30 January 2020
EMA/83618/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Budesonide/Formoterol Teva Pharma B.V.

International non-proprietary name: budesonide / formoterol fumarate dihydrate

Procedure No. EMEA/H/C/004882/0000

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

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	Area under the curve
Bpm	Beats per minute
BE	Bioequivalence
BF Spiromax	Fixed-dose combination of budesonide and formoterol fumarate in the Spiromax Inhaler
BID	Twice daily
BUD	Budesonide
BMI	Body mass index
CDA	Critical device attribute
CEP	Certificate of suitability to the monographs of the European Pharmacopoeia
CI	Confidence interval
CMA	Critical material attribute
C MAX	Maximum plasma concentration
COPD	Chronic obstructive pulmonary disease
CPP	Critical process parameter
CQA	Critical quality attribute
CRF	Case report form
CSR	Clinical study report
DBP	Diastolic blood pressure
DD	Delivered dose
DoE	Design of experiments
DPI	Dry powder inhaler
DSC	Differential scanning calorimetry
EC	European Commission
ECG	Electrocardiogram
EDQM	European Directorate for the Quality of Medicines
EMA	European Medicines Agency
FDC	Fixed dose combination
FEV1	Forced expiratory volume in 1 second
FPD	Fine particle dose
FU	Follow-up
FVC	Forced vital capacity
GC	Gas chromatography
GCP	Good clinical practice
GMP	Good manufacturing practice
HPA	Hypothalamic pituitary adrenal
HPLC	High performance liquid chromatography
HR	Heart Rate
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS	Inhaled corticosteroid
ITT	Intent-to-treat
KF	Karl Fischer titration
LABA	Long acting beta2 agonist
LC	Label claim
LC-MS/MS	Liquid chromatography-mass spectrometry/mass spectrometry
LLOQ	Lower limit of quantification
LS	Least squares
M	Mean
MDI	Metered dose inhaler
Min	Minute
mL	Milliliter
MMAD	Mass mean aerodynamic diameter
mmHg	Millimetres of mercury

mPEF	Morning peak expiratory flow
NGI	Next generator impactor
OIP	Orally inhaled product
PAPP	Polyester/aluminium/polyester/polypropylene
PEF	Peak expiratory flow
PEFR	Peak expiratory flow rate
PFT	Pulmonary function test
PET	Polyethylene terephthalate
Ph. Eur.	European pharmacopoeia
PK	Pharmacokinetics
PP	Polypropylene
ppm	Parts per million
PSD	Particle size distribution
QC	Quality control
QTPP	Quality target product profile
RH	Relative humidity
RMP	Risk management plan
RSD	Relative standard deviation
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
Sec	Second
SE	Standard error
SEM	Scanning electron microscopy
SmPC	Summary of product characteristics
TEAR	Treatment-emergent adverse events
TSE	Transmissible spongiform encephalopathy
T ½	Terminal phase half-life
Tmax	Time of maximum plasma concentration
UDD	Uniformity of delivered dose
UV	Ultraviolet

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Teva Pharma B.V. submitted on 30 July 2019 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 July 2017. 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, as defined in Article 10 (2)(a) of Directive 2001/83/EC, 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.

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

The applicant applied for the following indication:

Budesonide/Formoterol Teva B.V. is indicated in adults 18 years and above 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 β_2 adrenoceptor agonist) is appropriate:

- in patients not adequately controlled with inhaled corticosteroids and "as needed" inhaled short-acting β_2 adrenoceptor agonists *or*
- in patients already adequately controlled on both inhaled corticosteroids and long-acting β_2 adrenoceptor agonists.

COPD

Symptomatic treatment of patients with COPD with forced expiratory volume in 1 second (FEV_1) < 70% predicted normal (post bronchodilator) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators

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 and bioequivalence studies with the reference medicinal product Symbicort Turbohaler.

The chosen reference product is:

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

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

  - Member State (EEA): Sweden
    - National procedure
- Marketing authorisation number: 16047

- Product name, strength, pharmaceutical form: Symbicort Turbuhaler, 320 mikrogram/9 mikrogram/inhalation, inhalationspulver
- Marketing authorisation holder: AstraZeneca AB
- Date of authorisation: 28-12-2001
- Marketing authorisation granted by:
  - Member State (EEA): Sweden
    - National procedure
- Marketing authorisation number: 17443

Medicinal product authorised in the Union/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(320/9mcg)
- Marketing authorisation granted by:
  - Member State (EEA): Sweden
    - National procedure
- Marketing authorisation number: 16047/17443

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

- Product name, strength, pharmaceutical form: Symbicort Turbohaler 400/12 mcg, Inhalation powder
- Marketing authorisation holder: AstraZeneca UK Limited
- Marketing authorisation granted by:
  - Member State (EEA): United Kingdom
    - National procedure
  - Marketing authorisation number: PL 17901/0200
- Bioavailability study number: BFS-AS-101 / 2008-006163-36

- Product name, strength, pharmaceutical form: Symbicort Turbohaler 100/6 mcg, Inhalation powder
- Marketing authorisation holder: AstraZeneca UK Limited
- Marketing authorisation granted by:
  - Member State (EEA): United Kingdom
    - National procedure
  - Marketing authorisation number: PL 17901/0091
- Bioavailability study number: BFS-AS-102 / 2008-006185-28

- Product name, strength, pharmaceutical form: Symbicort Turbohaler 100/6 Mikrogramm/Dosis

Pulver zur Inhalation

- Marketing authorisation holder: AstraZeneca GmbH
- Marketing authorisation granted by:
  - Member State (EEA): Germany
    - National procedure
  - Marketing authorisation number: 50703.00.00
- Bioavailability study number: BFS-AS-103 / 2009-014496-48

- Product name, strength, pharmaceutical form: Symbicort Turbohaler 160/4.5 Mikrogramm/Dosis Pulver zur Inhalation
- Marketing authorisation holder: AstraZeneca GmbH
- Marketing authorisation granted by:
  - Member State (EEA): Germany
    - National procedure
  - Marketing authorisation number: 50703.01.00
- Bioavailability study number: BFS-AS-104 / 2010-021663-32

- Product name, strength, pharmaceutical form: Symbicort Turbohaler 320/9 Mikrogramm/Dosis Pulver zur Inhalation
- Marketing authorisation holder: AstraZeneca GmbH
- Marketing authorisation granted by:
  - Member State (EEA): Germany
    - National procedure
  - Marketing authorisation number: 50703.02.00
- Bioavailability study number: BFS-AS-105 / 2009-014499-23

- Product name, strength, pharmaceutical form: Symbicort Turbohaler 80/4.5 Mikrogramm and Symbicort Turbohaler 320/9 Mikrogramm/Dosis Pulver zur Inhalation
- Marketing authorisation holder: AstraZeneca GmbH
- Marketing authorisation granted by:
  - Member State (EEA): Germany
    - National procedure
  - Marketing authorisation number: 50703.00.00; 50703.02.00
- Bioavailability study number: BFS-AS-106 / 2010-021655-64

- Product name, strength, pharmaceutical form: Symbicort Turbohaler 320/9 Mikrogramm/Dosis Pulver zur Inhalation
- Marketing authorisation holder: AstraZeneca GmbH
- Marketing authorisation granted by:
  - Member State (EEA): Germany
    - National procedure
  - Marketing authorisation number: 50703.02.00
- Bioavailability study number: BFS-AS-107 / 2010-021656-25

