teva Pharma B.V. is indicated in adults 18 years of age and older only and in addition section 4.2 states that Budesonide/Formoterol Teva Pharma B.V. 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.

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 confidence intervals not only for formoterol fumarate but also for budesonide and for the middle strength product, with the exception of C_{max} without charcoal for formoterol fumarate. The confidence intervals 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 *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.

The study design, objectives and endpoints of Study BFS-AS-106 are acceptable. 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 C_{max}. 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. The Pharmacodynamic study BFS-AS-106 demonstrated equivalence with the reference product.

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. Additional data provided 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.

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.

The Pharmacodynamic study BFS-AS-106 demonstrates equivalence with the reference product.

2.5. Clinical efficacy

The development of Budesonide/Formoterol Teva Pharma B.V. 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.

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 Spiromax and the corresponding strength of the reference product, Symbicort Turbohaler and supported by a pharmacodynamic study.

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) as equivalence has been demonstrated for the high strength (320/9 µg per dose) and the middle strength (160/4.5 µg per dose) products.

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 long-acting β2 agonist, formoterol fumarate have been assessed in Study BFS-AS-106 (see section 'Pharmacodynamics').

Six-hundred and twenty eight adult healthy volunteers and 77 paediatric patients with persistent asthma received at least one dose of study treatment in the clinical development program for BF Spiromax. In the single-dose PK studies, 268 subjects received high strength, 198 received middle strength and 106 received low strength products. A total of 56 subjects received cumulative doses of high and low strength products in the PD study and 77 subjects received 2-weeks treatment with low strength products in the paediatric study.

The number of subjects and patients exposed is appropriate to the type of development; all strengths were studied and no issues arise from the safety data presented.

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) as equivalence has been demonstrated for the high strength (320/9 µg per dose) and the middle strength (160/4.5 µg per dose) products.

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

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 high dose and the medium dose of Budesonide/Formoterol Teva Pharma B.V. 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 indication and posology of the reference product.

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.

Risk management plan

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

The RMP is acceptable. The following minor points should be taken in account in the next RMP update:

- In part II module SI, due to their differences in indications, the names of the products concerned should be specified for each disease considered.

The CHMP endorsed this advice without changes, but requested to update the Risk Management Plan with the final invented name of the product.

The applicant updated the RMP in line with PRAC comment (minor point) and included the final invented name.

The CHMP endorsed the Risk Management Plan version 1.8 with the following content:

Safety concerns

Table 21. 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 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 breastfeeding women • Use in renal impairment • Use in hepatic impairment • Use in children and adolescents

Pharmacovigilance plan

Not applicable.

Risk minimisation measures

Table 22. Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Systemic	Section 4.4, special warnings and precautions for use, SmPC:	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
glucocorticosteroid effects	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. 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	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	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. 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. xanthinederivatives, steroids and diuretics, may add to a possible hypokalaemic effect of the $beta_2$-adrenoceptor agonist. Particular	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	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. 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 bronchospasm responds to a rapid-acting inhaled bronchodilator and should 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 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	None
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 andolder only. *Section 4.2, Posology and method of administration, SmPC:*	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	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.	
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"	*For DuoResp® Spiromax® and BiResp® Spiromax® 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 *For Vylaer Spiromax, Budesonide/Formoterol Teva, Budesonide/Formoterol Teva Pharma B.V* *Section 4.2, Posology and method of administration, SmPC:* Budesonide / Formoterol Spiromax 320 micrograms / 9.0 micrograms should be used as maintenance therapy only. *Recommended doses:* 1 inhalation twice daily. Some patients may require up to a maximum of 2 inhalations twice daily Prescription-only medicine	None
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*	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	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 threefold 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 (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.	
Use in pregnant or breast feeding women	*Pregnancy* 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 dehydrate 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 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	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	adolescents under the age of 18 years. Prescription-only medicine	

2.8. Product information

2.8.1. 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 has demonstrated 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 with the high strength (320/9 µg per dose) and the middle strength (160/4.5 µg per dose) products 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 when used in line with the approved indication 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.

Risks

Unfavourable effects

The high dose and the medium dose of Budesonide/Formoterol Teva Pharma B.V. 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 indication and posology of the reference product. This is supported also by equivalence shown in the study of extra-pulmonary pharmacodynamic effects, including effects on QT interval.

A risk of "off-label" use in children and adolescents exists and has been addressed in Product Information.

Uncertainty in the knowledge about the unfavourable effects

For the high and middle dose of BF Spiromax (strengths applied for in this submission) it is not expected that the unfavourable effects will differ from those of the reference product.

Benefit-risk balance

Budesonide/Formoterol Teva Pharma B.V. will be an alternative to high dose and medium dose Symbicort Turbohaler available for doctors and patients. However the low dose (80/4.5 micrograms per dose) is not available. This brings in the risk of lack of alternative for down-ward titration of dose when required. The lack of evidence of equivalence in adolescents and children and the non-availability of a lower strength product precludes the use of Budesonide/Formoterol Teva Pharma B.V. in these populations. The risk of "off-label" use in children and adolescents 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 of age and older only and by appropriate labelling.

Discussion on the benefit-risk balance

The high dose and the medium dose of Budesonide/Formoterol Teva Pharma B.V. have been shown to be equivalent in adults to the reference product Symbicort Turbohaler.

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 when this product is used in adults, 18 years of age and older. In respect of 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 these orally inhaled fixed-dose combination products for use in adults are acceptable.

The proposal not to seek an indication for use in children and adolescents is in line with the current data. The risk of "off-label" use in these populations 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 of age and older only and by appropriate product labelling.

The CHMP recommends development of a lower strength of this new fixed-dose combination (80/4.5 micrograms per dose, inhalation powder) in line with the reference product, Symbicort Turbohaler and the development of this lower strength for use in children and adolescents. Therapeutic equivalence in respect of both efficacy and safety and an appropriate benefit/risk balance must be demonstrated in these age groups.

The applicant is strongly encouraged to carry through the proposed development of these products in children and adolescents as soon as possible. The applicant is also encouraged to complete the development of the low strength product for use in both adults and children.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Budesonide/Formoterol Teva Pharma B.V. in the 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), 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 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 agreed 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 submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.