- Product name, strength, pharmaceutical form: Symbicort Turbohaler 200/6 mcg, Inhalation powder
- Marketing authorisation holder: AstraZeneca UK Limited
- Marketing authorisation granted by:
  - Member State (EEA): United Kingdom
    - National procedure
  - Marketing authorisation number: PL 17901/0092
- Bioavailability study number: BFS-AS-108 / 2012-000486-20

- Product name, strength, pharmaceutical form: Symbicort Turbohaler 400/12 mcg, Inhalation powder
- Marketing authorisation holder: AstraZeneca UK Limited
- Marketing authorisation granted by:
  - Member State (EEA): United Kingdom
    - National procedure
  - Marketing authorisation number: PL 17901/0200
- Bioavailability study number: BFS-AS-109 / 2012-000485-37

- Product name, strength, pharmaceutical form: Symbicort Turbohaler 200/6 mcg, Inhalation powder
- Marketing authorisation holder: AstraZeneca UK Limited
- Marketing authorisation granted by:
  - Member State (EEA): United Kingdom
    - National procedure
  - Marketing authorisation number: PL 17901/0092
- Bioavailability study number: BFS-AS-110 / 2011-004207-20

- Product name, strength, pharmaceutical form: Symbicort Turbohaler 80/4.5 Mikrogramm/Dosis Pulver zur Inhalation
- Marketing authorisation holder: AstraZeneca GmbH
- Marketing authorisation granted by:
  - Member State (EEA): Germany
    - National procedure
  - Marketing authorisation number: 50703.00.00
- Bioavailability study number: BFS-AS-305 / 2010-019082-29

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.

Scientific advice

The applicant received Scientific advice on 24 September 2009 (EMEA/H/SA/1371/1/2009/III), 22 April 2010 (EMEA/H/SA/1371/1/FU/1/2010/II), 18 November 2010 (EMEA/H/SA/1371/1/FU/2/2010/I), 22 September 2011 (EMEA/H/SA/1371/1/FU/3/2011/II), 16 February 2012 (EMEA/H/SA/1371/1/FU/4/2012/I), 24 October 2013 (EMEA/H/SA/1371/1/FU/5/2013/PED/II) and 24 September 2015 (EMEA/H/SA/1371/1/FU/6/2015/III) for the development programme supporting the indication granted by the CHMP. The Scientific advice pertained to the following quality and clinical aspects:

- Quality: Acceptability to have the same metered dose label claim as the innovator product, test plan and acceptance limits for delivered dose uniformity through container life, characterisation the aerodynamic particle size distributions and 90% CI limits to establish in vitro bioequivalence between the test product and the reference product, proposed flow rates to compare the in vitro performance, proposed matrixing design for stability studies, data to support the inclusion of the second manufacturing site for commercial production, proposal to use the delivered dose and fine particle dose as the parameters for measuring dose linearity and an equivalence approach for determining dose linearity for multi-strength combination products, acceptability not to perform measurement of mouthpiece deposition, and not conduct stability studies on placebo devices. Acceptability of IVIVC to support an approval of low strength DuoResp Spiromax in adults with asthma. Paediatric development issues.

- Clinical: Design and sufficiency of PK programme for marketing authorisation. Discussion of differences in PK observed between low strength BF Spiromax and Symbicort Turbohaler. Design of a PD study to compare extrapulmonary effects of BF Spiromax and Symbicort Turbohaler after cumulative delivered doses. Studies evaluating inspiratory flow rates in order to bridge findings in healthy volunteer PK studies to the asthma population. Acceptance not to include a formoterol alone arm in the Phase 3 clinical studies. Acceptance not to include a middle strength BF Spiromax Phase 3 clinical study assuming dose linearity for BF Spiromax and Symbicort Turbohaler is demonstrated in vitro. Proposed margin for demonstration of non-inferiority of BF Spiromax to Symbicort Turbohaler in the Phase 3 clinical programme. Proposed sample sizes, patient exposure, duration and safety evaluations for Phase 3. Adequacy of the clinical programme to support the proposed indication. Paediatric development issues.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: John Joseph Borg

The application was received by the EMA on	30 July 2019
The procedure started on	19 August 2019
The CHMP/PRAC Rapporteur's Assessment Report was circulated to all CHMP members on	24 September 2019

The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	03 October 2019
The CHMP/PRAC Rapporteur's updated Assessment Report was circulated to all CHMP members on	10 October 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	17 October 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	29 November 2019
The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	06 January 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	16 January 2020
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. on	30 January 2020

2. Scientific discussion

2.1. Introduction

Budesonide/Formoterol Teva 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 beta-2-adrenoreceptor agonist. This combination of actives substances is already approved both centrally and at national level in several EU countries.

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 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 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 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.

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 micrograms per dose, inhalation powder and

-Budesonide/Formoterol Teva Pharma B.V. 320/9 micrograms per dose, inhalation powder

The proposed indications are in adult only for the:

- Regular treatment of asthma, where use of a combination (inhaled corticosteroid and long-acting beta2-adrenoceptor agonist) is appropriate and
- Symptomatic treatment of patients with Chronic Obstructive Pulmonary Disease (COPD) (FEV1) < 70% predicted normal (post bronchodilator) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators.

Budesonide and formoterol are well-known active substances and a fixed dose combination of budesonide and formoterol has well-documented and demonstrated positive benefit-risk in the claimed indications.

This application has been submitted in accordance with Directive 2001/83/EC Article 10(3) – hybrid application – application for a medicinal product referring to a so-called reference medicinal product with a Marketing Authorisation in a Member State or in the Community on the basis of a complete dossier in accordance with the provisions of Article 8 of Directive 2001/83/EC and which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA.

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

- Symbicort Turbohaler 160Mikrogramm/4.5 Mikrogramm pro Dosis Pulver zur Inhalation and

- Symbicort forte Turbohaler 320 Mikrogramm/9 Mikrogramm pro Dosis Pulver zur Inhalation

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

The development of Budesonide/Formoterol Teva 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 Spiromax1 and the corresponding strength of the reference product, Symbicort Turbohaler.

Budesonide/Formoterol Teva is a duplicate of the centrally approved medicinal product DuoResp Spiromax.

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 and budesonide 320 μg and formoterol (as fumarate dihydrate) 9 μg. The only other ingredient is lactose monohydrate. The product is administered *via* an inhalation-driven multi-dose dry powder inhaler (DPI) with active dose metering known as the Spiromax inhaler. Each inhaler contains either 60 doses (high strength) or 120 doses (low strength) and is foil-wrapped.

2.2.2. Active substance

The finished product contains two well-known active substances, formoterol fumarate dihydrate (a long-acting β_2-agonist), and budesonide (a corticosteroid anti-inflammatory). There are monographs for both active substances for both active substances in the European Pharmacopoeia (Ph. Eur.).

Budesonide

General Information

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

The chemical structure of budesonide is shown in Figure 1.

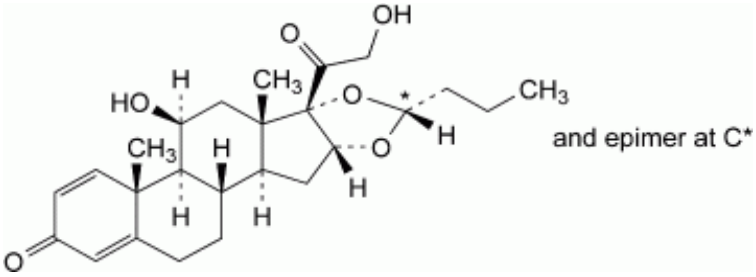


Figure 1: budesonide structure

Manufacture, characterisation and process controls

As there is a monograph for budesonide in the European Pharmacopoeia, the single manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) which has been provided within the current Marketing Authorisation Application. The information provided regarding the manufacturing process and the control of the active substance was assessed and approved by the European Directorate for the Quality of Medicines. Satisfactory quality of budesonide is ensured through the CEP. Budesonide is micronized by a separate manufacturer before formulation.

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.

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

Specification

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.

Analytical data demonstrating compliance with the drug substance specification have been provided for 3 batches of budesonide.

Stability

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 of 60 months in the proposed container at a temperature not exceeding 25 °C.

Formoterol Fumarate Dihydrate

General Information

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

The chemical structure of formoterol fumarate dihydrate is shown in Figure 2.

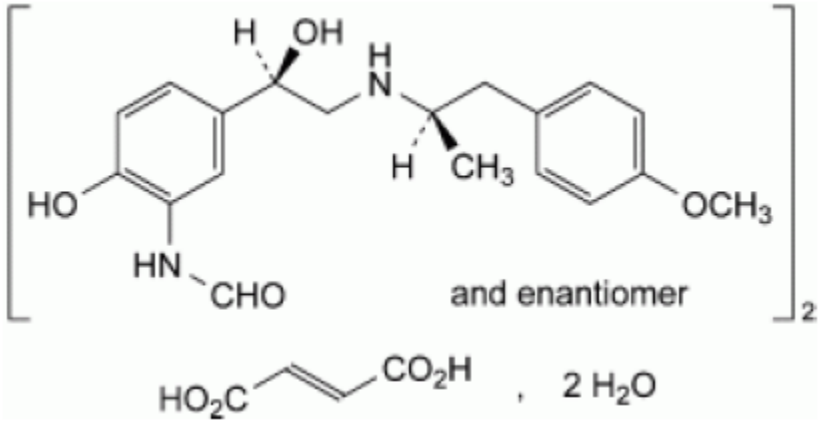


Figure 2: formoterol fumarate dihydrate structure

Manufacture, characterisation and process controls

As there is a monograph for formoterol fumarate dihydrate in the European Pharmacopoeia, the manufacturer of the active substance has been granted Certificate of Suitability of the European Pharmacopoeia (CEP) which has been provided within the current Marketing Authorisation Application. The information provided regarding the manufacturing process and the control of the active substance was assessed and approved by the European Directorate for the Quality of Medicines. Satisfactory quality of the active substance is ensured through the CEP. Formoterol fumarate dihydrate is supplied by a single manufacturer and micronized by a separate manufacturer before formulation.

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.

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

Specification

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.

Analytical data demonstrating compliance with the drug substance specification have been provided for 3 batches of formoterol fumarate dihydrate.

Stability

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 of 60 months in the proposed container at a temperature not exceeding 25 ºC.

2.2.3. Finished medicinal product

Pharmaceutical development

Description of the product and Pharmaceutical Development

The finished product is a fixed dose combination of budesonide and formoterol fumarate dihydrate (formoterol) drug substances with lactose monohydrate (lactose) as the excipient. The product is presented in an inhalation-driven multi-dose dry powder delivery device called the Spiromax inhaler.

The objective was to develop a dry powder for inhalation containing a fixed dose combination of formoterol fumarate dihydrate, a selective and long acting β_2-agonist bronchodilator, and budesonide, a corticosteroid anti-inflammatory, to treat the symptoms of asthma and COPD. The product is to be delivered *via* the Spiromax inhaler, an inhalation-driven multi-dose dry powder delivery device. The product is designed to have an equivalent performance to the reference product, Symbicort Turbohaler. As such, Budesonide Formoterol Teva Pharma B.V. has been developed following the EMA

"Guideline on the requirements for clinical documentation for orally inhaled products including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease in adults and for the use in the treatment of asthma in children and adolescents" (CPMP/EWP/4151/00 Rev. 1). Akin to the reference product, the formulation is a simple combination of the two active substances and lactose.

The principles of Quality by Design were applied to the pharmaceutical development, although no design space was applied for and manufacture and validation are carried out classically. The applicant defined key parameters of the reference product (flow resistance, uniformity of delivered dose (UDD) and aerodynamic particle size distribution (APSD). Pharmacokinetic studies were carried out to establish relationships between these parameters and the *in vivo* performance (bioequivalence) of each active substance. A quality target product profile (QTPP) was then defined for the finished product 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 both 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

The manufacturing process consists of 4 main parts: 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 relevant guidelines. Validation data was provided for three batches of each strength product 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 low (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 each strength of finished product stored under long term conditions (25 ºC / 60% RH) for up to 18 months and under accelerated conditions (40 ºC / 75% RH) for up to 6 months according to the ICH guidelines were provided. The batches of finished product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

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

Samples were tested according to the release specifications except that slightly wider limits were 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. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

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

2.3.2. Pharmacology

Primary pharmacodynamic studies

Budesonide

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

Budesonide was shown to inhibit the adhesion of neutrophils and monocyte/macrophages to the capillary endothelial cells in inflamed tissue, block the effect of macrophage migration inhibitory factor and inhibit phospholipase A2 activity, thereby reducing the formation of prostaglandins and leukotrienes in the local tissue.

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

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

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

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

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

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

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

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

Formoterol

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

In [^{125}I] iodocyanopindolol-labelled bronchial membranes, formoterol and salmeterol (a β2-adrenergic receptor agonist) induced high-affinity states of the ß2-receptor, the former inducing a higher percentage

(57 versus 28). Formoterol and salmeterol were highly selective for the ß2- versus ß1-subtype (pK_i values were 8.2 and 6.25, and 8.3 and 5.7, respectively). Albuterol (a β2-adrenergic receptor agonist) and fenoterol (a β2-adrenergic agonist) were less selective for the ß2- versus ß1-subtype (pKI values were 5.83 and 4.71, and 6.33 and 5.67, respectively; Roux, 1996).

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

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

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

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

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

The effects of formoterol on rat and guinea pig hypersensitivity reactions and on mouse IgE antibody formation were investigated. The inhibitory effect of intravenously and orally administered formoterol on (mouse) IgE-mediated 24-hour passive cutaneous anaphylaxis (PCA) in rats was 6.3 and 33 times, respectively, more potent than that of salbutamol (a short-acting β2-adrenergic receptor agonist). This action was antagonised by pretreatment with propranolol (a sympatholytic non-selective β blocker). The dose of formoterol which inhibited PCA had no effect on histamine- and 5-hydroxytryptamine (5HT)-induced skin reactions. Formoterol, administered intravenously or orally, inhibited (guinea pig) IgE-mediated 8-day PCA in guinea pigs. In the isolated guinea pig lung, both formoterol and salbutamol exhibited dose-dependent inhibition of antigen-induced histamine release. However, in the isolated rat mesenterium these two drugs showed only partial inhibition of antigen-induced mast cell degranulation. Neither formoterol nor salbutamol affected the hapten-specific IgE antibody response in female mice (Tomioka, 1981).

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

Combination studies

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

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

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

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

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

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

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

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

Secondary pharmacodynamic studies

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

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

Safety pharmacology programme

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

Pharmacodynamic drug interactions

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

2.3.3. Pharmacokinetics

Pharmacokinetic studies

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

Methods of analysis

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

Absorption

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

An isolated and perfused rat lung model with negative pressure ventilation was used in further lung absorption experiments. The total recovery of budesonide in the perfusate, trachea and lung tissue was 94% of the administered dose. The high absorption rate of budesonide, in combination with a relatively low extent of air-to-blood absorption, suggested that the drug was bound to the lung tissue. The lung-tissue affinity of budesonide was demonstrated and measured using the isolated and perfused lung model but was not detected from the Caco-2 cell monolayer apparent permeability values obtained from *in vitro* transport studies. The lung affinity of budesonide after intratracheal administration to isolated perfused rat lungs was also reported (Tronde, 2003).

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

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

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

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

Distribution

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

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

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

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

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

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

Metabolism

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

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

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

Excretion

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

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

Pharmacokinetic drug interactions

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

Other pharmacokinetic studies

No other pharmacokinetic studies have been reported in this application. This was considered acceptable by the CHMP.

2.3.4. Toxicology

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

Single dose toxicity

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

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

The LD_{50} values of budesonide and formoterol are as follows (taken from the applicant's non-clinical overview):

Table 6: BUDESONIDE

Species	LD_{50}	Route	Effects
mouse	124 mg/kg	intravenous	altered sleep time, somnolence, convulsions
mouse	4750 mg/kg	oral	altered sleep time, somnolence
mouse	1700 mg/kg	oral	somnolence, weight loss
mouse	179 mg/kg	intraperitoneal	altered sleep time, somnolence

mouse	113.8 mg/kg	intraperitoneal	somnolence, weight loss
mouse	53.6 mg/kg	subcutaneous	altered sleep time, somnolence
rat	96.9 mg/kg	intravenous	altered sleep time, convulsions
rat	2435.9 mg/kg	oral	somnolence, weight loss
rat	>3200 mg/kg	oral	weight loss
rat	138 mg/kg	intraperitoneal	altered sleep time, changes in spleen
rat	58.4 mg/kg	subcutaneous	altered sleep time, changes in spleen
dog	173 mg/kg	subcutaneous	ulceration or bleeding from stomach, diarrhea, changes in spleen

Table 7: FORMOTEROL

Species	LD_{50}	Route	Effects
mouse	71 mg/kg	intravenous	cardiac arrhythmia, acute pulmonary edema, dyspnea
mouse	6700 mg/kg	oral	cardiac arrhythmia, acute pulmonary edema, dyspnea
mouse	210 mg/kg	intraperitoneal	cardiac arrhythmia, acute pulmonary edema, dyspnea
mouse	640 mg/kg	subcutaneous	cardiac arrhythmia, acute pulmonary edema, dyspnea
rat	3130 mg/kg	oral	cardiac arrhythmia, acute pulmonary edema, dyspnea
rat	98 mg/kg	oral	cardiac arrhythmia, acute pulmonary edema, dyspnea
rat	170 mg/kg	intraperitoneal	cardiac arrhythmia, acute pulmonary edema, dyspnea
rat	1 g/kg	subcutaneous	cardiac arrhythmia, acute pulmonary edema, dyspnea

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

Repeat dose toxicity

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

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

formoterol. Thus, the studies conducted were considered adequate to evaluate the toxicity of formoterol in terms of its local (respiratory) and systemic effects.

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

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

Genotoxicity

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

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

Carcinogenicity

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

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

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

Reproduction Toxicity

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

<u>Fertility and early embryonic development</u>

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

<u>Embryo-fœtal development</u>

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

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

Combination: The budesonide and formoterol combination was shown to be teratogenic in rats following inhalation exposure to high doses. In an embryo-fetal development study, rats were exposed to a combination of budesonide/formoterol (in a Symbicort HFA pMDI formulation) by nose-only inhalation at actual doses of 2.5/ 0.14, 12/0.66 and 80/4.4 µg/kg/day from Days 6 to 16 of gestation. Deposited doses of budesonide/formoterol for low, mid, and high dose groups were 0.24/0.014, 1.01/0.057 and 6.8/0.39 µg/kg/day, respectively. The mid and high doses were found to be teratogenic. An external malformation, umbilical hernia, was observed in a single fetus at the mid dose and 2 fetuses at the high dose. These incidences (of 0.4 and 0.9%) exceeded the mean historical control incidence of 0.01%. A visceral malformation, aortic arch: right sided, was observed in one fetus in the high dose group. Fused stemebra was also observed in a single fetus in the high dose group. The relationship of these findings to treatment was unclear. Incidences of no or incomplete ossification were increased in the high dose group. The incidence of a 14th right rib was reported to be higher in the treatment groups. Maternal toxicity was evident in the high dose group.

Prenatal and postnatal development, including maternal function

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

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

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

Toxicokinetic data

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

Local Tolerance

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

Other toxicity studies

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

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

Impurities: The impurity profiles of the Symbicort Turbohaler 80 microgram/4.5 microgram/inhalation, inhalation powder and budesonide/formoterol Spiromax 80/4.5, 160/4.5, 320/9 µg per dose, inhalation powder products are reported to be similar. The impurities levels were reported to be below the

qualification threshold, as defined by the ICH Note for Guidance on Impurities in New Drug Products (CPMP/ICH/2738/99) and should not cause any safety concerns.

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

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

2.3.5. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment studies were submitted. This was justified by the applicant as the introduction of Budesonide/Formoterol Teva Pharma B.V. manufactured by Teva Pharma B.V. is considered unlikely to result in any significant increase in the combined sales volumes for all budesonide / formoterol fumarate dihydrate containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar.

2.3.6. Discussion on non-clinical aspects

Pharmacology, pharmacokinetics and toxicology studies in vitro, ex vivo and in vivo have been conducted with budesonide and formoterol alone and in combination. The applicant has presented a review based on literature reports of budesonide and formoterol activity alone and in combination.

No safety pharmacology studies and pharmacodynamic drug interactions have been provided by the applicant. This is considered acceptable by the CHMP since this information is already known from the clinical use of the two components. Further, pharmacodynamic drug interactions are well characterised and are described in relevant sections of the SmPC.

The pharmacokinetics, absorption, distribution, metabolism and excretion of budesonide and formoterol were investigated through a series of in vitro, ex vivo and in vivo studies in the mouse, rat, rabbit, dog and human. The applicant described ADME profiles of budesonide and formoterol based on FDA assessments of previous applications and published literature reports. This is considered acceptable by the CHMP since the pharmacokinetics of both formoterol and budesonide are clinically well characterised.

The toxicology studies were taken from the FDA Pharmacology Reviews of the Symbicort Turbohaler reference medicinal product (FDA, 2001; FDA 2006).

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 and 320/9 µg per dose, inhalation powder products are considered unlikely to present a risk to the environment when use as prescribed.

Therefore, based on 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 the approved therapeutic indications.

2.3.7. Conclusion on the non-clinical aspects

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

2.4. Clinical aspects

2.4.1. Introduction

The development of this new fixed-dose combination orally inhaled product (OIP) follows the CHMP Guideline on OIPs (CPMP/EWP/4151/00 Rev. 1) and aims to demonstrate therapeutic equivalence of this new product to the reference product authorised in a Member State or in the Community on the basis of a complete dossier. The development is based on the demonstration of pharmacokinetic equivalence between each strength of this fixed-dose combination, BF Spiromax and the corresponding strength of the reference product, Symbicort Turbohaler.

Budesonide (a corticosteroid) and formoterol fumarate dihydrate (a long-acting β2-agonist) are established drug substances and are the subjects of monographs in the European Pharmacopoeia. This combination of drug substances has previously been authorised as an inhalation drug product; Symbicort Turbohaler inhalation powder.

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.

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 8: Tabular overview of clinical studies

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

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

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

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

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

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

2.4.2. Pharmacokinetics

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 and discussed below.

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/m2 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 Cmax in the ANOVA crossover model exceeded 0.30, indicating high intra-subject variability, the acceptance criteria for Cmax could be widened to a maximum of (0.6984, 1.4319) in line with the CHMP Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr 2012). Comparison of 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 5g activated charcoal in water was administered 2 minutes before and 2, 62, 122, and 242 minutes after dose inhalation.

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

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

- area under the plasma concentration-time curve from time zero to the last quantifiable concentration as measured up to 24 hours post-dose (AUC_{0-t}) and
- maximum observed plasma concentration (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 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 AUClast were contained within the acceptance limits of 0.8, 1.25. For the secondary endpoints $AUC_{0\text{-}inf}$ 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 Cmax which was slightly higher for BF Spiromax than for Symbicort Turbohaler with the 90% CI for the ratio just outside the acceptance range (0.95, 1.30).

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

This study was a single dose, four-period crossover study set up to compare the pharmacokinetic profiles of budesonide and formoterol fumarate following administration of BF Spiromax 320/9 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 9: 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 10: 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 Cmax for formoterol fumarate as the 90% CIs for all ratios were marginally outside the accepted bioequivalence range (0.8, 1.25) – see the table above. However, in the presence of charcoal blockade, bioequivalence was demonstrated for all three variables (90% CIs for the ratios were all contained within (0.8, 1.25).

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

Table 11: Systemic Exposure in BFS-AS-105 (ITT population)

Data shown are Geometric Mean (CV%)	N	BUD		FOR	
		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 12: 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 13: 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 14: 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 t_{max} and $t_{1/2}$, this represents the estimated treatment difference.

Table 15: Statistical Comparison of FOR after First and Second Administration of BF Spiromax and Symbicort Turbohaler in Study BFS-AS-107 (PP population)

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

BE = bioequivalence

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

Pivotal pharmacokinetic study 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 Turbohaler (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.

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/m2, 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/m2 (s.d. 2.8) forty-eight were male.

Table 16: Pharmacokinetics of budesonide (geometrical mean and cv% for AUC and Cmax; 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 $t_{½}$

Table 17: Pharmacokinetics of formoterol (geometrical mean and cv% for AUC and Cmax; 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 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)[1] for the comparison of BF Spiromax with Symbicort Turbohaler.

Table 18: Statistical Comparison of PK Parameters of BUD in Study BFS-AS-104 (PP populations)

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

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

Table 19: 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 20: 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 Cmax, suggested that a change in the micronisation process for the drug substance, to produce a larger particle size, might enable the achievement of pharmacokinetic bioequivalence for the formoterol fumarate comparisons of test and reference products.

The findings were as follows:

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

$_{inf}$ were contained within (0.8, 1.25); however, C_{max}, for both batches was not contained within (0.8, 1.25). Both of these batches utilised the original formoterol fumarate drug substance;

- For batch B of BF Spiromax, the systemic availability of plasma formoterol fumarate was comparable with Symbicort Turbohaler and the 90% CIs for the ratios of AUC_{0-t}, AUC_{0-inf} and Cmax 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 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.

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 21: 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 22: 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 23: 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 than 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 or in patients with COPD.

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

Taking the above into account, the applicant submitted data on the inhalation characteristics of healthy adult volunteers (aged 18 to 45 years), adults (18 to 45 years), adolescents 12 to 17 years) and children (6 to 11 years) with asthma and adults over 50 years of age with COPD in order to bridge the findings in the clinical pharmacology studies in healthy volunteers to different patient populations, including those where this fixed-dose combination product will be used. The indication proposal from the applicant does not include children and adolescents; therefore, data in this population 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 with chronic obstructive pulmonary disease and in other populations with low inspiratory capacity, considering 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
- 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 24: 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

Study Group	Turbohaler			Spiromax		
	10th	50th	90th	10th	50th	90th
Adult Asthma (18-45 years; n=50)	54	82	94	66	88	104
COPD (50+ years; n=50)	38	60	84	45	68	93
Healthy volunteers (18-45 years; n=50)	77	92	102	83	104	105

Healthy volunteers and patients were able to generate a slightly higher inspiratory flow rate from the Spiromax device than from the Turbohaler device.

In asthma, the 10th percentile was equal to or greater than 50L/min in children, adolescents and adults using both inhalation devices.

In COPD, the 10th percentile was approx. 40L/min through both devices.

The PIFR 90th percentile was between 84-105L/min for all patient groups (asthma and COPD).

The PIFR 50th percentile was between 60-88L/min for all patient groups (asthma and COPD).

Few subjects had a mean PIFR below 40L/min – with no clustering by age or asthma severity (as defined by the measurement of forced expiratory volume in one second (FEV_1) percent predicted

Table 25: 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)

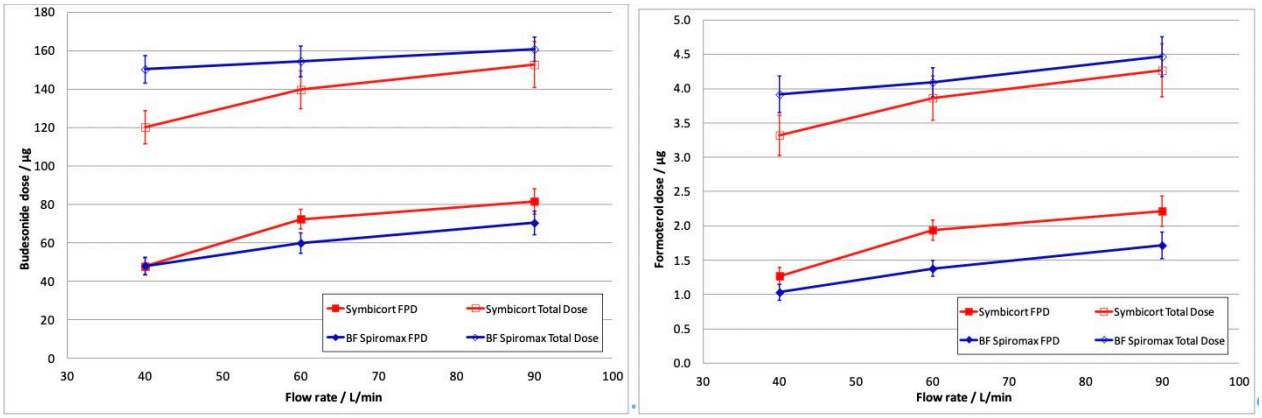
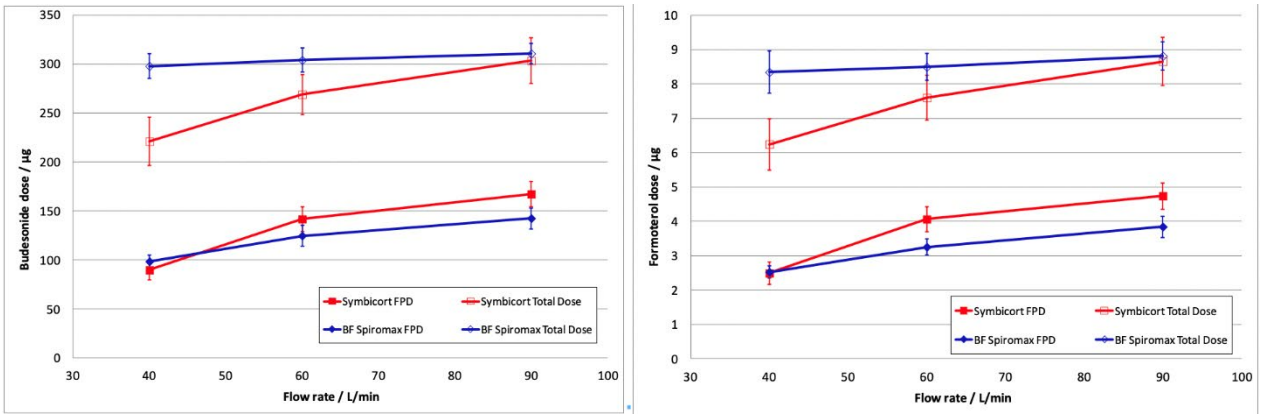


Figure 4. : High Strength Flow Rate Dependency of Total Dose (NGI) and FPD (left: Budesonide; right: Formoterol)



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 than 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 accepted by CHMP.

Secondary pharmacology

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

Study BFS-AS-106

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/m2 (s.d. 2.8) thirty-eight were male.

Data for the primary variable QTcF for the low strength 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 26: 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

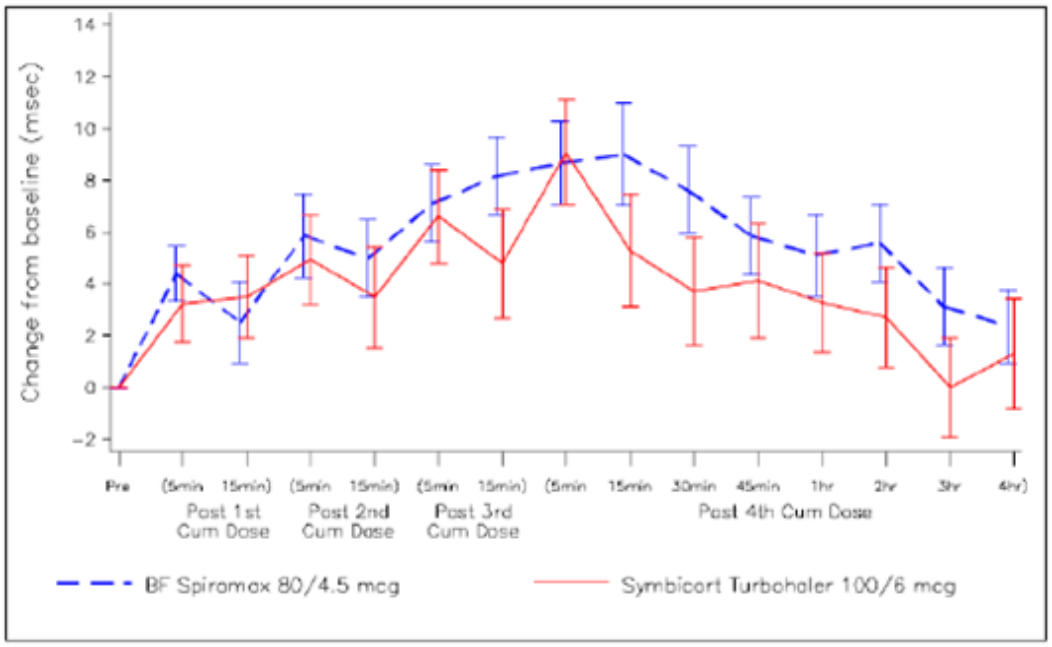


Table 27: QTcF (msec) five minutes post cumulative doses (high strength inhaler) PP population data are mean (s.d)

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

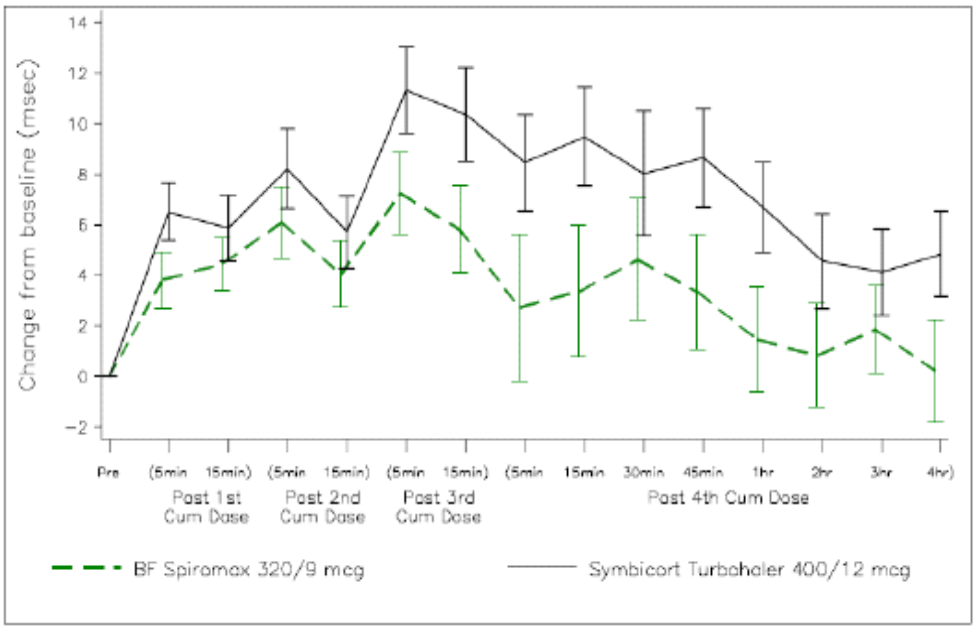


Figure 7. Mean change from baseline for uncorrected QT intervals over time PP population BF Spiromax 320/9 mcg vs. Symbicort 400/12 mcg

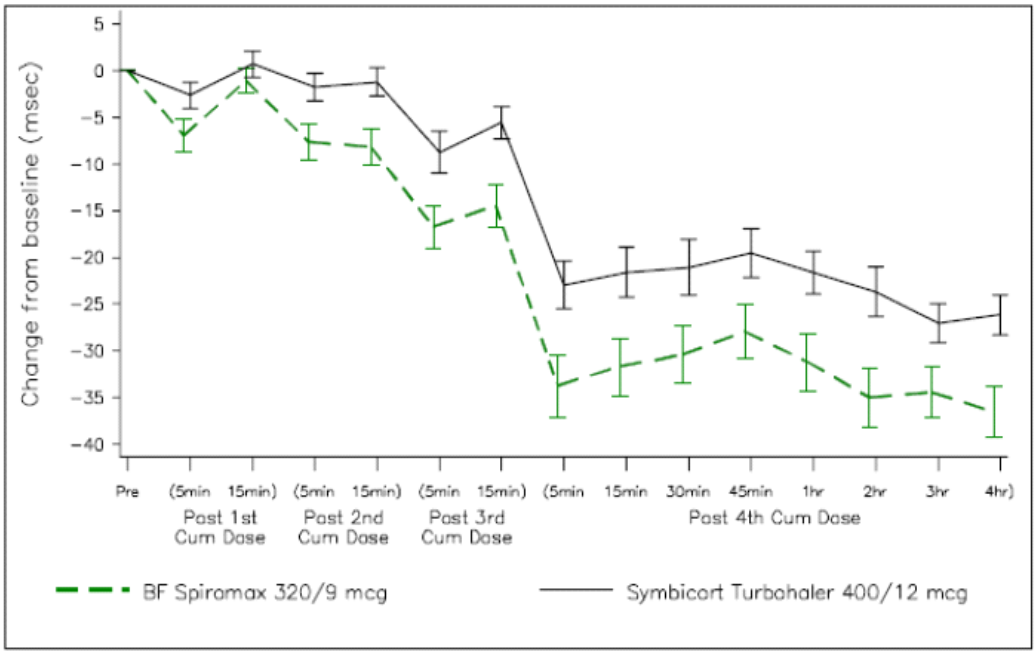


Figure 8. Mean change from baseline for potassium over time PP population BF Spiromax 80/4.5 mcg vs. Symbicort 100/60 mcg

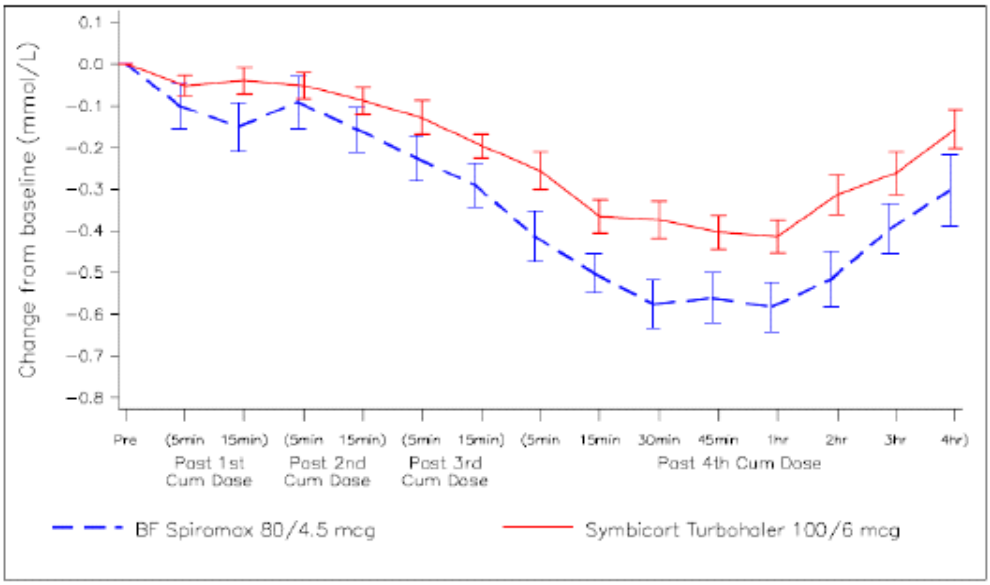


Figure 9. Mean change from baseline for potassium over time PP population BF Spiromax 320/9 mcg vs. Symbicort 400/12 mcg

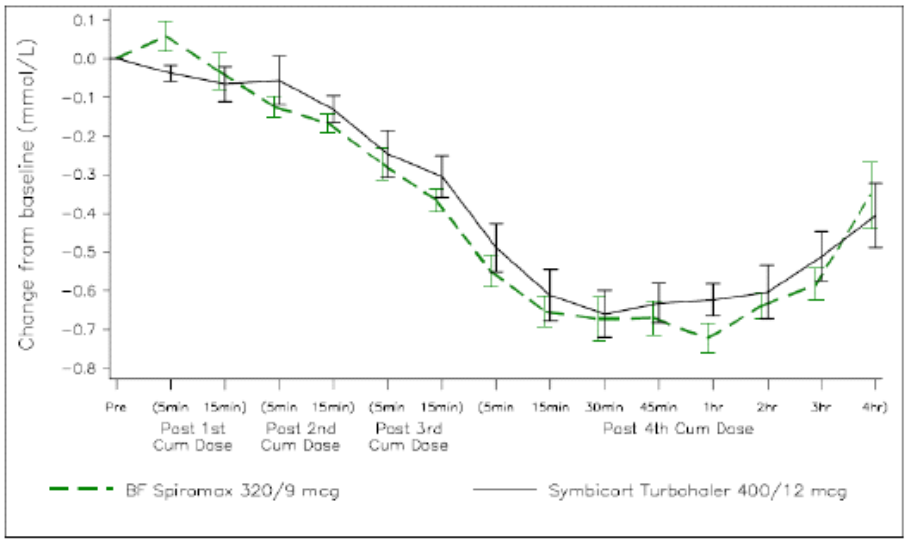


Figure 10. Mean change from baseline for glucose over time PP population BF Spiromax 80/4.5 mcg vs. Symbicort 100/60 mcg

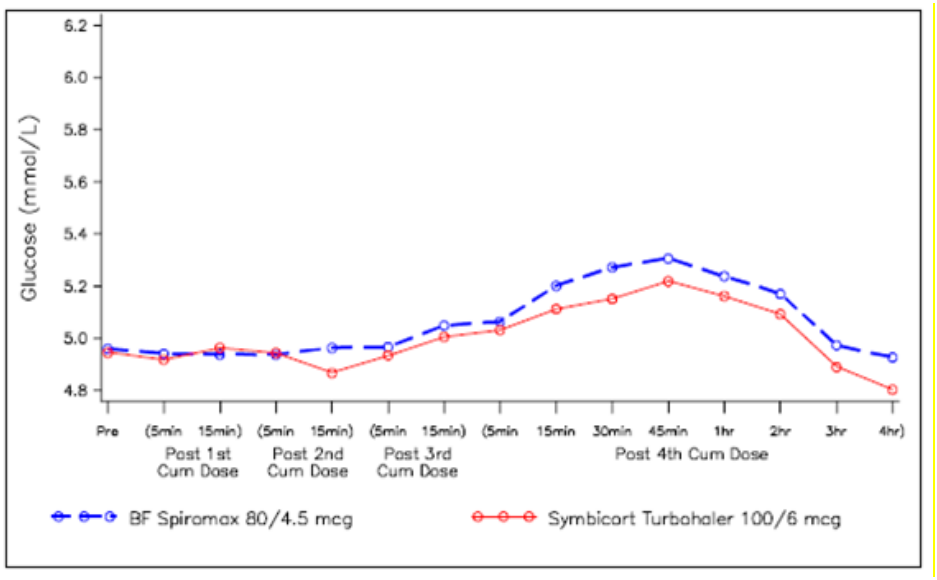
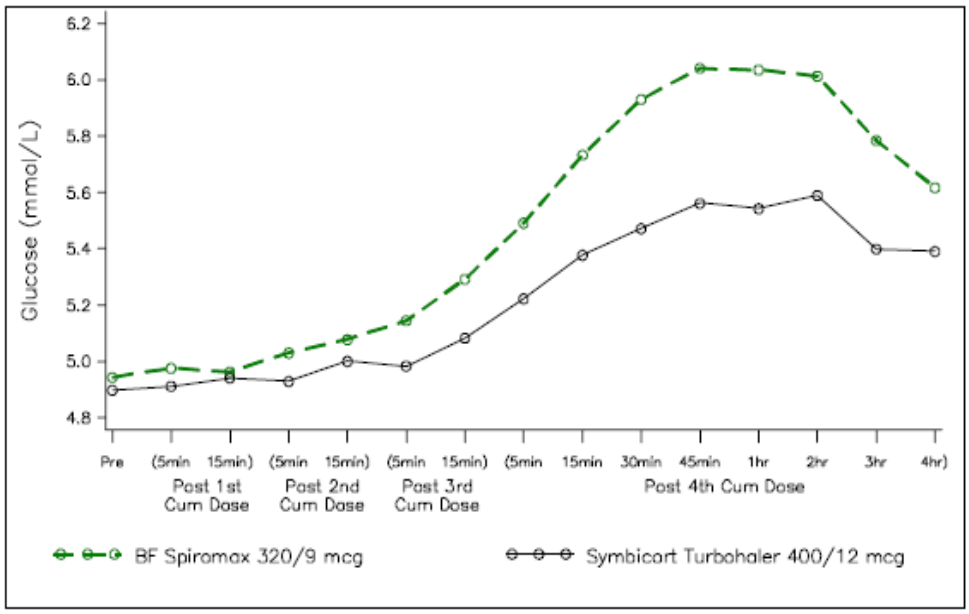


Figure 11. Mean change from baseline for glucose over time PP population BF Spiromax 320/9 mcg vs. Symbicort 400/12 mcg



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 development program of clinical studies to demonstrate the bioequivalence of the BF Spiromax (leading application) 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 program 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.

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

The CHMP concluded the following:

- Regarding the use in COPD, it would appear that regardless of age and underlying disease severity, children, adolescents and adults with asthma, as well as patients with COPD can achieve inspiratory flow rates through both the Spiromax device and Turbohaler device.
- While flow through both devices was lower in patients with asthma or COPD relative to healthy volunteers, the mean PIFR achieved by asthma and COPD patients was over 60 L/min, flow rates at which the Spiromax device and the Turbohaler device are known to deliver comparable amounts of drug to the lungs 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.

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.

2.5. Clinical efficacy

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

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

2.5.1. Discussion on clinical efficacy

The clinical development was performed in line with the CHMP Guideline on orally inhaled products (CHMP/EWP/4151/00 Rev. 1). The clinical development of Budesonide/Formoterol Teva Pharma B.V. (duplicate of DuoResp 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.

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

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.

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 PK studies were all single dose crossover studies and therefore provide limited safety information. Nevertheless, the nature and intensity of AEs for BF Spiromax was very similar to that for Symbicort Turbohaler. Headache was amongst the most common AEs in each of the PK studies.

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.

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

2.6.2. Conclusions 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 presence of a full clinical safety programme is not considered necessary in this type of application and is in line with the CHMP Guideline on orally inhaled products (CHMP/EWP/4151/00 Rev. 1) since equivalence has been demonstrated for the high strength (320/9 µg per dose) and the middle strength (160/4.5 µg per dose).

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

2.7. Risk Management Plan

Safety concerns

Important identified risks	• Systemic glucocorticosteroid effects • Life-threatening and fatal asthma events with long-acting adrenergic β2 receptor agonists • Paradoxical bronchospasm
Important potential risks	• Growth retardation in children receiving prolonged treatment due to off-label use in children and adolescents under 18 years • Drug interactions (with β-adrenergic blockers and strong inhibitors of CYP3A4)
Missing information	• Use in pregnant or breastfeeding women

Pharmacovigilance plan

Additional pharmacovigilance activities are not considered necessary and routine pharmacovigilance activities are considered sufficient to monitor the benefit-risk profile of the product and to detect any safety concerns.

Risk minimisation measures

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are proposed.

Conclusion

The CHMP and PRAC considered that the risk management plan version 3.2 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

The following statement in section 4.4 of the SmPC, under the systemic effect sub-heading, was initially present in the proposed product information for Budesonide/Formoterol Teva:

'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.'

The inclusion of the above text in section 4.4 of the SmPC was considered inappropriate and misleading as this medicinal product is indicated for adults only. Further, according to the SmPC guideline, a specific paediatric subsection in 4.4 is foreseen '*When the product is indicated in one or more subsets of the paediatric population and there are warnings and precautions for use that are specific to the paediatric population or any subset of the paediatric population, they should be identified under this subheading*. (…)'. Therefore, as requested by the CHMP, the applicant removed the above text from section 4.4. of the SmPC.

2.9.1. 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

This application concerns a hybrid version of budesonide/formoterol, inhalation powder. The approved indications of the reference product Symbicort Turbohaler are as follows:

Asthma
Symbicort Turbuhaler is indicated in adults and adolescents (12 years and older) for the regular treatment of asthma, where use of a combination (inhaled corticosteroid and long-acting β2 adrenoceptor agonist) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and "as needed" inhaled short-acting β2 adrenoceptor agonists.

or

- patients already adequately controlled on both inhaled corticosteroids and long-acting β2 adrenoceptor agonists.

Chronic Obstructive Pulmonary Disease (COPD)
Symbicort Turbuhaler is indicated in adults, aged 18 years and older, for the symptomatic treatment of

patients with COPD with forced expiratory volume in 1 second (FEV1) <70% predicted normal (postbronchodilator)and an exacerbation history despite regular bronchodilator therapy (see also section 4.4).

Nonclinical studies have not been provided for this application and the literature review is considered sufficient. Pharmacodynamic, pharmacokinetic and toxicological properties of the active substances budesonide/formoterol are well known.

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. 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. This was considered to be acceptable 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.

The bioequivalence studies form the pivotal basis with a cross-over design. The studies design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Budesonide/Formoterol Teva met the protocol-defined criteria for bioequivalence when compared with the Symbicort Turbohaler. The point estimates and their 90% confidence intervals for the parameters AUC0-t and Cmax were all contained within the protocol-defined acceptance range of 80.00 to 125.00%. Bioequivalence of the two formulations was demonstrated.

Benefits-risk assessment and discussion

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 high dose (320/9 µg per dose) and the medium dose (160/4.5 µg per dose) of Budesonide/Formoterol Teva have been shown to be equivalent in adults to the reference product Symbicort Turbohaler. The doses and dose regimens stated for these orally inhaled fixed-dose combination products for use in adults are acceptable.

This fixed-dose combination product is expected to have the same benefits as the reference product (Symbicort Turbohaler) in improving lung function and relieving symptoms in patients with asthma and COPD when used in line with the approved indications and posology. The unfavourable effects are expected to be similar to the well-known safety profile of the reference product (Symbicort Turbohaler) when used in line with the approved indications and posology of the reference product.

Budesonide/Formoterol Teva 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. Further, the absence of evidence of equivalence in adolescents and children and the non-availability of a lower strength product precludes the use of Budesonide/Formoterol Teva 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.

The CHMP recommends the 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.

Conclusion

The overall benefit/risk balance of Budesonide/Formoterol Teva is positive in the proposed indication.

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. is favourable in the following indication:

Regular treatment of asthma, where use of a combination (inhaled corticosteroid and long-acting β2 adrenoceptor agonist) is appropriate (in patients not adequately controlled with inhaled corticosteroids and "as needed" inhaled short-acting β2 adrenoceptor agonists, or in patients already adequately controlled on both inhaled corticosteroids and long-acting β2 adrenoceptor agonists), and in the symptomatic treatment of patients with COPD (FEV1 < 50% predicted normal) and a history of repeated exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators.

The CHMP 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.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Report

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates 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.